MEDICAL RADIOLOGY

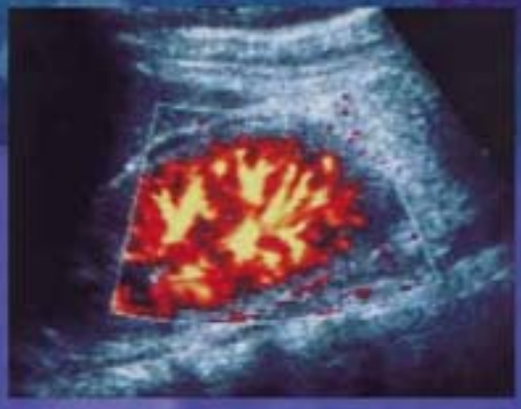
Diagnostic Imaging

A. L. Baert
M. Knauth
K. Sartor

Pediatric Uroradiology

2nd Revised Edition

R. Fotter
Editor



Springer

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R. Fotter (Ed.)

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2nd Revised Edition

With Contributions by

F. E. Avni · G. Benz-Bohm · H. Brisse · A. M. Cahill · M. Cassart · C. Cellier · M. Claudon
F. Collier · D. Couanet · J.-N. Dacher · N. Damry · V. Donoghue · R. Fotter · I. Gassner
T. E. Geley · I. Gordon · J. D. Grattan-Smith · M. Hall · M. P. Hiorns · M. E. Höllwarth
B. Hoppe · K. Ismaïli · R. A. Jones · C. Kuhn · C. J. Mache · A. Massez · C. A. McLaren
S. Neuenschwander · Ø. E. Olsen · W. Rascher · M. Riccabona · E. Ring
S. Rudnik-Schöneborn · C. Schulman · T. Schurmans · E. Sorantin · G. Staatz
R. B. Towbin · K. Zerres

Foreword by

A. L. Baert

With 419 Figures in 809 Separate Illustrations, 36 in Color and 68 Tables

Springer

Richard Fotter, MD
Professor and Chairman
Department of Radiology
Head of Division of Pediatric Radiology
University Hospital
Medical University Graz
Auenbruggerplatz 34
8036 Graz
Austria

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Foreword

Six years after the successful first edition of this comprehensive textbook on pediatric uroradiology, a second edition was mandatory.

Indeed, due to the rapid advances in imaging modalities and technology, as well as new therapeutic procedures, an update was needed on several important areas of pediatric urology such as vesicoureteric reflux, urinary tract infection and upper urinary tract dilatation.

I am very much indebted to Prof. Dr. R. Fotter, chairman of the department of radiology at the university of Graz and internationally renowned pediatric uroradiologist, not only for his personal contributions, but in particular for his expert, expeditious and efficient editorial coordination of this superb volume. I would also like to express my appreciation to the large group of individual authors, all recognised leaders in the field of pediatric uroradiology, for their excellent chapters.

This second revised edition is highly recommended not only to pediatric radiologists and radiologists in training, but also to pediatricians, pediatric surgeons and urologists who will find in this book excellent guidance for the clinical management of their patients.

Leuven

Albert L. Baert

Preface to the 2nd Edition

Never before in the history of pediatric uroradiology have concepts, expert opinions and recommendations changed as significantly and as quickly as over the last 5--7 years. Even established scientific concepts which we thought would never be debated again, are now back on the discussion table. This even applies to the treatment and imaging management of very common but serious nephrourological disorders such as urinary tract infection and vesicoureteric reflux, where the benefit of antibiotic prophylaxis and therefore the role of imaging are called in to question. These changes are not only triggered by the latest scientific findings, some of which contradict formerly established scientific concepts, but by the growing awareness of evidence-based medicine and, last but not least, also by new imaging techniques and technologies.

However, many old concepts still remain and many facts established in the last millennium are still true and pertinent today. This leads to some confusion even among experts, who are still searching for consensus-based imaging management recommendations.

Therefore, the invitation to compile a second revised and extended edition of the book *Pediatric Uroradiology* came at the right moment. In many aspects, the first edition could be used as a reliable basis for the development of the second edition. Thus this new book embraces both the new, taking recent advances in knowledge and technology into account, and the old. It is a complete rewrite where necessary, containing new contents with regard to latest developments such as genetics, and it provides the newest recommendations and discussions on clinical and imaging management of common nephrourologic disorders.

Thanks to the contributions of the distinguished and renowned international experts in the field of diagnostic and interventional pediatric uroradiology and of neighbouring fields such as genetics and pediatric nephrourology, a comprehensive volume containing all the latest advances could again be prepared, fulfilling the demands of a textbook covering all aspects of pediatric uroradiology in its broadest context. This book should satisfy the needs of the practising (pediatric) radiologist, pediatrician, pediatric surgeon and urologist; it should also offer up-to-date information and references to the researcher.

In view of the ongoing, rapid and significant changes, it was the intention of the editor to include a number of somewhat varying and overlapping views of the individual contributors for this second edition. Precisely this approach guarantees the requisite comprehensiveness and allows a degree of diversity reflecting the continuous reorientation process in pediatric uroradiology.

Again, it was a great honour and pleasure to work as an editor for this book project. I would like to acknowledge the dedication and expertise of each contributor, and I thank all of them sincerely.

Mrs. Irene Stradner, my secretary, was an indispensable member of our team; she did a marvelous job for this book project and I would like to express my warmest gratitude to her.

I hope that this second revised edition will again become a standard working and reference text for pediatric uroradiology.

Graz

Richard Fotter

Preface to the 1st Edition

A substantial change in the diagnostic and therapeutic management of urogenital disorders in children has taken place in recent years. There are two main reasons for this phenomenon: first, the growing integration of (new) imaging modalities such as magnetic resonance imaging and helical computed tomography and of advanced ultrasound techniques into pediatric uroradiologic imaging protocols; second, dramatic advances in our knowledge on the natural history of important urogenital pathologies of childhood as a consequence of maternal – fetal screening ultrasound.

Changing indications and limitations and comprehensive multimodality interpretation should be in the field of the (pediatric) radiologist's expertise. To enhance the role of the radiologist, she/he should have a profound knowledge of urinary symptoms as well as the principles of medical and surgical treatment in children and should also be able to interpret laboratory data.

This growing challenge for the (pediatric) radiologist seems to justify the idea of a book specifically devoted to pediatric uroradiology. Therefore, we were delighted to be invited by the series editor, Prof. Baert, to write such a book. Thanks to the contributions of the well-known international experts in the field of diagnostic and interventional pediatric genitourinary radiology who wrote the different chapters, a comprehensive volume could be prepared fulfilling the demands on a textbook covering all aspects of pediatric uroradiology in its broadest context. The book is written to satisfy the needs of the practicing radiologist and pediatrician but also to offer up-to-date information and references to the researcher.

In view of the above-mentioned changes in the field, one central goal was to discuss the reorientation of diagnostic and interventional radiological approaches to problems of the pediatric genitourinary tract and to elucidate the contributions made by different diagnostic and interventional uroradiologic techniques.

The focus of this book is primarily the point of view of the (pediatric) radiologist, but it offers all the necessary information for the pediatrician, pediatric surgeon and urologist as well putting decisions on imaging management on a reasonable basis. To meet the demands on a (pediatric) radiologist today, pertinent clinical observations, important pathophysiologic concepts, operative options, postoperative complications and clinical as well as radiological normal values have been included.

Dedicated chapters are devoted to specific problems of the newborn and infant, such as imaging and interpretation of upper urinary tract dilatation, postnatal imaging of fetal uropathies, associated urinary problems with imperforate anus, epispadias

– exstrophy complex and lower urinary tract anomalies of urogenital sinus and female genital anomalies.

Detailed discussions focus on the management of common problems in pediatric uroradiology such as urinary tract infection, vesicoureteric reflux and functional disorders of the lower urinary tract including enuresis and incontinence.

In dedicated contributions, embryology and the changing anatomy and physiology and pathophysiology of the growing organism are discussed to facilitate understanding of the disease processes and anticipated complications and form the rationale for interventions.

Specific chapters deal with agenesis, dysplasia, parenchymal diseases, neoplastic diseases, stone disease, vascular hypertension, renal failure and renal transplantation and genitourinary trauma in children. Specific problems of childhood neurogenic bladder are discussed.

Interventional uroradiologic procedures in children are discussed in full detail not only to show their value in treatment and diagnosis of a given problem, but also to serve as a source guiding the performance of these interventions.

It was the intention of the editor to respect the views of the individual contributors as far as possible. This is reflected in a diverse writing style and some degree of overlap and repetition. In the opinion of the editor, just this approach guarantees the necessary comprehensiveness.

After an always enjoyable time as editor I would like to acknowledge the dedication and expertise of each contributor; I thank all of them sincerely. Mrs. Renate Pammer, my secretary, was an important member of our team and I would like to express my warmest gratitude to her for the excellent job she did for this book project.

We all hope that this book will be accepted as the standard working and reference text for pediatric uroradiology. Moreover, we hope that it will prove useful to physicians in training and specialists alike as a reference source during preparation for examinations and conferences. The bibliography should readily satisfy the needs of all kinds of readers.

Graz — Richard Fotter

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Diagnostic Procedures

1

1.1 Diagnostic Procedures Excluding MRI, Nuclear Medicine and Video-Urodynamics

Jean-Nicolas Dacher

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1.1.1 Introduction

In the introduction of his course on Pediatric Uroradiology at Harvard Medical School, Prof. Robert L. Lebowitz, MD, cited the following sentence by L.L. Weed: "Just as important as doing the thing right is doing the right thing." This seems an excellent opening to this chapter about technique. As a matter of fact, many techniques compete today in the field of pediatric uroradiology, and we radiologists should be familiar with all of them. Indications, limitations, and of course interpretation should be within the field of our expertise. Overall, radiologists involved in this field should be familiar with the anatomy of the normal and malformed urinary tract, urinary symptoms in children, and the principles of medical and surgical treatment. Of course, radiologists should also be able to interpret biological data such as urinary culture and blood studies. At least, even if one does not practice any kind of examination, one should know the indications for it and the risks and stresses involved.

The requirements play a role in the success of any procedure. It is extremely important to know what the problem is and also to know what the parents (and the child, when old enough) expect of the test and its results. If the question is unclear, if there is any discrepancy between the requisition sheet, the medical records, and the parents' interview, direct communication should be established with the referring physician before proceeding.

J. N. Dacher, MD, PhD
Professor, Department of Radiology, University Hospital of Rouen, 1, Rue de Germont, 76031 Rouen, France

In this section of Chapter 1, ultrasound, X-ray procedures, and computed tomography (CT) are analyzed. Each subsection starts with the main indications for the study concerned. Then the technique as we perform it in our institution is described, as well as the limitations and risks. Normal findings and imaging strategies are beyond the scope of this chapter; they are discussed in the relevant parts of the book. A short paragraph on radiological reports concludes this section.

1.1.2 Ultrasound and Doppler

Ultrasound (US) is usually the first examination to be performed in a child presenting with any urinary tract or renal disease. Lack of ionizing radiation, low cost, wide feasibility, and excellent anatomic resolution owing to the small amount of fat in children all contribute to making US an irreplaceable technique.

1.1.2.1 Indication

First of all, exploring the kidneys and urinary tract is routine when performing abdominal ultrasound in any Department of Pediatric Radiology. In children, the lack of specificity of abdominal symptoms and the high prevalence of renal and urinary tract disease both justify this practice.

Nowadays, most cases of urinary tract malformation are detected by maternal-fetal US. Postnatal US became the cornerstone examination in following up infants who had the prenatal diagnosis of hydronephrosis. Comparative sonograms even represent the only imaging modality required by most situations. The first postnatal ultrasound examination is recommended by day 4 of life. The rationale to perform sonography several days after birth is the relative dehydration of neonates. Dehydration decreases diuresis; hence, a dilated segment of the urinary tract would be under-evaluated by precocious sonogram. A second US study is commonly performed for comparison by 6 weeks of life (Ismaili 2004). Further studies [isotope studies, voiding cystourethrography (VCU), MR urography] can be scheduled depending on clinical symptoms and the results of serial ultrasound studies (aggravation vs. improvement of dilatation, presence vs. absence of associated renal dysplasia). An excellent communication between the prenatal ultrasound staff and the radiologists, pediatricians, and surgeons taking care of children is of utmost importance. The decision-making process is facilitated when images can be stored and retrieved via a PACS.

A very common indication for renal US is urinary tract infection. Primarily performed to rule out hydronephrosis, abscess or calculus, US can also detect (or confirm) underlying malformation. It is usually combined with other studies, especially VCU. The great success of US over the past few years has been in detecting malformation and preventing infection, which is known to be life-threatening in neonates and devastating for function in growing kidneys (Berg and Johansson 1982). However, in a recent study, the role of US in the evaluation of UTI in children was critically evaluated (Hoberman et al. 2003). Hoberman et al. reported a 12% rate of sonographic abnormalities in a population of children with UTI. Moreover, these authors have stated that prenatal US could detect most children with urinary tract malformation. They concluded that in a child referred for UTI, renal US would not be relevant if his/her prenatal US examinations were normal. This approach can be criticized for several reasons. First of all, prenatal US was shown to be unable to detect all children with congenital vesicoureteric reflux, the most frequent malformation associated with UTI (Anderson et al. 2003; Phan et al. 2003; Moorthy et al. 2003). Secondly, hydronephrosis as a consequence of uretero-pelvic junction obstruction can be diagnosed at any age of life in patients who had had normal prenatal sonograms and can become complicated with severe infection. Thirdly, communication between pre- and postnatal medical teams can fail for several different reasons (Dacher et al. 1992). The main drawback of US in the context of pediatric UTI is its reported sensitivity. US sensitivity varied among the different published studies regarding acute pyelonephritis (Hoberman et al. 2003; Dacher et al. 1996; Morin et al. 1999; Hitzel et al. 2002). This may be explained by different operators (expert pediatric radiologists involved in this field in some studies vs. young residents or sonographers in others), different techniques (using a ventral scanning approach or dorsal, lateral and ventral ones, using B-mode only or B-mode plus color/power Doppler, allowing sedation in non-cooperative children, allowing contrast medium injection, using high frequency/har-

monic techniques, considering the subtle reflectivity abnormalities of acute pyelonephritis, etc.), as well as variable equipment. Even under optimal technical conditions, the diagnostic accuracy of color Doppler US for APN ranged from 80 to 90% (Morin et al. 1999; Hitzel et al. 2002) and remained below that of DMSA scintigraphy, enhanced CT, or MRI. A normal US examination cannot definitely eliminate renal involvement in a child with acute pyelonephritis.

In follow-up of children with refluxing or obstructive malformation, sonography has replaced intravenous urography (IVU) in assessing renal growth and dilatation.

After blunt abdominal trauma, hematuria is very common, and its grade does not correlate with injury (Mayor et al. 1995). CT is the unanimous gold-standard method, but has been shown not to be cost effective (Filiatrault and Garel 1995). When US can be performed in satisfactory conditions, it seems able to exclude severe renal injury. Of course, any clinical or sonographic abnormality should lead to CT. Patients with multiple injuries are also investigated by enhanced CT on an emergency basis.

In children with spontaneous hematuria, US can rule out urolithiasis or tumor. In renal failure, US can exclude renal vein or artery thrombosis (Laplante et al. 1993). Doppler US can confirm diagnosis and help follow-up of hemolytic-uremic syndrome (Patriquin et al. 1989). In children with palpable abdominal mass, US and plain film of the abdomen are usually sufficient to establish the diagnosis, which is then confirmed by enhanced CT or MRI. In patients with arterial hypertension, B-mode US can detect renal scar, hypoplasia, or nephropathy. Then, Doppler examination of renal vessels and parenchyma can orient diagnosis toward vascular cause. Renal angiography remains the reference examination (Garel et al. 1995).

Periodic screening US is recommended in children with characteristics that are known to be associated with renal benign or malignant tumors (aniridia, hemihypertrophy, Drash syndrome, Beckwith-Wiedemann syndrome, tuberous sclerosis). In patients with malformation known to be associated with renal abnormality (the VATER association, imperforate anus, internal genital anomalies, Fanconi anemia), one postnatal US examination is recommended. However, abnormal external ears, unique umbilical artery, hypospadias, and undescended testis have not been proven to be associated with renal malformation and do not represent indications for renal screening (Currarino et al. 1993).

Longitudinal evaluation of renal allografts is based on comparative US and Doppler examinations. Estimation of bladder wall and capacity in neurogenic bladder and voiding dysfunction can be made by US. Association with perineal electromyography and flowmetry helps understanding and management of functional voiding anomalies (Pfister et al. 1999). Finally, US can be used as a guide for interventional procedures. Renal biopsy, nephrostomy tube, and abscess drainage can be performed using real-time US guidance.

1.1.2.2 Technique

1.1.2.2.1 Equipment

Results intimately depend on technique. Recent equipment–high-frequency transducers with duplex color and power Doppler modes–is recommended. Harmonic imaging may be useful, especially when exploring obese children or adolescents, for detection of reflux after intravesical injection of contrast medium, and even for improving visualization of the bladder and kidneys from a dorsal approach (Bartram and Darge 2005). Most examinations of the urinary tract can be performed with a 5- to 7.5-MHz sector or phased-array transducer. A high-quality scanner is especially useful for severely ill patients who need bedside and emergency examinations. This point should be kept in mind by radiologists and hospital managers when purchasing a new scanner and by the radiology staff when planning daily schedules.

1.1.2.2.2 Neonates

Since the advent of maternal fetal US, many children have to be examined during the neonatal period, some of them still inpatients in the intensive care unit. In ICU practice, radiologists and technologists should follow basic rules of neonatal care. Incubator doors should be kept closed as much as possible, and extreme caution should be taken to prevent any catheter or tube contamination or withdrawal. Sterile preheated jelly should be used, and studies should be performed as quickly and silently as possible. Direct communication with the ICU staff and proper addressing of the medical question at hand always contribute greatly to the avoidance of handling mistakes.

1.1.2.2.3 Older Children

Cooperative children are first scanned in the supine position, then in the right and left lateral decubitus positions. The examination is completed with the patient in the prone position. A variety of positions, sometimes unconventional as the opportunity arises, are often necessary for the examination of a moving, playing, or crying child. Imaginative games can be useful at this time.

Absence of cooperation can sometimes compromise the quality of study. Medications are usually not used for US scanning, but light sedation (equimolecular mixture of nitrous oxide and oxygen, midazolam, hydroxyzine) could be considered in some circumstances, such as Doppler recordings. For further information on sedation, refer to VCU and CT sections in the same chapter.

1.1.2.2.4 Lower Urinary Tract

A basic study of the urinary tract should start with an explanation to the parents, and to the child if he or she is old enough to understand. The bladder is studied first, especially in infants, since reflex micturition is frequent when the transducer is placed on the abdominal wall (avoid unheated jelly). Examination of the full bladder includes analysis of urine echogenicity and the bladder wall. It is extremely important to look for dilated ureters(s) behind the bladder (Fig. 1.1.1) or an ureterocele inside it. It should be remembered that US approximates bladder capacity, which is best assessed by VCU (Koff 1983; Berger et al. 1983). Bis and Slovis (1990) proposed the following equation:

$$\text{Volume (ml)} = 0.9 \times \text{DHW}$$

(DHW stands for depth × height × width in centimeters) to obtain the bladder capacity from US in children with normally shaped bladders. Automatic devices are very useful and seem accurate to estimate bladder capacity and residual urine after micturition (Bladder Scan®), especially in patients with neurogenic bladders or any kind of voiding dysfunction.

When the shape is abnormal or the bladder is empty, capacity should not be inferred from US measures (Bis and Slovis 1990). The transperineal approach can be useful to visualize dilated posterior urethra in boys with valves (Teele and Share 1997). Finally, ureteral jets into the bladder can be detected with color Doppler (Leung et al 2007).

1.1.2.2.5 Upper Urinary Tract

Measurements include longitudinal (Fig. 1.1.2) and transverse size of each kidney and renal pelvis AP diameter. Results have to be compared to those of prior examinations (sonographic, prenatal, or others) as well as to normal values (Siegel 1995). Echogenicity

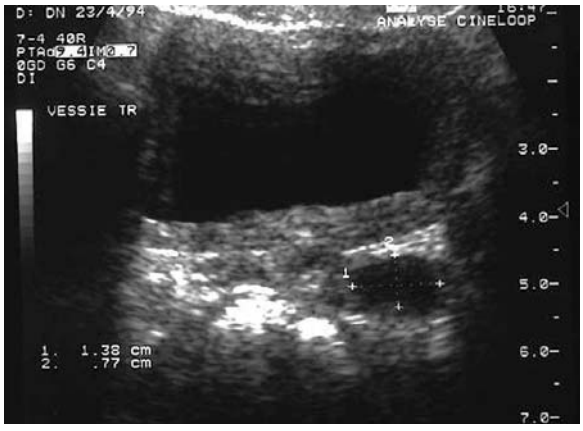

Fig. 1.1.1. US axial scan of the bladder in a 10-year-old girl. Dilated left upper pole ureter identified through a full bladder in a child with duplicated ureter and ectopic implantation of the upper pole ureter

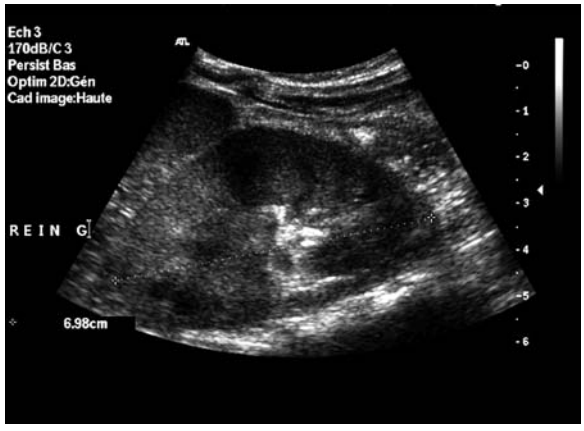

Fig. 1.1.2. US scan. Longitudinal measurement of the left kidney in a girl with acute pyelonephritis. Note the abnormal echogenicity (loss of corticomedullary differentiation) of the upper pole due to infection

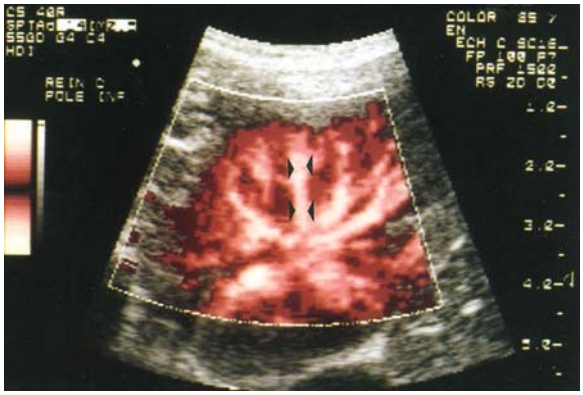

Fig. 1.1.3. Transverse power Doppler US scan of the left kidney in a normal child. Normal intrarenal vessels. The straight course of interlobar arteries (*arrowheads*) is shown

of both the cortex and medulla is assessed and compared to that of the liver. High-frequency examination can sometimes be useful to increase spatial resolution. A vascular map is preferably performed in the prone position in color or power Doppler mode (Fig. 1.1.3) with adapted filter and pulse repetition frequency. In some instances, duplex Doppler recordings are necessary. Parenchymal indices are taken at three locations (upper and lower pole, middle part). Then, renal artery waveforms can be recorded in the prone position at the ostium and hilum.

1.1.2.2.6 US Detection of Reflux

Several studies (Atala et al. 1993; Darge et al. 1999) have shown potential value for voiding sonography in detection of reflux. A contrast agent can be instilled in the bladder. An increase in echogenicity of the renal pelvis and the ureter appears in cases of reflux. There is no ionizing radiation, but examination time is longer than that required for voiding cystourethrography (VCU), and voiding sonography does not eliminate the need for a bladder catheter.

This practice remains unused in some countries (e.g., in France) mainly for financial reasons. Voiding sonography could become part of the diagnostic algorithm of reflux and would thus decrease the need for VCU. Voiding sonography appears inadequate for imaging the urethra (first reflux study in boys), but follow-up examinations and family screening appear to be excellent indications. However, widespread use of this technique will remain difficult as long as contrast media continue to be so expensive.

1.1.3 Voiding Cystourethrography (VCU)

Contrary to IVU, which was supplanted by sonography, MRI and nuclear medicine, VCU remains the gold-standard examination for imaging the bladder and the urethra and detecting vesicoureteral reflux.

1.1.3.1 Indication and Scheduling

Detecting vesicoureteral reflux in children with a history of urinary tract infection (Lebowitz 1992) or prenatal diagnosis of abnormal dilatation (Avni et al. 1998; Zerin et al. 1993) is the primary role for VCU. Alternative techniques are radionuclide cystography (Willi and Treves 1983) and voiding urosonography (see above). Radionuclide cystography delivers less ionizing radiation than VCU, allows permanent recording, and, for this reason, is probably more sensitive to transient reflux. However, the anatomic detail provided by radionuclide cystography and voiding urosonography is poor, and therefore none can be recommended as a first-step examination. First evaluation of children with urinary tract infection is usually made by US and VCU. Then, if reflux is shown, antibiotic prophylaxis is prescribed, surgery is considered, and follow-up is based on either voiding urosonography or radionuclide cystography. Follow-up VCU should be limited to medical centers where none of these techniques is available.

Up to now, there was no consensus on the age/gender conditions that should lead to VCU after a first episode of urinary tract infection. A European group has suggested performing VCU in children aged less than 4 years who had a proven urinary tract infection (Riccabona et al. 2006). In older children, the prevalence of reflux being less important, the decision to perform VCU or not could be taken on an individual basis.

There has been a lot of debate on the optimal timing of VCU relative to the infectious episode. Should examination be performed during acute infection or 1–2 weeks later? There is no scientific consideration to sustain one hypothesis or the other. In our opinion, VCU is an important examination in children with a history of infection simply because reflux has been shown to be

associated with infection, and it can devastate the kidney. Experience shows that the longer the delay is between infection and examination, the higher the rate of people who do not show up. On the other hand, it does not seem reasonable to conduct VCU in children with either fever or persistent dysuria. In summary, we would recommend performing the examination as soon as clinical symptoms have disappeared.

With modern antibiotic therapy, urine is usually sterile by the time of VCU, and catheterization can present a good opportunity to analyze a specimen. However, it should be kept in mind that bacteriuria can be physiological, especially in girls. Hence, there is no reason to postpone VCU when the dipstick test is positive for nitrites.

If reflux is suspected and VCU has been decided upon, the patient should be maintained on antibiotics until the examination is performed (antibiotic therapy if VCU is performed quickly, antibiotic prophylaxis if VCU is performed later on).

Other indications are rarer. Imaging of urethral malformation or trauma remains based on the voiding part of VCU. Patients with cloacal anomalies, ambiguous genitalia, or imperforate anus can be explored. On the other hand, the role of VCU in investigating pelvic or bladder tumors has decreased since the advent of cystoscopy and MRI.

1.1.3.2 Technique

Both digital fluoroscopy and fluorography provide excellent diagnostic quality and require a lower radiation dose. They have advantageously replaced the film-screen combination, which should no longer be used to perform VCU in children.

1.1.3.2.1 Information

Before proceeding, it is important to take time to give information to the parents and to the child if he or she is old enough. The family can be given an information sheet before the study. Drawing a diagram of VCU is an excellent means to provide effective information. Psychological consequences of urethral catheterization should not be underestimated.

1.1.3.2.2 Plain Film

An AP radiograph of the entire abdomen is taken unless one has been obtained recently for any reason and there was no breakthrough event. An additional film in upright position is unnecessary. Abnormal calcification, nephrocalcinosis, spinal deformation, bony abnormality, spinal surgery, pubic symphysis abnormality, and the position of prosthesis (VP shunt, JJ tube, bladder catheter, nephrostomy tube or other) all can easily be shown prior to administration of contrast medium. Attention should be paid to extra urinary anatomy (think of congenital hip dislocation).

1.1.3.2.3 Pain and Sedation

In many cases, no sedation is required except that provided by sterile Xylocaine (lidocaine) jelly that lubricates the catheter in boys. A quick examination performed by an experienced radiologist should not be painful. Postprocedural minor discomfort can occur, and it seems less worrisome when announced. Improvement by hydration and local care is the rule. In some children, major anxiety can be present. Inhalation of an equimolecular mixture of nitrous oxide and oxygen (Entonox) in fasting children can be helpful (Schmit and Sfez 1997). In uncooperative children who are too young to breathe gas, rectal midazolam can occasionally be used (Hypnovel; 0.3 mg/kg, maximal dose 5 mg). For safety, sedation procedures should preferably be organized in collaboration with the department of anesthesiology.

1.1.3.2.4 Retrograde or Suprapubic?

Retrograde access seems to be the most frequently used procedure and has a very low rate of complications; its main risk is post-procedural infection. The suprapubic approach is mainly used in neonates with posterior urethral valves and in children in whom catheter placement can be difficult or painful (urethral trauma, hypospadias, cloacal malformation). Suprapubic access requires preliminary bladder US. It can fail when the child voids during puncture. Leakage around the catheter in the prevesical space is common and benign. The risk of post-procedural infection decreases when using the supra-pubic approach.

1.1.3.2.5 Catheter Risks

Urinary tract infection is rare, but it represents the main risk of VCU. Parents should be informed of this possibility. The risk of developing infection seems higher in children presenting with a urinary tract malformation predisposing to urine stagnation (high-grade reflux, intrarenal reflux, megacystis-megaureter association, posterior urethral valve, ureteropelvic junction syndrome associated with ipsilateral reflux) (Dacher et al. 1992). In patients with such abnormalities, post-procedural infection can be life threatening. While performing VCU, sterility is extremely important in all patients, since one cannot know at the time of catheterization that such a malformation is present (Fig. 1.1.4). Urethral trauma has been described, but we have never observed a case since we have been using feeding tubes in boys.

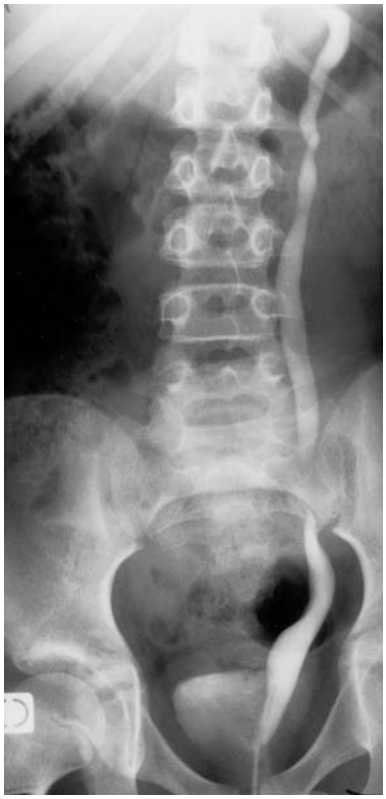

Fig. 1.1.4. Accidental introduction of the tube in the ectopic orifice of the upper pole ureter of a duplicated kidney. No consequence was observed. Catheter was withdrawn, then introduced again in the bladder. This type of accident illustrates the importance of sterility in any maneuver while performing VCU

1.1.3.2.6 Catheter Placement and Filling

When possible, the child should void his/her bladder prior to examination. One of the child's parents can make a first cleaning of the perineum. Clinical examination by the radiologist before introducing the catheter is a unique occasion to have a thorough look at the child's perineum/genitalia with a powerful lighting. Proceeding in this way can allow difficult diagnoses such as fused labia, phimiosis, male or female hypospadias, or permanent dribbling. In the case of fused labia, gentle manual opening can be performed. Another treatment consists in applying an estrogenic cream for several days preceding the examination. A second sterile cleaning is performed and then the catheter is placed. In all cases, the urethral meatus should be visualized before placing the catheter. In girls, the meatus is close to the vagina. In young boys, the foreskin should not be forced. Resistance is usually perceived when the tip of the catheter reaches the external sphincter. Continuous pressure overcomes this resistance, and efflux of urine confirms the proper position of the catheter inside the bladder. Vaginal insertion of the catheter is common. In such cases, the misplaced catheter can be left in place in order to facilitate positioning of the second one. The catheter is safely taped on the medial aspect of the thigh, and the child is centered under the X-ray tube. The bladder is filled with a bottled dilute contrast medium (120 mgI/ml concentration is recommended) under 30 cm H2O pressure. Bladder capacity is evaluated. It can be compared to the theoretical volume (Koff 1983):

$$\text{Bladder capacity (ml)} = [\text{age (years)} + 2] \times 30$$

Flow should be continuous until bladder repletion is attained. Interruption or back flow can be due to contractions of the detrusor muscle when an unstable bladder is present (see Chap. 14). Spot films are taken during filling in order to detect passive reflux.

1.1.3.2.7 Radiation Dose

The ALARA principle (As Low a radiation dose As Reasonably Achievable) should be applied. If a reflux study is required, the non-radiating voiding urosonography should be preferred, except if anatomic depiction is necessary. In such case, low-dose fluoro-

scopic VCU (Avni et al. 1994; Kleinman et al. 1994) should be encouraged. Diagnostic yield was shown to be sufficient in diagnosing reflux while delivering a dose that competes with that of radionuclide cystography.

1.1.3.2.8 Cyclic VCU

Cyclic VCU has been shown to be more efficient in detecting reflux (Jéquier and Jéquier 1989; Paltiel et al. 1992; Gelfand et al. 1999). In our institution, we have chosen to perform three cycles of filling in non-toilet-trained children and only one in older children. In the cyclic technique, the child voids twice around the catheter. Then, when the third micturition starts, the catheter is removed, and voiding pictures are taken (Fig. 1.1.5).

1.1.3.2.9 Micturition

A good micturition study requires sequential filming (two spots/second) or a videotape recording (Fotter et al. 1986) in order to detect voiding dysfunction (absence of coordination between blad-

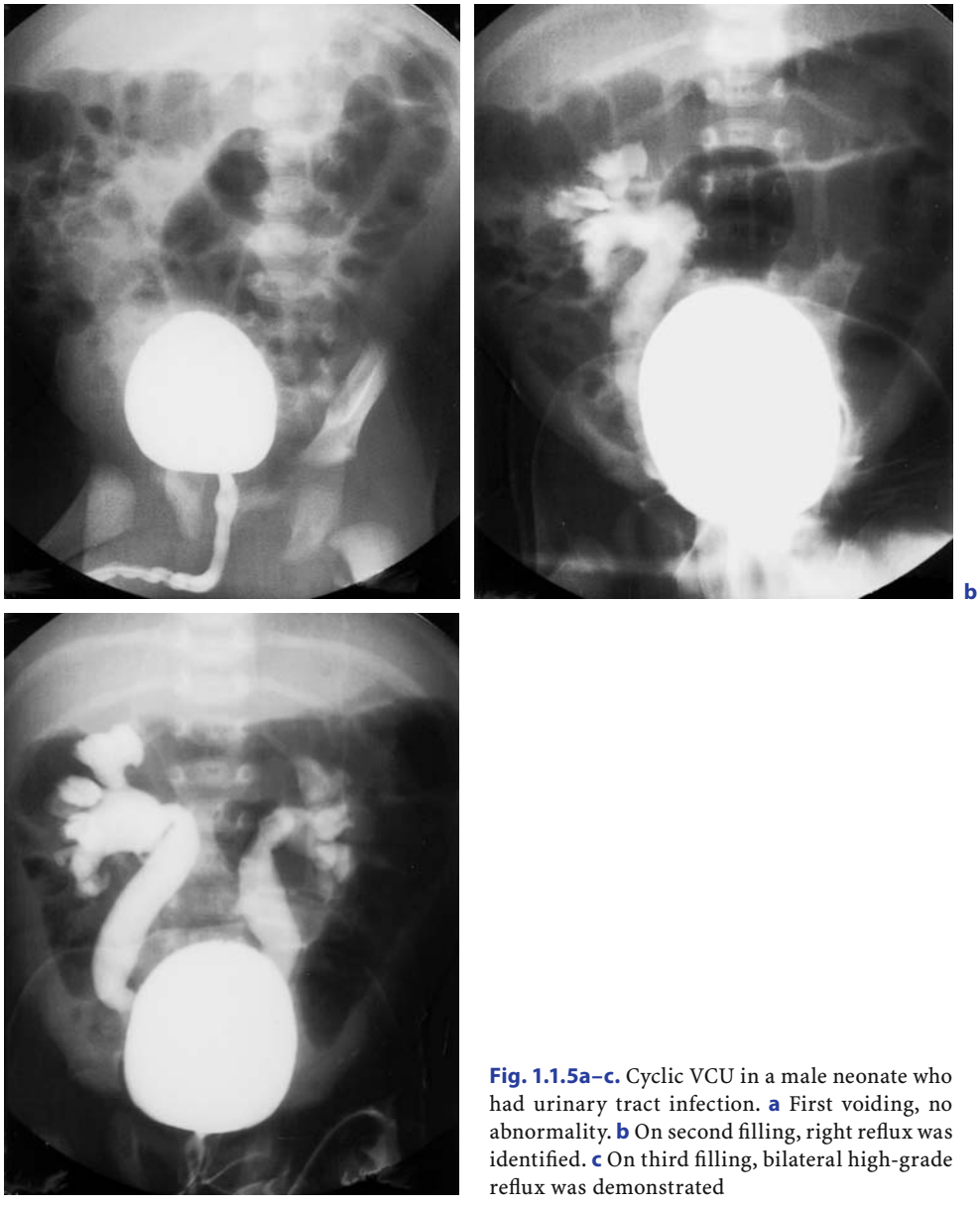

Fig. 1.1.5a–c. Cyclic VCU in a male neonate who had urinary tract infection. **a** First voiding, no abnormality. **b** On second filling, right reflux was identified. **c** On third filling, bilateral high-grade reflux was demonstrated

der contraction and external sphincter opening) or urethral abnormality. Centered AP views in girls and oblique views in boys are adequate to analyze the urethra (Fig. 1.1.6). If reflux is detected during micturition (active reflux), oblique bladder views are useful to completely visualize the refluxing ureter including its retrovesical portion. The relationship of the refluxing ureter and a bladder diverticulum is analyzed on this film. AP views of kidneys should be taken to grade reflux (Lebowitz 1985), to look for intrarenal reflux (Fig. 1.1.7), and to analyze the anatomy of the excretory system (reflux into the lower or upper pole of a duplex system, association of reflux, and ureteropelvic junction obstruction in the same renal unit) (Fig. 1.1.8). A post-voiding film is taken to assess residual urine; it can also be useful to detect a bladder diverticulum (Fig. 1.1.6). In case of reflux, a 5-min delayed film is valuable to evaluate its clearance. Reflux associated with prolonged stasis is thought to increase the risk of severe infection.

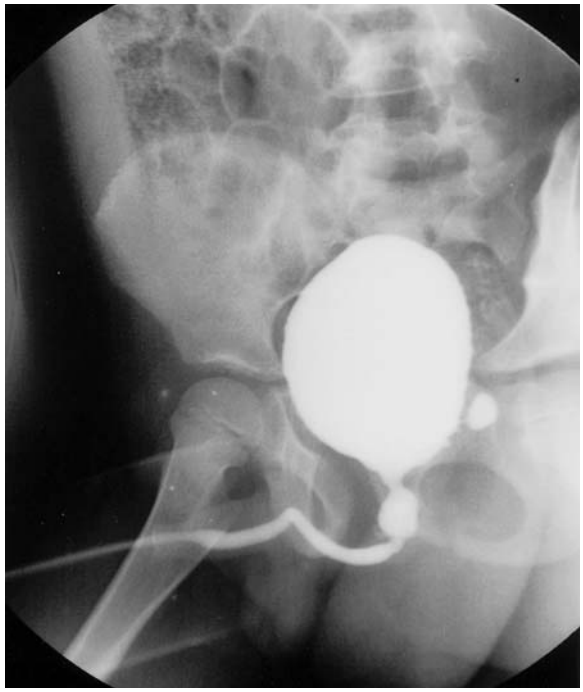

Fig. 1.1.6. VCU in a 7-year-old boy who complained of dysuria. Oblique view during micturition. Slightly irregular bladder cannot be interpreted as abnormal during micturition. Bladder diverticulum (the same was shown on the opposite side). Moderate dilatation of the posterior urethra. Valves were suspected. Cystoscopy confirmed the diagnosis, and coagulation was performed. However, the orifices of the diverticula were not seen by the surgeon

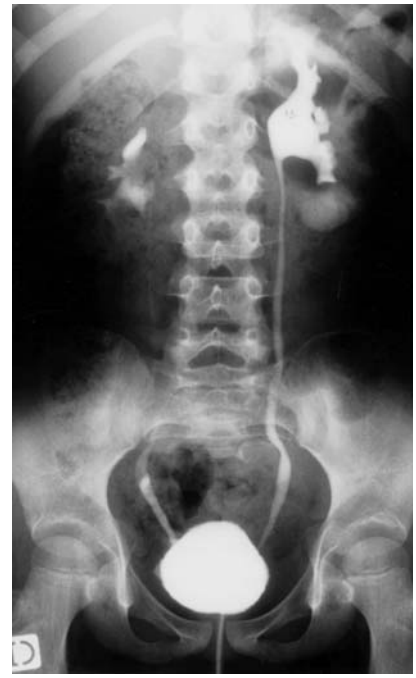

Fig. 1.1.7. VCU in a girl with a history of urinary tract infection. Bilateral reflux. Note intrarenal reflux on both upper and lower poles of the left kidney

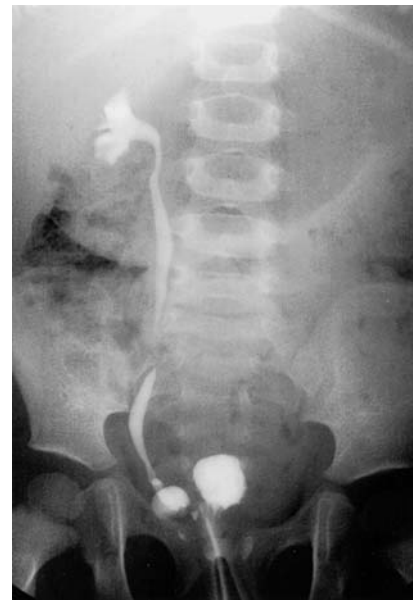

Fig. 1.1.8. VCU in a girl with prenatal diagnosis of a duplex system on the right side. A huge right ureterocele was shown by ultrasound. Reflux into the lower pole is inferred from the visualization of the incomplete kidney. Ectopic ureterocele was everted during the procedure

1.1.4 Retrograde Urethrography

Retrograde urethrography is rarely indicated, and retrograde or suprapubic VCU should be preferred in most patients. Such an examination is usually performed to rule out a ruptured urethra in an adolescent. A Foley catheter is inserted in the distal urethra. The balloon is then inflated in the fossa navicularis, and the urethra is slowly and retrogradely injected. Lateral and oblique pictures are taken. In most instances, the posterior urethra is not opacified. This should not be considered abnormal.

1.1.5 Intravenous Urography

During the 1990s, the development of US, nuclear medicine, and MRI had substantially diminished the impact of intravenous urography (IVU) in pediatric uroradiology. Multi-detector computed tomography (MDCT) and MR have now replaced IVU in its remaining indications such as tuberculosis, papillary necrosis, or permanent urinary dribbling in girls. If IVU belongs now to history, its physiology-based principles should not be forgotten. In postoperative children, AP view of the abdomen 10 min after IV injection of iodinated contrast medium remains a possible technique to approach the renal function.

1.1.6 Multi-Detector Computed Tomography (MDCT)

1.1.6.1 Indications

Because MDCT can deliver a substantial amount of ionizing radiation (Cordoliani et al. 1999), it should rarely be performed as a first line investigation of the urinary tract in a child. Children with multiple injuries are an exception to this rule. Other indications for CT are tumor, urolithiasis, severe or unusual urinary tract infection, and evaluation of parenchymal disease (Siegel 1999). Any condition requiring an excellent anatomic depiction should consider MDCT due to its spatial resolution, volume acquisition, and multiple plane reformatting (MPR) capabilities.

1.1.6.2 Technique

1.1.6.2.1 IV Access, Contrast Medium, and Allergy

A safe IV line is always necessary, and our preference goes to an antecubital catheter. The largest possible size is chosen. Placement of the catheter is ideally performed by a nurse in the outpatient suite after skin preparation with anesthetic cream (lidocaine–prilocaine, Emla®). This catheter makes it possible to use a power injector. Power injection provides an excellent examination quality, and continuous flow decreases the risk of extra vascular passage. The injection should be visually monitored and stopped in case of extra-vascular passage. In younger children, hand injection under visual control seems safer.

Central lines should not be routinely used. However, in some patients with malignancy, peripheral veins are severely damaged, and a central catheter is the only possible venous access. In such cases, catheter handling and rinse should be performed by a trained nurse. Epicranial needles can be occasionally used in young children (placed on the radial aspect of the wrist, the ankle, or scalp veins). The external jugular vein should be considered the last possible alternative, since its puncture is uncomfortable, it usually causes inelegant ecchymosis, and the procedure is quite impressive for the parents or accompanying persons.

Nonionic iodinated contrast media (2 ml/kg) are preferred because they have been shown to decrease the incidence of minor events (Katayama et al. 1990). Diluted barium sulfate can be administered per os (the preferred drink of the child is recommended for dilution) or by enema to beacon the digestive tract. A child with a proven history of a severe accident with iodinated contrast medium should be referred to an allergist and an anesthesiologist who will make medical decisions about any further injection. In case a new injection is mandatory, a different contrast medium

has to be injected. Patients with common allergies or asthma can be given an antihistamine medication (hydroxyzine, Atarax®) for 24 h before examination. Latex allergy is a frequent occurrence in children with a history of multiple surgical procedures. Latex-free materials and gloves should be used in such patients.

Adverse reactions are extremely rare in pediatric practice. However, preventive measures should be taken, and any reactions that do occur should be managed in collaboration with anesthesiologists. Adverse events justify the presence of at least two persons during any examination with contrast medium injection (one to take care of the patient and one to call the anesthesiologist).

Vasovagal reaction (bradycardia, pallor, and loss of consciousness) is related to pain rather than contrast medium. The lower limbs are elevated; atropine is sometimes useful. Mild allergic accident (itching, urticaria) can be treated by corticoids and an antihistaminic medication.

Severe allergic accidents can occur (tachycardia, severe hypotension) and radiologists and technicians should be aware of first-aid principles (good venous access, perfusion of saline solution, oxygen, preparation of a syringe of diluted adrenaline). The emergency phone number should be visible from anywhere in the CT suite and dialed as soon as possible. Adrenaline can induce severe side effects. For this reason, it would be safer to have only anesthesiologists administer it.

1.1.6.2.2 Sedation

Natural sleep is the safest. Sleep deprivation during the hours preceding CT (or MR) is often successful. However, except in rare instances in children under 6 months old, natural sleep is rarely obtained in a busy noisy CT room. Immobilization is strongly recommended even in sedated children (the venous access needs to be maintained visible). Immobilization avoids undesirable movement by the patient and keeps him or her warm. Sedation is rarely useful to examine the urinary tract by MDCT. Any sedation protocol should be discussed and written with anesthesiologists. In our institution, we occasionally use rectal midazolam (Hypnovel®, 0.3 mg/kg body weight), but heart rate and pulse oxymetry have to be monitored during the procedure and later. Hydroxyzine (Atarax®) decreases anxiety and is fairly sedative.

A fasting period is only required for sedated children (not for contrast medium injection). It should be limited to 3 h in young children and to 4 h in older ones. Dehydration should always be prevented.

1.1.6.2.3 Imaging Protocol

Attention to radiation should be a priority in pediatric CT (Vade et al. 1996; Scheck et al. 1998). The ALARA principle is applied, and pediatric protocols of quality-controlled CT equipment should be applied. Substitution by a non-radiating procedure (MRI, US) when feasible should be encouraged. The exposition length should be limited to the organs of interest. The kVs should be limited to the 80–100 range in most children. Attention should be paid to the mA/s level, which often can be reduced with no image degradation. The detector configuration should be adapted to the explored pathology. The CT dose index and dose length product should be mentioned in the report.

Pre- and post-contrast series are combined. Time delay should be adapted to pathology; arterial time should be acquired in the context of trauma or tumor. Very delayed acquisition can sometimes be necessary to look for stagnant iodine within the parenchyma in acute pyelonephritis (Ishikawa et al. 1985; Dalla Palma et al. 1995) or a peri-renal leak in cases of renal fracture. Two-dimensional reformatting is especially useful in evaluating renal fractures or retroperitoneal tumors (Fig. 1.1.9). Maximal intensity projection images in the coronal and sagittal planes advantageously replace IVU at any time of the examination.

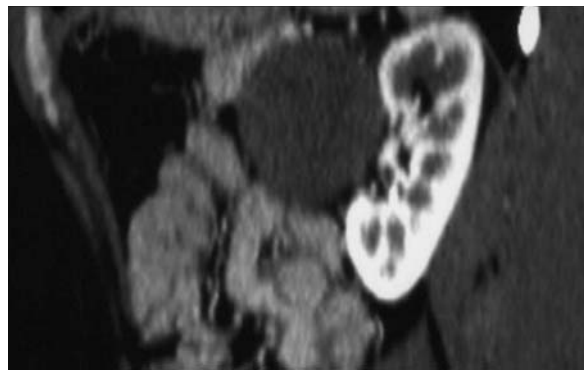

Fig. 1.1.9. MDCT Evaluation of an adrenal tumor. Multiplanar reformatting of arterial phase acquisition

1.1.7 Antegrade Pyelography

Antegrade pyelography has lost much of its interest since the advent of MR urography (Borthne et al. 1999) and MAG3-Lasix scintigraphy, which respectively investigate urinary tract anatomy and renal function and excretion. Antegrade pyelography (Fig. 1.1.10) can be performed in patients with poorly functioning and dilated kidneys. In such cases, association with urodynamic study (the Whitaker test) can help in decision making (surgical repair versus nephrectomy) (Dacher et al. 1999) (Figs. 1.1.11, 1.1.12). In the Whitaker test, pelvic, bladder and differential (pelvic minus bladder pressures) pressures are recorded under general anesthesia. A Foley catheter is placed in the bladder. The patient is then placed in the prone position. One or two needles are placed within the renal pelvis under sonographic guidance. Obstruction is considered when differential pressure rises above 22 cm H_2O (normal pressure should remain below 15 cm H_2O).

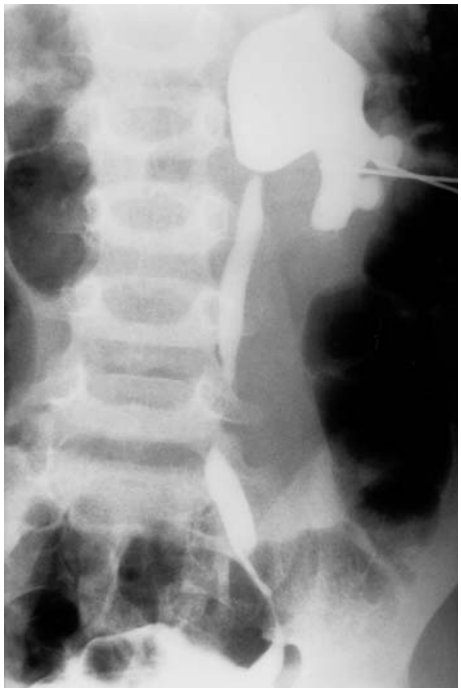

Fig. 1.1.10. Antegrade pyelography combined with the Whitaker test on general anesthesia in a 6-month-old baby. No reflux. Slight dilatation on ultrasound and IVU. Diuresis renography had not been conclusive, and the Whitaker test showed obstruction at the ureteropelvic junction. Surgery was subsequently performed

1.1.8 Renal Biopsy

In our institution, US-guided renal biopsies are performed under general anesthesia in the operating room. The child is in the prone position. Conventional US is performed first targeting the lower pole of the right kidney. Two or three fragments are taken in the most peripheral location. Post-procedural US is performed. A second US examination is performed 24 h later, before the child is allowed to leave the hospital. The risk of post-procedural arteriovenous fistula justifies a color-/power-Doppler examination of the biopsy site.

1.1.9 Renal Angiography

Nowadays, Doppler US and gadolinium-enhanced MR angiography tend to replace renal angiography in most diagnostic procedures. Angiography is a complex procedure in children. Risks are that of general anesthesia and arterial puncture. Renal angiography is usually justified by a therapeutic procedure (angioplasty in renovascular hypertension, occlusion of posttraumatic fistula, embolization of arteriovenous malformation).

1.1.10 Reports

The end product of any examination is the radiological report. A successful examination includes a clear and well-built report. Blais and Sanson (1995) published an excellent guide for reports that refers to the model of a scientific article. Introduction puts examination in the clinical context. The referring physician can check that the question was properly understood. The "Patients and Methods" section describes the technique. The procedural features, amount and nature of contrast medium, venous access, and incidents are indicated. Such information is valuable in case of follow-up. Then, in the "Results" section, pertinent radiological

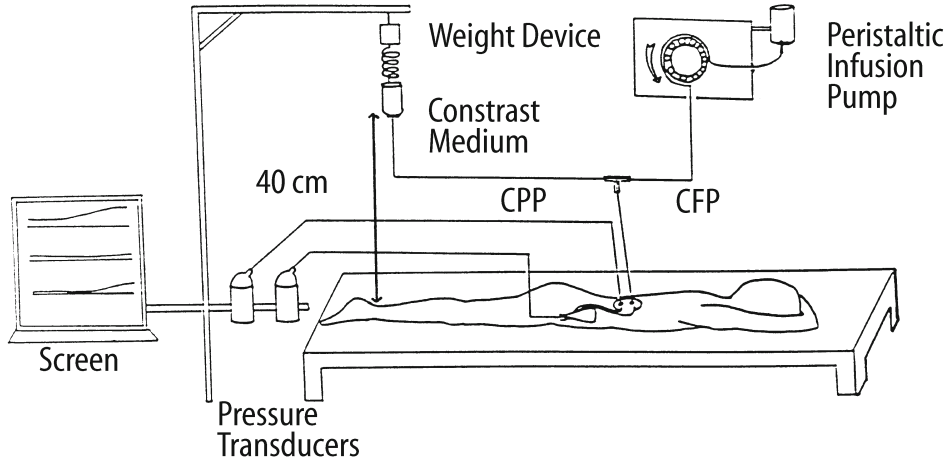

Fig. 1.1.11. Antegrade pyelography combined with the Whitaker test. Patient is in the prone position on general anesthesia. A Foley catheter is placed in the bladder and pressure is monitored. Two needles are placed in the renal pelvis with sonographic guidance. One is used to infuse contrast medium on either constant pressure perfusion or constant flow perfusion. The other one is connected with a pressure transducer. (Drawing by V. Genne, MD)

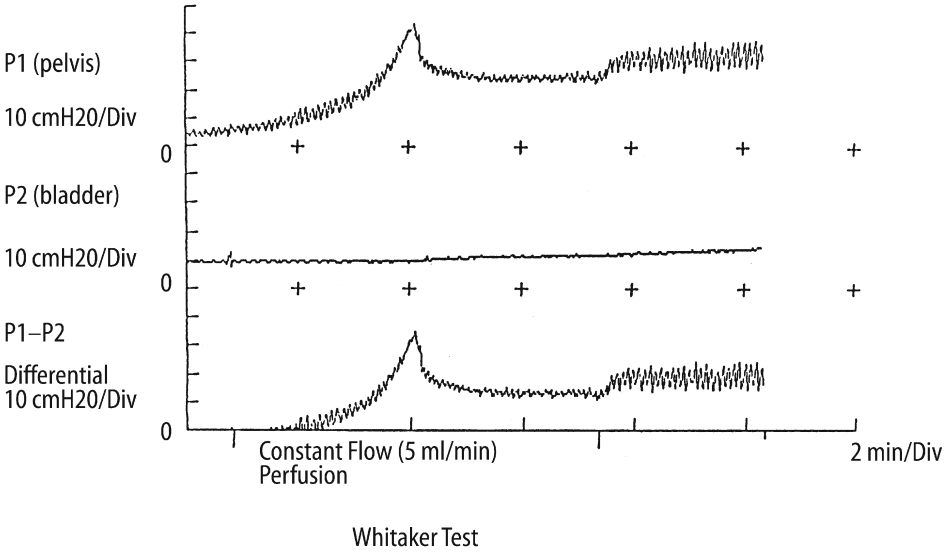

Fig. 1.1.12. Antegrade pyelography combined with the Whitaker test. Intermittent obstruction at the ureteropelvic junction in a child with equivocal results on diuresis renography. Constant flow renal perfusion (5 cc/min). Transient peak in pelvic and differential pressures are shown and complete the criteria for obstruction

findings are provided. Finally, the conclusion synthesizes the findings. Diagnostic hypotheses are classified in this section in decreasing order of probability. The report can be written differently depending on who the referring physician was (different information can interest the family doctor and the surgeon).

Conclusion

As well as performing a good imaging examination, it is important to minimize irradiation, pain, and risk; the chosen technique must also be well adapted to the patient (age, condition, disease) and the question posed by the referring physician.

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1.2 MR Urography in Children

J. Damien Grattan-Smith and Richard A. Jones

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1.2.1 Introduction

MR urography provides a comprehensive evaluation of the urinary tract in a single examination that does not use ionizing radiation and represents the next step in the evolution of uroradiology in children. Over the last 7 years there have been rapid development and refinement of imaging protocols for evaluating the urinary tract in children using MR urography (Grattan-Smith et al. 2003; Jones et al. 2004; Perez-Brayfield et al. 2003; Jones et al. 2005; McDaniel et al. 2005). This work builds on the efforts of several authors who recognized the potential utility of MR imaging in the evaluation of renal tract disease (Avni et al. 2002; Borthne et al. 1999; Borthne et al. 2000; Nolte-Ernsting et al. 2001; Riccabona 2004; Riccabona et al. 2004; Riccabona et al. 2004; Rohrschneider et al. 2000; Rohrschneider et al. 2003; Rohrschneider et al. 2002; Rohrschneider et al. 2000). MR urography combines intrinsically high spatial and contrast resolution with rapid temporal resolution. In addition to high-resolution anatomic images of the entire urinary tract, functional information about the concentration and excretion of the individual kidneys can be obtained. By scanning dynamically after injection of contrast agents, the signal changes related to perfusion, concentration and excretion of the contrast agent can be evaluated sequentially both in the renal cortex and medulla. Urinary tract anatomy is assessed using a combination of both T2-weighted and contrast-enhanced images. The functional information obtained routinely includes renal transit time calculation, graphs of signal intensity versus time curves, differential renal function calculation and estimation of individual kidney GFR using a Patlak plot.

The improved anatomic and functional information obtained with MR urogaphy will provide new insights into the underlying pathophysiology of urinary tract disorders. As a result, it is likely that MR urography will replace renal scintigraphy in the evaluation of renal tract disorders in children in the near future.

J. D. Grattan-Smith, MBBS
R. A. Jones, PhD
Department of Radiology, Children's Healthcare of Atlanta, 1001 Johnson Ferry Road, Atlanta, GA 30342, USA
and
Department of Radiology, Emory University School of Medicine, Atlanta, GA 30342, USA

1.2.2 Technique

The imaging protocols used for clinical studies consist of conventional T1, FSE T2-weighted sequences

prior to contrast administration and dynamic 3D gradient echo sequences after contrast administration (Grattan-Smith et al. 2003; Jones et al. 2004; Perez-Brayfield et al. 2003; Jones et al. 2005) (Figs. 1.2.1–1.2.3). There is a fundamentally complex relationship between signal intensity and gadolinium concentration, with T1 effects predominating at lower concentrations and T2* effects at higher concentrations, which may lead to signal loss. Phantom studies have shown that the relationship between signal intensity and gadolinium concentration is relatively linear at low concentrations (Jones et al. 2005). To stay within this linear portion of the curve, we keep the gadolinium concentration low by hydrating the patient, by giving furosemide 15 min before the contrast is administered and by infusing the contrast agent slowly for the dynamic series.

For our protocols, all children are hydrated prior to the study with an intravenous infusion of lactated Ringer's solution; for sedated children the volume infused is calculated to replace the NPO (nothing per mouth) deficit; otherwise, the volume is calculated using a guideline of 10 ml/kg. Typically, all children less than 7 years of age require sedation for the examination, and the department's standard sedation procedures are followed. A bladder catheter is placed to eliminate the possibility of reflux and to ensure free drainage of the bladder. Once the patient is positioned in the scanner, scout images are acquired to determine both the positioning of the kidneys and bladder and the combination of spine coil elements required to optimize the signal-to-noise ratio (SNR) for these anatomical structures. After the scout images were completed, axial T2-weighted (TR=5,600, TE=160, ETL=23) TSE images through the kidneys are obtained.

Furosemide (1 mg/kg, max. 20 mg) is then administered intravenously. We administer furosemide 15 min before we inject contrast for three reasons: (1) the urinary tract is distended, (2) the gadolinium concentration is diluted, which reduces the susceptibility artifacts and helps maintain the contrast-induced signal changes to within the range where they are linearly related to contrast agent concentration (Jones et al. 2005) and (3) the examination time is shortened. Coronal, 2D, flow-compensated T1-weighted (TR=475, TE=17) and T2-weighted (TR=5,500, TE=210, ETL=29) series and a respiratory gated, heavily T2-weighted 3D sequence (TE=600, ETL=109) are then acquired. The 2D series served to provide detailed anatomical reference scans, while the heavily T2-weighted 3D scan provided the basis for a pre-contrast maximum intensity projection (MIP) of the collecting system, ureters and bladder. In order to create the MIP other T2 structures with long T2 relaxation times, such as CSF and the gall bladder, are manually edited out from the images. The T2-weighted images are particularly useful to define the anatomy of non-functioning or poorly functioning systems. These systems are generally associated with marked hydronephrosis or cystic changes, and heavily T2-weighted images are able to delineate the anatomy even if little contrast excretion occurs (Fig. 1.2.3).

Once the above sequences are complete the acquisition of a 3D, coronal, dynamic, gradient echo sequence (TR=3.4 ms, TE=1.5 ms, flip angle=30°) orientated along the axis of the kidneys and including the bladder begins. The start of the dynamic series is approximately 15 min after the injection of furosemide, which coincides with the maximum effect of the furosemide (Brown et al. 1992). There is significant diuretic effect from about 5 min to 30 min after injection, so there is considerable latitude in the timing of the furosemide administration. A dose of 0.1 mmol/kg Gd-DTPA (Magnevist; Berlex Laboratories, Wayne, NJ) is slowly infused using a power injector. Previously we had administered a compact bolus of contrast, but this results in an aortic signal well above the linear range of gadolinium concentration. We now instill the contrast typically at a rate of 0.25 ml/s so that the injection lasts more than 30 s. Each time point of the dynamic sequence consisted of 36 slices, with the outer 3 slices on each side being discarded in order to limit variations in the flip angle related to the slice profile, and also to limit wrap-around artifacts. Parallel imaging with an acceleration factor of 2 is used to reduce the acquisition time per volume to 9 s. The scans are acquired contiguously for the first 3 min; subsequently intervals of progressively increasing duration are inserted between the scans until the scans are at 1-min intervals. For each volume acquisition, a maximum intensity projection (MIP) of the whole volume is automatically generated. If both ureters are clearly visualized 10 min after the injection of contrast media, no further dynamic series are acquired. Otherwise, the acquisition of dynamic images is continued for a further 5 min at 1 min intervals. After the completion of the dynamic series sagittal, axial and coronal 3D images with high spatial resolution are acquired for the purpose of reformatting and volume rendering on a 3D workstation. These images provide exquisite anatomic evaluation of the

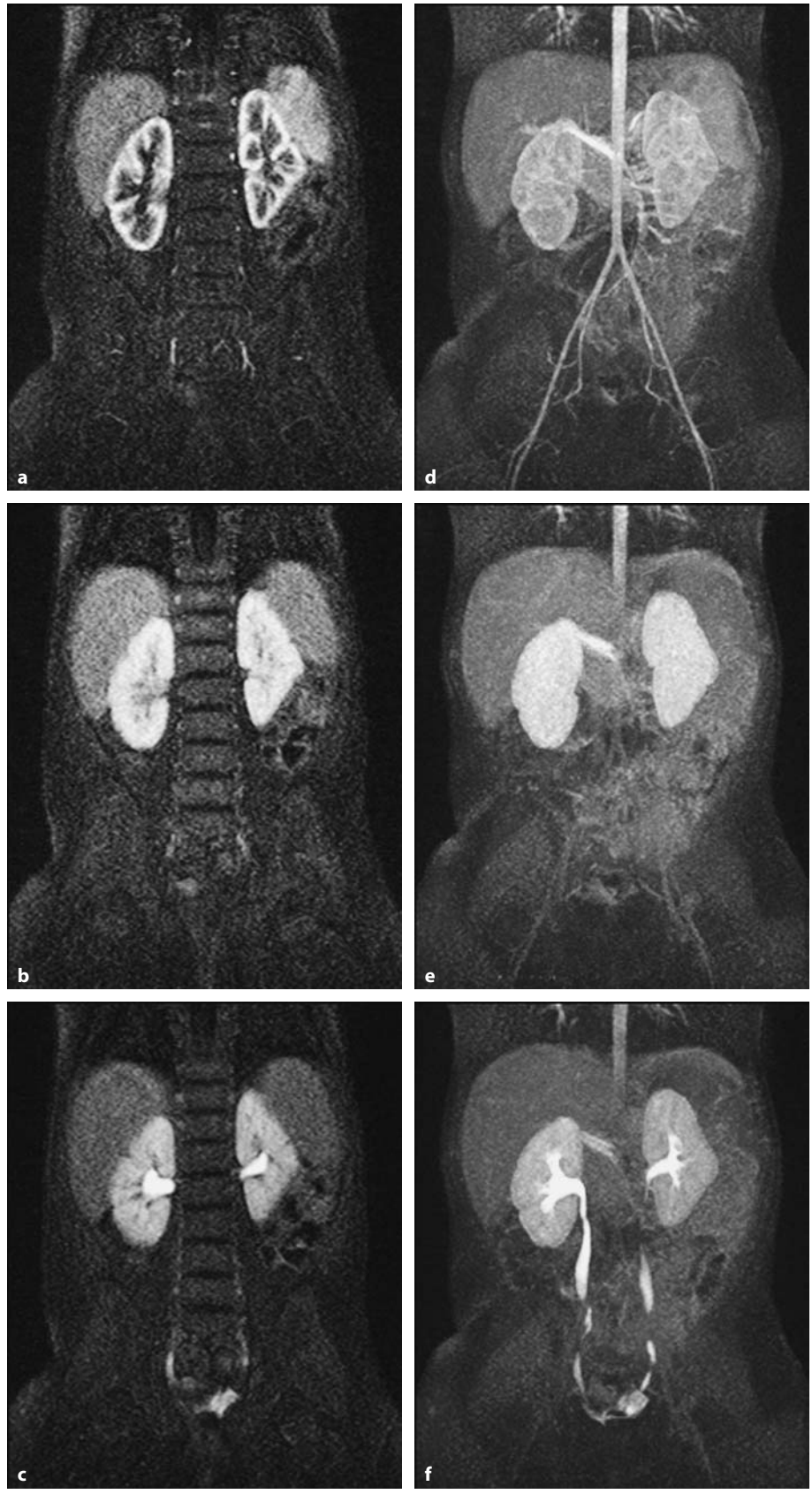
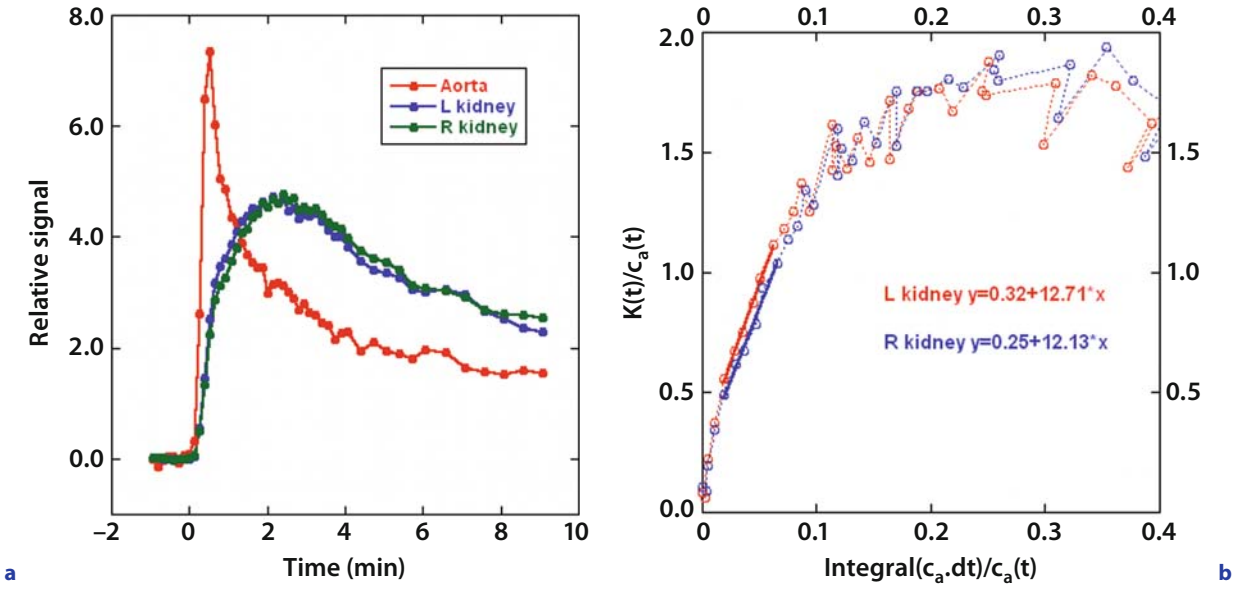
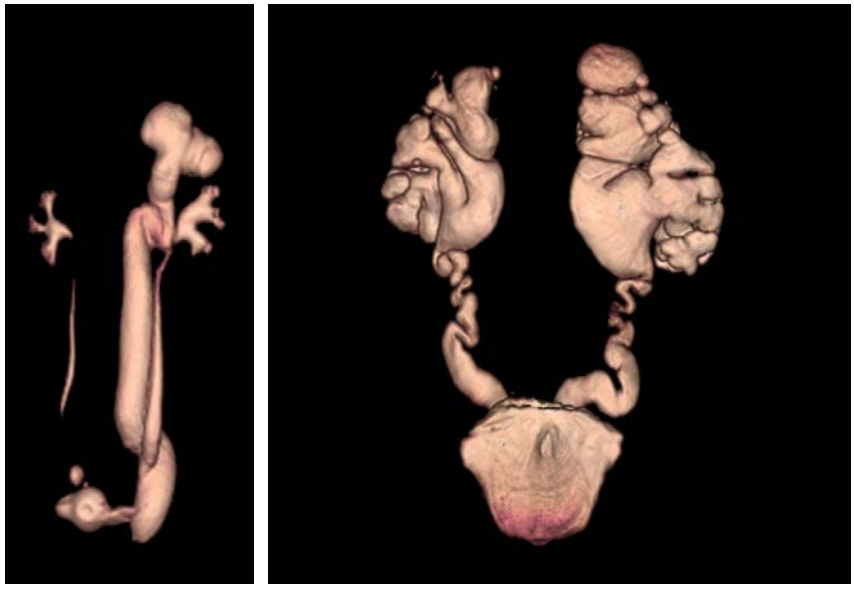


Fig. 1.2.1a–f. Normal MR urogram in 3-month-old boy with antenatal hydronephrosis. Images **a–c** show same slice from each of three separate volume acquisitions, whereas **d–f** show MIP projections derived from the same three separate time points. **a** and **d** show the cortical phase. **b** and **e** were acquired 60 s later and demonstrate enhancement of both the cortex and medulla with the signal intensity of the medulla exceeding the cortex. **c** and **f** were acquired 115 s after the vascular phase and show excretion into the calyces, renal pelvis and ureters. The renal transit time was 2 min and 20 s bilaterally and the volumetric DRF was 51:49



a b

Fig. 1.2.2a,b. Functional evaluation for 3-month-old boy shown in Figure 1.2.1. **a** Relative signal intensity versus time curve showing curves for the aorta and both kidneys. Note the symmetric parenchymal curves with equivalent perfusion, concentration and excretion of contrast agent. **b** The Patlak plot is used as an index of the individual kidney GFR. The slope of each plot reflects the GFR of each kidney (12.7 ml/min on left and 12.1 ml/min on right). The *y* intercept represents the fractional blood volume of each kidney. The body surface area corrected Patlak (BSA Patlak) is 102 ml/min. The Patlak DRF is calculated at 50:50



a b

Fig. 1.2.3a,b. Volume-rendered T2-weighted images. **a** Volume-rendered T2 images of duplex system with poorly functioning and obstructed upper pole moiety. Despite minimal excretion of contrast agent, anatomic images of the duplex system can be obtained that show the ectopic insertion of the upper pole ureter. **b** Volume-rendered T2 images of poorly functioning hydronephrotic kidneys in a boy with posterior urethral valves. Even with poor renal function exquisite anatomical images are easily obtained

kidneys and ureters. In cases where poor drainage from the renal pelvis means that no contrast is seen in the ureters during the 15 min of dynamic scanning, the patient may be turned prone to promote mixing of the contrast agent in the collecting system prior to the acquisition of high spatial resolution coronal and sagittal images. The total imaging time for non-obstructed patients is typically 45 min, for poorly draining kidneys the imaging time is typically 1 h.

The MIP images from each volume acquisition are placed in a single cine sequence to provide a rapid overview of the transit of the contrast agent through the kidney. The delayed high-resolution anatomic images are particularly valuable in the evaluation of congenital malformations including ureteric strictures and ectopic ureteric insertion as well as complex postoperative anatomy (Fig. 1.2.3).

1.2.3 Post-Processing

Differential renal function (DRF) is among the most widely used measures of renal function. The DRF as measured by dynamic renal scintigraphy (DRS) is based on the integration of the tracer curve over a range of time points at which the tracer is assumed to be located predominately in the parenchyma. Due to the limited spatial resolution of DRS studies, fixed time points are used since the exact location of the tracer cannot be confirmed by visual inspection of the images. Since DRS measurements are based on projection images of the whole kidney, they measure the activity in the whole kidney. The majority of techniques developed for measuring the DRF with MRI have attempted to duplicate this approach by combining the area under the time-intensity curve obtained from either a single slice, or a few slices, with a separate volume measurement (Huang et al. 2004; Lee et al. 2003; Taylor et al. 1997; Teh et al. 2003). We use a slightly different approach since the 3D volumes used in this study cover the full extent of both kidneys and the uptake of the contrast in each kidney can be followed volumetrically. We make the assumption that voxels represent either functional or non-functional tissue and that by summing the voxels that show a significant uptake of contrast one can calculate the functional volume of each kidney and hence the split renal function. The dynamic series are visually inspected to determine the volumes in which contrast is first seen in the collecting system of each kidney; the volume prior to this is then used for the calculation of the functional volume of each kidney (Fig. 1.2.4). In this way, possible differences between the two kidneys are taken into account, and it is not necessary to assume a particular time point, or range of times, for the calculation. In previous studies several authors have shown that the calculation differential renal function based on renal volume agrees well with the DRF calculated using nuclear medicine (Grattan-Smith et al. 2003; Perez-Brayfield et al. 2003; Heuer et al. 2003). The volume of functioning tissue has also been shown to be well correlated with creatinine clearance rates (Van den Dool et al. 2005). For the dose of contrast and the pulse sequence parameters used in our studies, the segmentation of the kidneys at this homogeneous enhancement phase is straightforward and can be performed using semi-automatic segmentation. While the renal volume

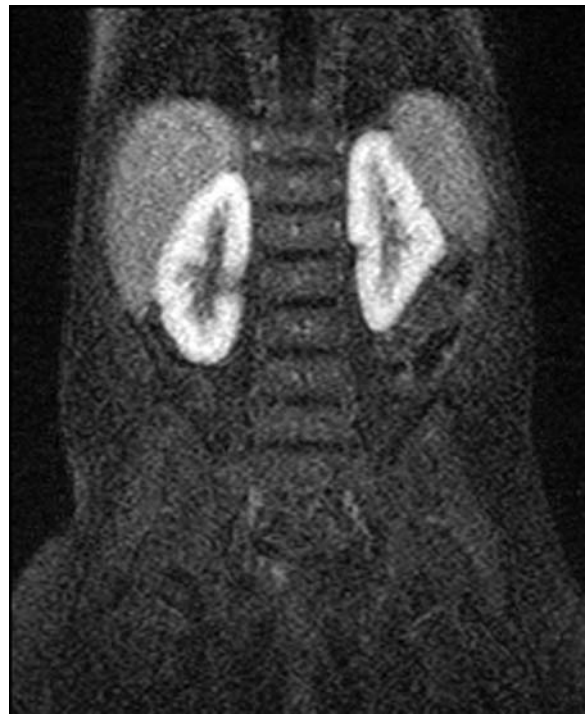


Fig. 1.2.4. Volumetric differential function. The time point for calculation of renal volumes is determined visually by defining the time when the kidneys have enhanced maximally and before contrast has been excreted into the collecting systems. At this time the kidneys are easily separated from the background with semi-automated techniques that produce volume calculations for each kidney depending on a user-defined threshold

can be estimated from T1- or T2-weighted images, this is much more user intensive (Bakker et al.1999; Lee et al. 2003). The methodology presented here makes a clear distinction between functioning and non-functioning tissue and accounts for the effects of cortical scarring or patchy enhancement, such as that seen in uropathic or dysplastic kidneys. In the evaluation of duplex kidneys, MR urography can separate the boundaries between the upper and lower pole moieties by delineating the column of cortex separating the upper and lower poles so that the relative contributions of the upper and lower poles can be calculated.

We generate signal intensity versus time curves for each kidney (Fig. 1.2.2a). Although it is possible to generate separate curves for the cortex and medulla, this is too time consuming for routine studies. The global curves for each kidney describe the perfusion, concentration and excretion of the contrast agent over time. The two kidneys are easily compared and contrasted, which is especially helpful when one kidney is normal. The signal versus time curves are converted to relative signal versus time curves by calculating $(S_t\text{-}S_0)/S_0$, where S_0 is the mean pre-contrast signal, for each time point. The relative signal has a linear relationship with contrast agent concentration over a limited range of concentrations and compensates for spatial variations in the background signal, facilitating comparison of the two kidneys (Jones et al. 2005).

The most widely used non-imaging clinical test of renal function is to measure the serum creatinine level. However, this test is a relatively insensitive measure of decreased glomerular filtration rate (GFR) and only measures the global, rather than single kidney function. Although GFR can be accurately measured using techniques such as inulin clearance, such tests are invasive and are not feasible in a clinical setting. Several methods have been developed for estimating the GFR from dynamic nuclear medicine data, but all of these are hampered by the poor counting statistics of such dynamic studies and the problem of accounting for the extra-renal component of the signal. More recently, several groups have applied the methods developed for nuclear medicine to dynamic MRI data acquired in conjunction with an injection of the contrast agent Gd-DTPA (Hackstein et al. 2003; Lee et al. 2003). When applying these techniques to MRI data, several issues have to be addressed; firstly, while nuclear medicine directly measures the activity, and hence the concentration, of the contrast agent, the MRI contrast agents change signal by altering the relaxation times of the tissue, and this produces a linear relationship with the concentration only over a limited range of concentrations. Secondly, the exact relationship between the signal and concentration depends on the flip angle used and, since the flip angle varies across the slice in 2D studies, time-consuming corrections are required for 2D data, making these unsuitable for routine clinical applications. Thirdly, in order to obtain adequate signal to noise, it is generally necessary to use surface array coils for the reception of the signal, which in turn can lead to local variations in signal intensity that complicate the analysis of the data. Our approach addresses these problems by using a slow injection of contrast in order to limit the arterial concentration, by using a 3D technique and discarding the outer slices to ensure a uniform flip angle, and by using the pre-contrast signal to correct for spatial variations in the signal intensity.

To estimate the GFR we use the Rutland-Patlak technique, which is based on a two-compartment model with unilateral flow of tracer from the first compartment (vasculature) into the second compartment (nephrons) (Rutland 1979; Patlak et al. 1983; Peters 1994) (Fig. 1.2.2b). The amount of contrast in any one kidney at a time point K(t) prior to the excretion of contrast can be expressed as the sum of the contrast in the vascular space and the contrast in the nephrons. Assuming that the plasma concentration of the contrast agent in the vascular space is proportional to that in the aorta, $c_a(t)$, then, defining the constants k1 and k2 to represent the vascular volume within the kidney and the clearance of the contrast from the vascular space respectively, one can write

$$K(t) = k_1 c_a(t) + k_2 . \int_0^t c_a(u)\,du$$

where t=0 is the time of arrival of the contrast; u(du) appears in conjunction with the integration symbol and represents a variable that is integrated over the limits 0 to t. This can be rewritten in the form:

$$\frac{K(t)}{c_a(t)} = k_1 + \frac{k_2 . \int_0^t c_a(u)\,du}{c_a(t)}$$

If one measures the average concentration of contrast within the kidney, then k_2 represents the clear-

ance per unit volume of tissue. A more conventional measurement of GFR can be obtained by multiplying k_2 by the renal volume. Alternatively, since K(t) represents the total amount of contrast in the kidney, it can be replaced by $c_k(t).V_k$, where $c_k(t)$ is the mean tissue concentration of Gd-DTPA in the kidney and V_k is the volume of the kidney. Thus, the equation can now be written as

$$\frac{c_k(t)}{c_a(t)} = \frac{k_1}{V_k} + \frac{k_2 \cdot \int_0^t c_a(u)\,du}{V_k . c_a(t)}$$

This can be plotted using an equation of the form $y = k_1 + k_2.x$ (Fig. 1.2.3). The slope of the graph between the time points following uniform distribution of the contrast in the vasculature and prior to excretion of contrast into the collecting system is equal to the clearance of contrast from the vasculature, i.e., the GFR. The x intercept (k_1) represents the fractional blood volume of the kidney. On the assumption of a linear relationship between the relative signal and the concentration of contrast agent, the terms $c_a(t)$ and $c_k(t)$ can be replaced by the relative signal from the aorta and kidney. Hence, the relative signal versus time curves from the aorta and kidney can be used to generate a Patlak plot, and hence estimate the GFR. The pre-contrast relaxation times of, and the relaxivity of the contrast agent in, the blood and kidneys are different; similarly, these quantities also differ between the sub-compartments within each of these compartments (e.g., plasma and red cells). When relative signal, as opposed to a measurement of the relaxation time, is used, this may lead to errors in the Patlak analysis. A correction for the difference in relaxation rates can be estimated from phantom studies (Rusinek et al. 2001; Hackstein et al. 2005) or from mathematical simulations based on the measured signal, but these do not accurately reflect the in-vivo situation where exchange effects between different compartments (e.g., plasma and red cells) contributes to the observed relaxivity. For this reason, the value derived from the slope of the Patlak plot is probably best regarded as a GFR index rather than an absolute measure of the GFR. When the Patlak DRF is calculated, such effects are assumed to be common to both kidneys and can hence be ignored. Other possible sources of error in the Rutland-Patlak analysis include the fact that the interstitial space is neglected, that pulsation of the descending aorta may distort the measurement of the vascular signal and the T2* shortening effects of the contrast agent may distort the relative signal measurements.

For each patient the key features derived from MR urography include calculation of differential renal function (both volume and Patlak) (vDRF and pDRF), signal versus time curves for each kidney and the aorta, individual kidney GFR index of each kidney, concentration and excretion from each compartment, renal and calyceal transit times and overall anatomic diagnosis. It is important to understand that we have two methods to determine the differential renal function: one based on volume and one based on the individual kidney GFR as determined by the Patlak plot. In most cases these are symmetric; however, when there is a difference in these two measures of DRF it implies a change in renal hemodynamics that may ultimately provide information about which kidneys will benefit from surgery.

Conclusion

The parameters routinely assessed by MR urography include the overall anatomic diagnosis, vDRF and pDRF, renal and calyceal transit times, signal intensity versus time curves and individual GFR index for each kidney.

1.2.4 Clinical Applications

1.2.4.1 Evaluation of Hydronephrosis

The most common indication for MR urography has been the evaluation of hydronephrosis, especially in infants and young children. Most experts currently advocate primary conservative management for infants with hydronephrosis with close follow-up and surgery only if there is evidence of decreased renal function or progressive hydronephrosis (Peters 1995; Csaicsich et al. 2004; Eskild-Jensen et al. 2005). The definition of obstruction is difficult clinically and is usually defined in one of two ways: either as a restriction to urinary outflow that, when left untreated, will cause progressive renal deterioration or as a condition that hampers optimal renal development. Obstructive uropathy refers to obstruction of urine flow from the kidney to the bladder that results in renal damage (O'Reilly 2002). In children, this is usually a result of chronic

partial obstruction typically related to ureteropelvic junction (UPJ) obstruction or obstructive megaureter. The consequences of the obstruction depend not only upon the degree of obstruction, but occur secondarily to a complex syndrome resulting in alterations of both glomerular hemodynamics and tubular function caused by the interaction of a variety of vasoactive factors and cytokines (Wen et al. 1999; Klahr 2001).

We see two distinct populations of UPJ obstruction: young infants diagnosed with antenatal hydronephrosis who are usually asymptomatic, and older children who present with symptoms related to abdominal pain or infection. The decision to operate is usually straightforward in the symptomatic population. The decision to operate in the antenatal and asymptomatic group is more difficult, with up to 50% of these children ultimately requiring surgical evaluation (Chertin et al. 2006).

Any attempt to separate obstructed from non-obstructed kidneys as distinct entities is artificial and unrealistic (Jones et al. 2004; Peters 1995). All hydronephrotic systems have some impairment of renal drainage, and we need to develop sensitive measures to detect early renal functional deterioration. The ultimate goal of the management of obstruction is the preservation of renal function. Currently, there is no imaging modality that can accurately assess the degree of obstruction and hence identify which kidneys are at risk for progressive loss of renal function.

Initially, we used MR urography to evaluate hydronephrosis and obstruction by calculating the renal transit time (RTT), which is defined as the time it takes for the contrast agent to pass from the renal cortex to the ureter below the lower pole of the kidney (Jones et al. 2004) (Fig. 1.2.5). If the transit time is less than 245 s, the system is considered non-obstructive. If the RTT is greater than 490 s, the system is probably obstructed. RTT times between 245 s and 490 s are considered equivocal and are managed conservatively with close follow-up to ensure that renal function is stable. Calculating the RTT from the images is relatively straightforward, because each individual volume acquisition is time-stamped: therefore, the time at which the cortex first enhances and the time when contrast is identified in the ureter are determined visually from the images. The RTT is simply the difference between these two time points. Our experience with RTT has emphasized that obstruction represents a spectrum of impairment to urinary flow, and the causes of progressive renal damage are not clearly known. Although we have shown that RTT calculation is similar to DRS for categorizing dilated systems, it still does not prospectively identify kidneys that will lose function if left untreated. It has also become apparent from the high resolution

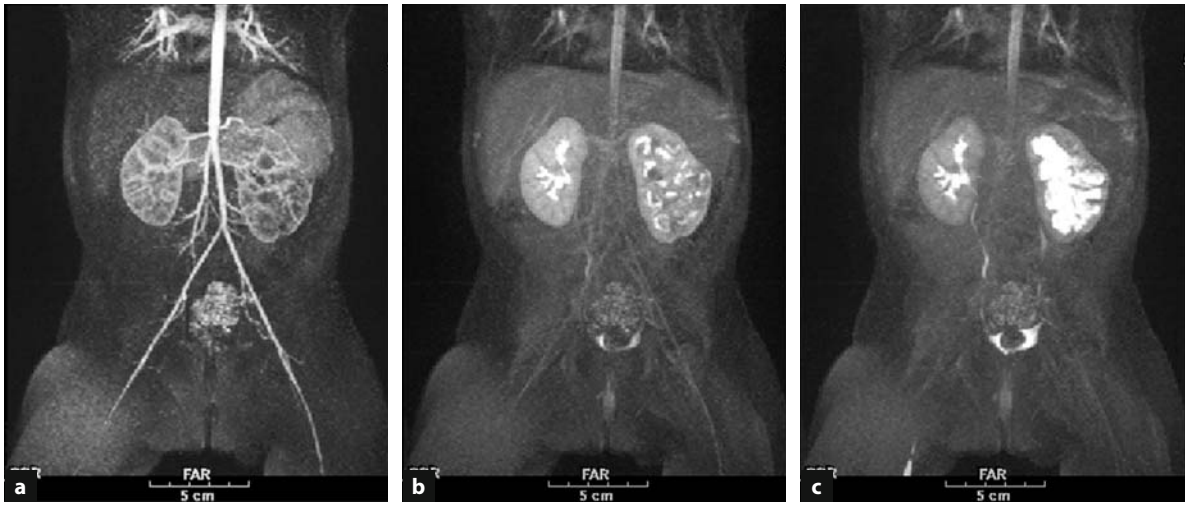


Fig. 1.2.5a–c. Renal transit time calculation. The renal transit time is calculated from the MIP images of each volume acquisition. Each acquisition has a unique time stamp depending on the MR vendor. Initially, the time of cortical perfusion is determined as 160215 (**a**) and is subtracted from the time points when contrast is identified in the proximal ureter. This is done for both kidneys (R=160407 and L=160615) so that the RTT is calculated on the right as 1 min and 58 s (**b**) and 4 min on the left (**c**)

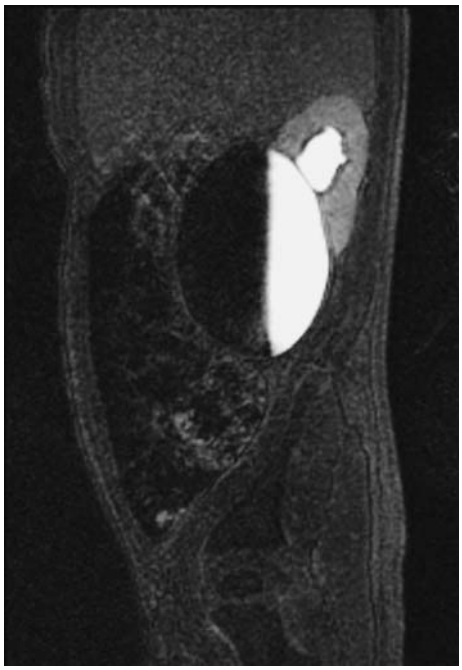


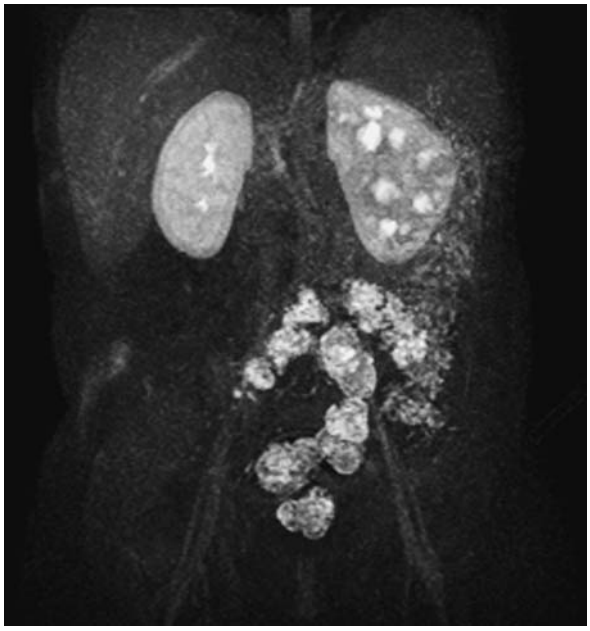
Fig. 1.2.6. Fluid levels. Fluid levels are often seen in the setting of marked hydronephrosis and are an indicator of stasis within the collecting system with the heavier contrast material layering along the dependent portions

anatomic images that the RTT or renal drainage is very dependent on the anatomy of the ureteroplevic junction, particularly the insertion of the ureter into the renal pelvis. For drainage to occur down the ureter, the contrast agent has to reach the level of the UPJ. In some children, the ureteric insertion is anteriorly located and in others posteriorly. As the Gd-DTPA macromolecule is heavier than water, there is a tendency for the contrast agent to layer in the dependent portions of the kidney. Knowing the position of the ureteric insertion into the UPJ helps in the interpretation of the RTT, and it is important to realize that the RTT is simply a measure of renal drainage and does not indicate which kidneys are likely to sustain progressive injury. Prolonged renal transit times simply indicate poor drainage, and stasis of urine is manifested by fluid levels (Fig. 1.2.6). When there has been significant loss of renal parenchyma and little urine is being produced, calculation of renal transit times is of limited value in evaluating the presence of superimposed obstruction.

The calyceal transit time is the time it takes for the contrast to pass through the kidney, i.e., from the initial enhancement of the cortex until it first appears as high signal intensity in the dependent calyces. The calyceal transit time is usually symmetric, and we use it as an indicator of pathophysiologic changes in the renal parenchyma itself. The calyceal transit time is determined both by the GFR as well as the tubular reabsorption of urine. Rapid calyceal transit times may be the result of glomerular hyperfiltration (pressure effect) or impaired concentration within the tubules (volume effect). The signal intensity and Patlak curves help to differentiate the level of the abnormality within the nephron.

Recently, we have begun to classify hydronephrotic systems as either compensated or decompensated based on the contrast dynamics within the renal parenchyma. It is more logical to focus on changes that occur to the kidney itself rather than relying on drainage patterns (Figs. 1.2.7, 1.2.8). In response to the fluid challenge created by the administration of intravenous fluids and furosemide, some kidneys develop signs of an acute-on-chronic obstruction with edema in the renal parenchyma seen as T2 hyperintensity. There may be a delay in excretion of contrast on the affected side with a delayed calyceal transit time. Additionally, the nephrogram becomes dense and persistent, indicating ongoing tubular reabsorption of fluid. Functionally, there is a discrepancy between the pDRF and the vDRF, and we classify a difference of greater than 4% as indicating a significant hemodynamic affect. The pDRF is typically decreased, indicating a relative decrease in single kidney GFR presumably due to an acute increase in the intra-pelvic pressure. Similarly, analysis of signal intensity versus time curves shows a persistent increase in signal intensity within the decompensated system. If a hydronephrotic system is "compensated" and able to accommodate the fluid challenge, there is symmetric calyceal transit time and symmetric nephrograms and signal intensity versus time curves. The pDRF and vDRF are within 4% points.

Following successful pyeloplasty there is typically rapid calyceal transit time, symmetric nephrograms and signal intensity curves as well as almost equivalent pDRF and vDRF. The degree of hydronephrosis is typically improved, although dilation and calyceal clubbing persist. The renal transit time often remains prolonged, indicating stasis and poor mechanical drainage (Kirsch et al. 2006). Our initial experience suggests that those children who have decompensated systems have significant



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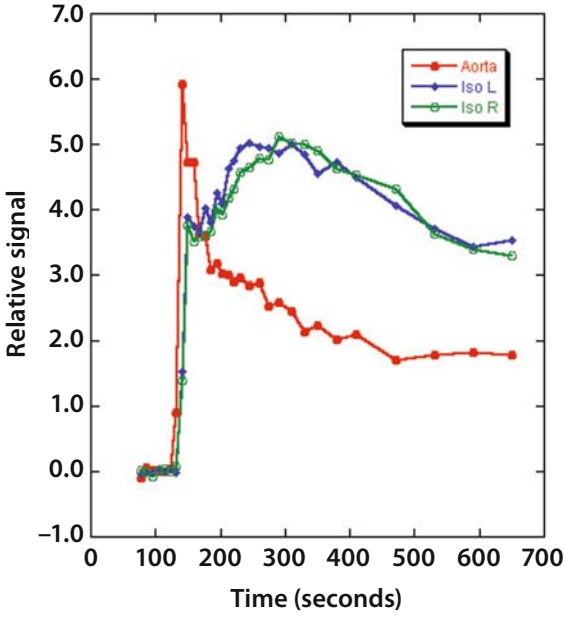

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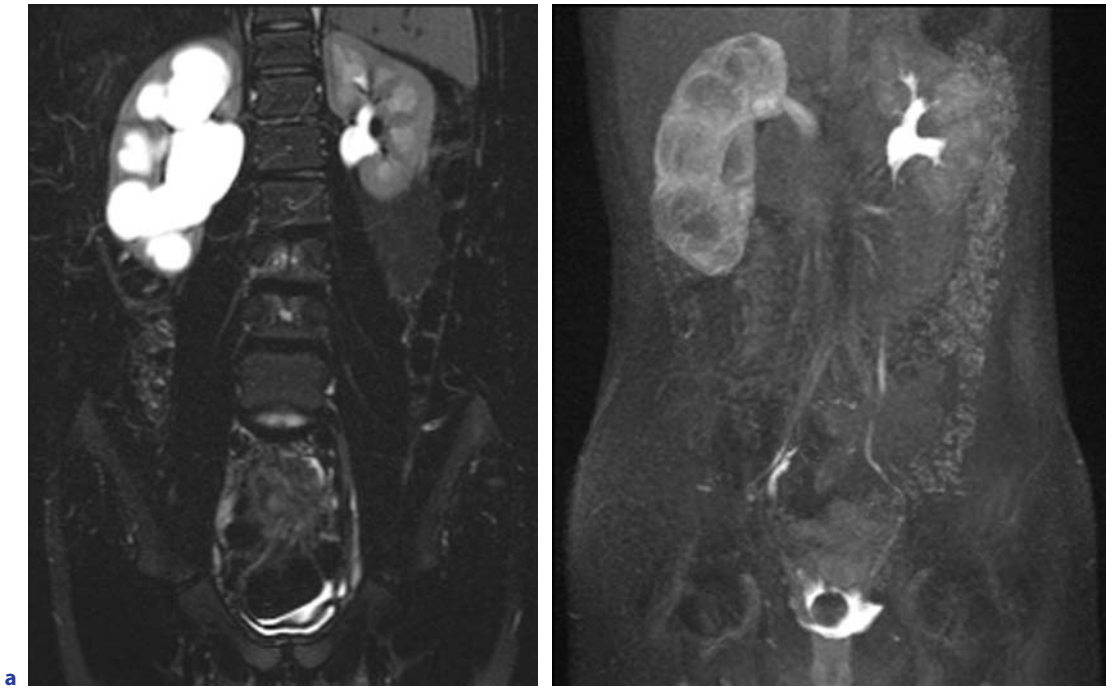
Fig. 1.2.7a–c. A 6-month-old boy with "compensated hydronephrosis." **a** There is moderate hydronephrosis and calyiectasis, and the renal transit time on the left was measured at 9 min, falling into the obstructed category. However, there was little effect on the renal parenchyma as the calyceal transit time is symmetric. **b** Delayed post-contrast volume-rendered images show the calyiectasis and transition in caliber at the UPJ. **c** Signal intensity versus time curve demonstrating symmetric perfusion, concentration and excretion of the contrast agent. The volumetric and Patlak differential functions were equivalent. All these parameters suggest that the hydronephrotic system can accommodate the fluid challenge with furosemide. Therefore, it is categorized as a compensated system that is unlikely to deteriorate and can be followed conservatively

improvement in renal function following pyeloplasty, whereas in those with compensated systems there is little change in renal function.

The aorta and main renal arteries are routinely visualized during the early dynamic imaging phase. Accessory and crossing vessels are commonly seen, and the 3D images from early and late data sets can be superimposed to delineate the relationship of these vessels to the anatomic change in caliber (Fig. 1.2.9). Although UPJ obstruction related to crossing vessels is typically seen in older children, we often see crossing vessels in association with UPJ obstruction in young infants (Rooks and Lebowitz 2001).

An advantage of MR urography is the ability to identify ureters reliably in most children using the combination of T2 and post-contrast images. The ability to delineate the ureteric anatomy has allowed us to confidently make the diagnosis of mid-ureteric strictures and persistent fetal folds (Grattan-Smith and Jones 2006). Fetal folds are typically seen in young infants being evaluated for antenatal hydronephrosis and are seen as a corkscrew appearance



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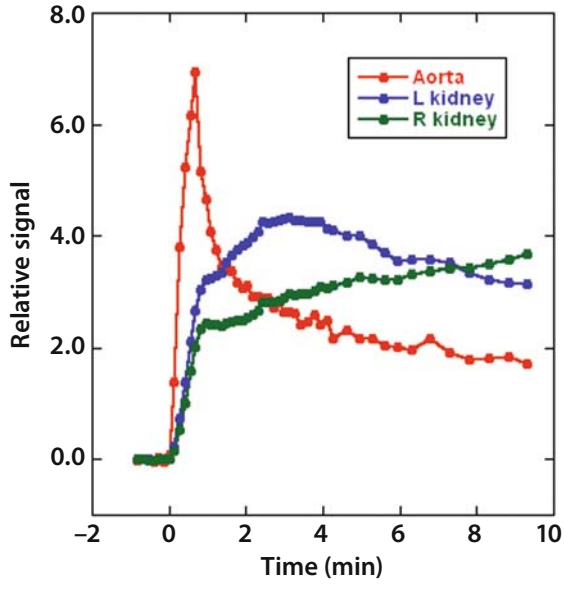

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Fig. 1.2.8a–c. A 2-year-old boy with decompensated hydronephrosis. **a** Coronal T2-weighted images showing marked hydronephrosis with parenchymal loss on the right. **b** Coronal MIP from the dynamic series showing normal excretion on the left. The right kidney has a delayed dense nephrogram with delayed calyceal transit time. The renal transit time was greater than 15 min and categorized as obstructed. **c** Signal intensity versus time curves demonstrating asymmetric concentration and excretion of contrast agent. The curve for the left kidney is normal and on the right represents the dense delayed nephrogram. The vDRF was 44% on the right, and the pDRF was 37%, indicating a significant change in the GFR presumably related to acute increase in intra-tubular pressure secondary to the fluid challenge. As a result this is classified as a decompensated system and will typically have improved function following pyeloplasty

to the upper ureter (Fig. 1.2.10). They are considered a normal variant in that the hydronephrosis tends to be mild and self-limited, and there is no or only minimal impairment of renal function. The combination of transition in ureteric caliber and delayed excretion are the key features in the diagnosis of ureteric stricture. Although mid-ureteric strictures have been considered a rare anomaly in children, it can be readily diagnosed by MR urography, and this condition has probably been under-diagnosed by traditional modalities (Smith et al. 2004).

The distal ureteric anatomy is also well demonstrated with MR urography (Avni et al. 2001). Ectopic ureteric insertion either in single systems or in combination with duplex systems can usually be obtained on the delayed post-contrast images or on the T2-weighted images in markedly dilated or poorly functioning system (Fig. 1.2.11). The diagnosis of

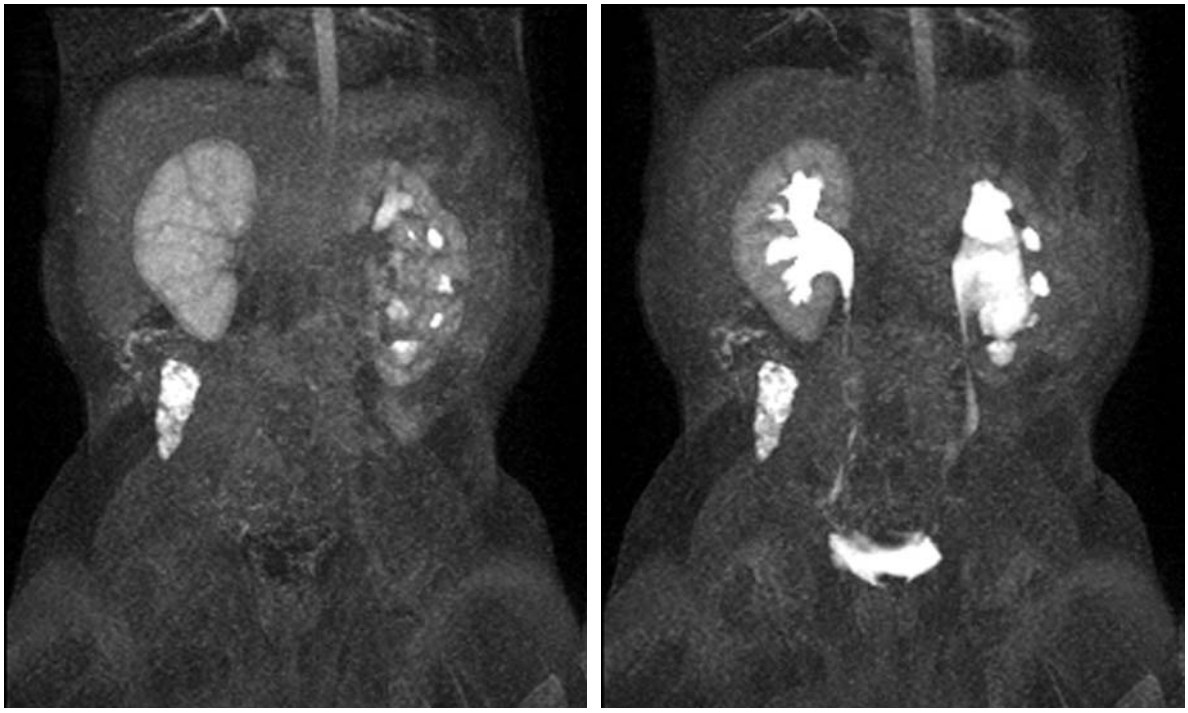

Fig. 1.2.9a,b. Successful pyeloplasty in a 9-month-old infant. **a** Coronal MIP from the dynamic series demonstrating rapid calyceal excretion on the left following pyeloplasty. In almost all successful pyeloplasties, there is a decrease in the degree of hydronephrosis and rapid calyceal transit on the operated side. If the calyceal transit is delayed, this is usually an early indicator of a failed pyeloplasty. **b** Coronal MIP from late in the dynamic series demonstrating delayed RTT (8 min), but with a wide open and straight border to the UPJ. The vDRF and pDRF are now equivalent

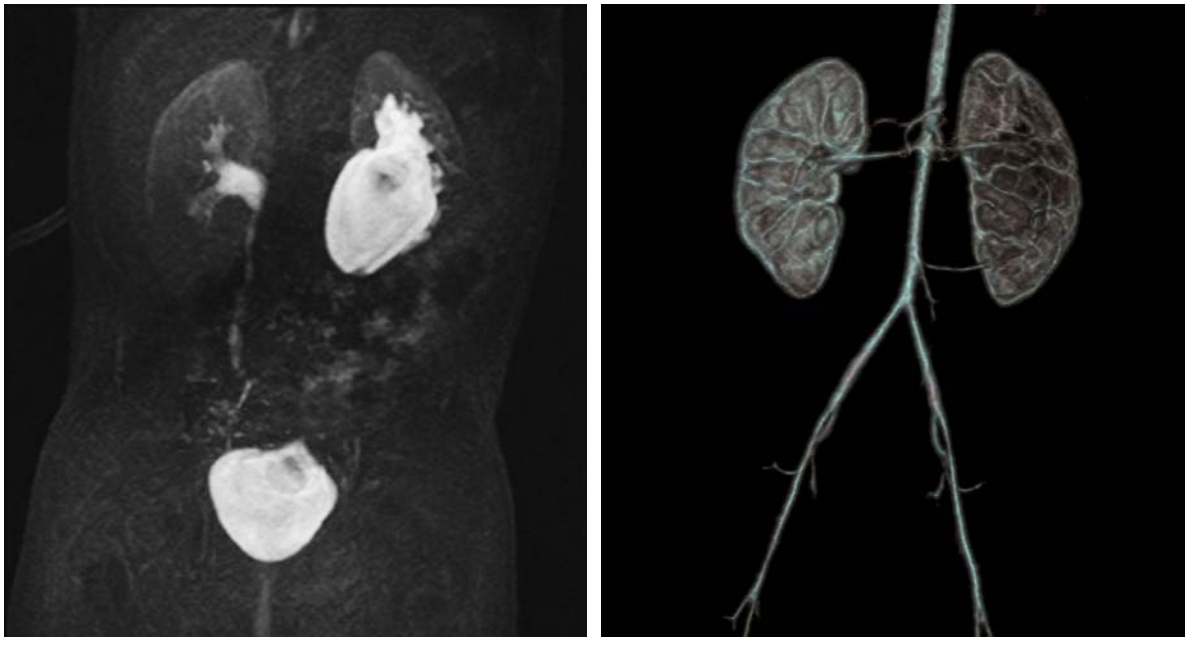

Fig. 1.2.10a,b. A 3-year-old boy with intermittent left-sided abdominal pain. **a** Delayed MIP image demonstrating a hydronephrotic left kidney with transition at the UPJ. **b** The MR angiogram generated from the immediate post-contrast enhanced dynamic series showing a crossing vessel to the left lower pole that at surgery was found to be causing obstruction by extrinsic compression

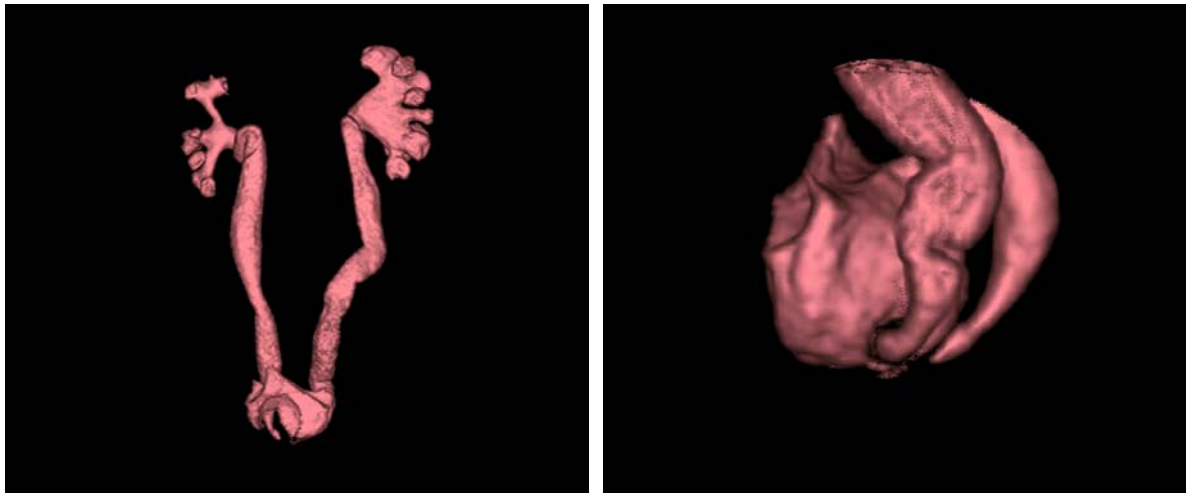

Fig. 1.2.11a,b. A 3-month-old boy with non-obstructive megaureter and simple ureteroceles. **a** Volume-rendered image showing bilateral hydroureteronephrosis. The renal transit time was normal bilaterally. **b** Detailed imaging of the ureterovesical junction showing simple ureteroceles

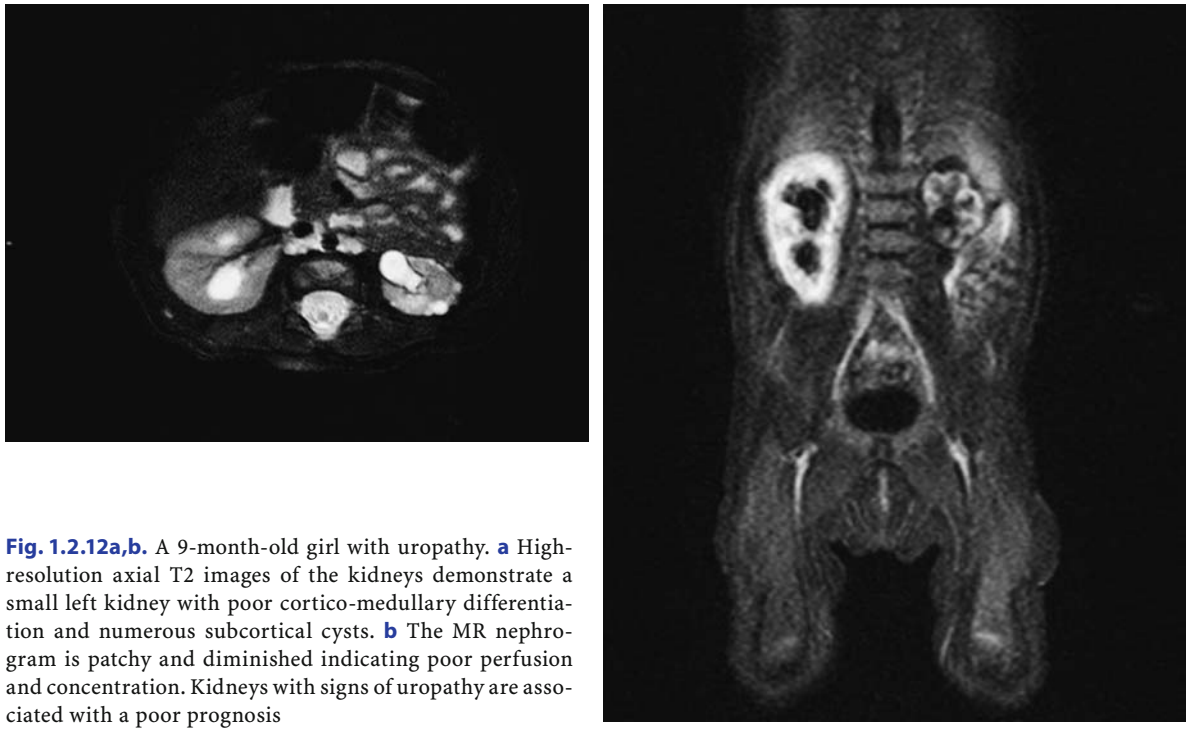

Fig. 1.2.12a,b. A 9-month-old girl with uropathy. **a** High-resolution axial T2 images of the kidneys demonstrate a small left kidney with poor cortico-medullary differentiation and numerous subcortical cysts. **b** The MR nephrogram is patchy and diminished indicating poor perfusion and concentration. Kidneys with signs of uropathy are associated with a poor prognosis

primary megaureter is made when the ureter measures more than 7 mm in diameter and the ureteric insertion into the bladder is normally located. The differentiation of obstructed from non-obstructed megaureter is arbitrarily made on the basis of renal transit times as most cases are followed conservatively. Most cases of megaureter appear as compensated hydronephrosis, and with follow-up studies there is elongation and lengthening of the ureter with improvement in RTT. MR urography can also demonstrate both simple and ectopic ureteroceles.

Another advantage of MR urography over other modalities is the ability to characterize the anatomy and morphology of the renal parenchyma itself.

The diagnosis of obstructive uropathy is made after analysis of the high-resolution T2-weighted images of the kidney and the quality of the nephrogram (Fig. 1.2.12). Signs of uropathy include small subcortical cysts, poor cortico-medullary differentiation, decreased signal intensity in the cortex and a poorly defined or patchy nephrogram indicating impaired concentration by the renal parenchyma. These findings are similar to the pathologic changes described in the literature (Elder et al. 1995; Huang et al. 2006; Pascual et al. 1998). In these papers there is poor correlation between the pathological changes and the renal functional studies. However, with MR urography a kidney contributing 30% of total renal GFR may simply be a decompensated system with normal renal parenchyma or it may be severely uropathic with little chance for return of function. Identification of obstructive uropathy has prognostic implications in that these changes appear to be permanent and that functional improvement is unlikely if surgery is performed.

Conclusion

Hydronephrotic kidneys that cannot accommodate a fluid challenge develop signs of "decompensation" on MR urography. These include a delayed, dense nephrogram, delayed calyceal and renal transit times and a difference between the pDRF and vDRF >4.

1.2.4.2 Congenital Malformations

Anomalies of renal position and rotation are well demonstrated by the high resolution anatomic images. Horseshoe and ectopic kidneys can be easily separated from the background and overlying tissues. Pelvic kidneys in particular, which often are significantly smaller than the normally positioned kidney, are well demonstrated with MR urography (Fig. 1.2.13). Hypoplastic kidneys associated with ureteric ectopia and supernumerary kidneys, which have been difficult to demonstrate with other imaging modalities, can usually be demonstrated even if there is minimal renal function.

Recently increased attention has been paid to the ureteric bud theory of Mackie and Stephens (Ichikawa et al. 2002; Mackie and Stephens 1975; Pope et al. 1999). Some authors have ascribed the acronym CAKUT (congenital anomalies of the kidney and urinary tract) to malformations that may result from abnormal development of the ureteric bud and subsequent abnormal interactions between the developing metanephros and the ureteric bud (Ichikawa et al. 2002; Pope et al. 1999). MR urograpy offers an opportunity to study these malformations in vivo with increased anatomic resolution. Although renal dysplasia is based on histological identification of undifferentiated mesenchyme such as cartilage and immature tubules, there are suggestive features on MR urography. The various forms of renal dysplasia include MCDK, cystic obstructive dysplasia, hypodysplasia and solid renal dysplasias (Glassberg et al. 1987). MR urography is excellent at demonstrating anomalies of the upper and lower tracts such as ureteroceles and seminal vesicle cysts associated with cystic and dysplastic kidneys. Anomalous calyceal development is better defined on MR urography than on other imaging studies, and the identification of maldeveloped calyces associated with hypoplasia supports the diagnosis of renal hypodyplasia secondary to abnormal interaction between the metanephros and the ureteric bud, which can affect the entire urinary tract (Fig. 1.2.14).

Renal impairment associated with fetal reflux is present at birth and may be due to renal dysplasia (Stock et al. 1998). Renal scintigraphy performed in patients with fetal reflux show unexpected renal abnormalities even in the absence of infection (Anderson and Rickwood 1991; Najmaldin et al. 1990). Renal damage detected by scintigraphy in infants with no demonstrable UTI has been termed "congenital reflux nephropathy" (Yeung et al. 1997). The appearance of congenital reflux nephropathy is peculiar because it is usually characterized by generalized parenchymal loss instead of focal scarring (Polito et al. 2000). MR urography is able to show both focal defects and generalized hypoplasia (Fig. 1.2.15). Additionally, MR urography characterizes the calyceal anatomy, which is a helpful clue in identifying more generalized abnormalities of the kidneys. It remains controversial whether these congenital renal abnormalities are due to poor nephrogenic differentiation from an improper ureteral budding or from back pressure effect on the developing fetal kidney from refluxed urine. Mackie and Stephens (1975) suggested that renal dysplasia closely correlated with an abnormal ureteral orifice location. A laterally positioned ureteral bud provides an embryological explanation for reflux. The mismatch between the laterally positioned ureteral bud and the metanephros during early gestation results in dysplasia as well as vesico-ureteric

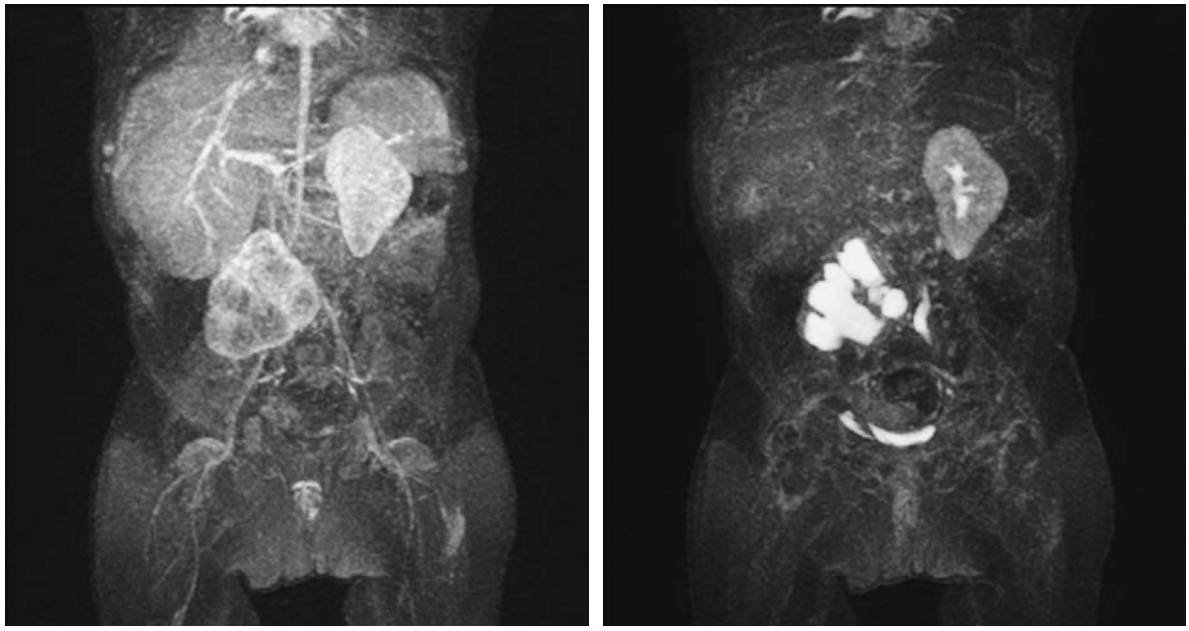

Fig. 1.2.13a,b. Ectopic, hydronephrotic and hypoplastic kidney. **a** Coronal post-contrast MIP showing a pelvic kidney on the right. The vDRF was calculated at 32% on the right. **b** Delayed images demonstrate hydronephrosis, but no evidence of obstruction was seen with a renal transit time less than 4 min

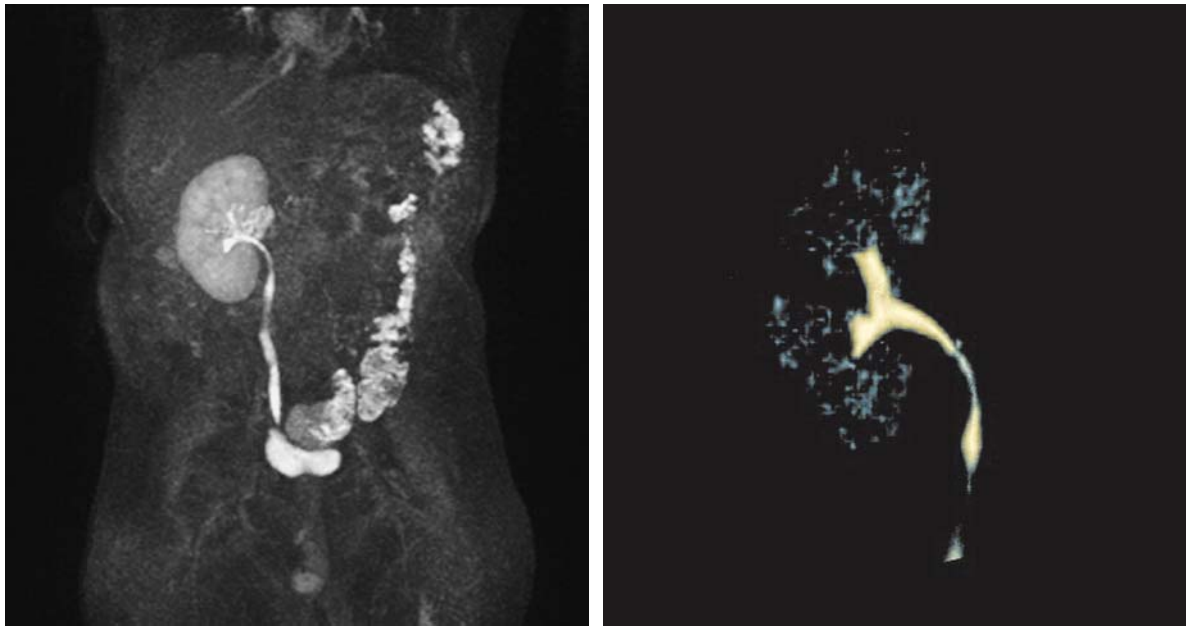

Fig. 1.2.14a,b. Single functioning hypodysplastic kidney. **a** Coronal delayed post-contrast MIP showing a single functioning kidney on the right. At first inspection the right kidney appears normal. **b** Evaluation of the pelvicalyceal system demonstrates marked hypoplasia with only two identifiable calyces on the right. This indicates hypodysplasia and the corresponding BSA Patlak number was low at 67 ml/min

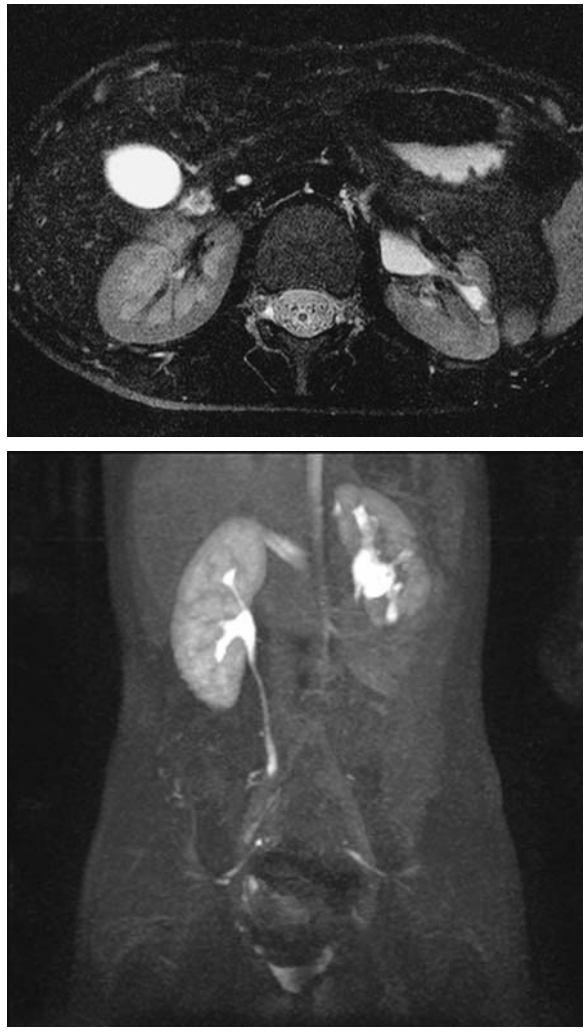

Fig. 1.2.15a,b. Renal scarring in a 5-year-old girl with recurrent UTI. **a** High-resolution axial T2-weighted images showing transmantle scarring of the left kidney with associated dilatation of the adjacent calyx. **b** Delayed coronal MIP from the dynamic series demonstrates a generally small left kidney with multiple cortical scars associated with clubbed calyces

reflux. Risdon (1993) has described hypoplasia and dysplasia in a large majority of boys with gross reflux. MR urography may be able to provide greater understanding into these congenital anomalies.

Conclusion

MR urography characterizes congenital abnormalities of the urinary tract including abnormalities of calyceal development better than other modalities. This may allow greater understanding of the underlying disorders.

1.2.4.3 Pyelonephritis and Renal Scarring

There have been several reports evaluating the role of MR urography in the evaluation of acute pyelonephritis and renal scarring (Kavanagh et al. 2005; Lonergan et al. 1998; Pennington et al. 1996; Weiser et al. 2003). MR urography is equal to and in some cases superior to DMSA renal scintigraphy in the evaluation of both acute pyelonephritis and renal scarring. Initial descriptions used fast IR pulses following contrast administration to demonstrate areas of acute pyelonephritis as areas of increased signal intensity on a background of low signal intensity (Lonergan et al. 1998; Pennington et al. 1996). The normal kidney becomes diffusely low signal intensity, and areas of pyelonephritis are seen as higher signal intensity areas. Cortical scars are seen as focal areas of volume loss with deformity of the renal contour (Fig. 1.2.15). The underlying calyx is often deformed. More recently, the use of the cortical phase of the dynamic post-contrast scan demonstrates cortical perfusion defects similar to those seen on CT, and these may obviate the need for the longer IR sequences in the evaluation of acute pyelonephritis. Evaluation of the parenchymal defects with MR urography is relatively straightforward, because of the easy differentiation of renal parenchyma from the background. Fluid debris levels may be seen with pyonephrosis (Fig. 1.2.16).

Some authors have recommended the use of DMSA scanning as the first line of investigation in children with UTI (Camacho et al. 2004; Tseng et al. 2007). These authors focus on renal involvement as being the most important predictor of long-term sequelae whether vesico-ureteric reflux is present or not. Similar arguments can be made for the use of MR urography as the first investigation of UTI. One of the distinct advantages of MR urography over DMSA scanning is the ability to distinguish acute pyelonephritis from chronic scarring at the time of initial evaluation. Additionally, MR has the ability to identify underlying malformations such as renal dysplasia that have become secondarily infected (Fig. 1.2.16).

Conclusion

MR urography is superior to DMSA scanning in the evaluation of renal scarring and pyelonephriti.

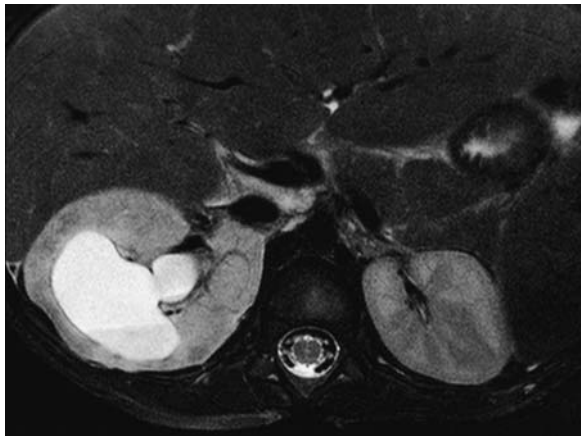

Fig. 1.2.16. Pyelonephritis with underlying dysplasia. High-resolution axial T2-weighted image through the kidneys demonstrates diffuse enlargement on the right with increased signal intensity. There is poor corticomedullary differentiation and multiple small subcotical cysts are seen in the parenchyma. Also note the fluid level in the renal pelvis indicating pyonephrosis

1.2.5 Conclusion

MR urography has the potential to revolutionize imaging of the urinary tract in both adults and children, providing an unprecedented level of anatomic information combined with quantitative functional evaluation of each kidney individually. MR urography will improve our ability to categorize renal malformations in vivo and contribute significantly to our understanding of renal dysplasia. MR urography can now provide useful assessment of obstructive uropathy and may provide predictive information about which children will benefit from surgery. It has the potential to identify parameters that indicate a significant obstruction as opposed to self-limited hydronephrosis. Further technical developments in the field such as BOLD and diffusion imaging as well as molecular imaging with USPIOs will produce greater insights into the pathophysiology of not only urologic disorders, but also disorders of the kidney itself.

Conclusion

MR urography has the potential to revolutionize the imaging of the urinary tract.

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1.3 Nuclear Medicine

Isky Gordon

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1.3.1 Introduction

Functional assessment is undertaken by radionuclides with the dynamic renogram being used to evaluate differential function and drainage. Static technetium-99m dimercaptosuccinic acid (Tc-99m DMSA) scintigraphy is used to assess the renal parenchyma. Catheter cystograms have changed, whereby radiation burden may be markedly reduced using an isotope (direct radioisotope cystography, DIC) or, more recently, ultrasound cystography. However, the possibility of undertaking a cystogram without a bladder catheter (indirect radioisotope cystogram, IRC) offers a totally noninvasive procedure that is physiological, providing new information about vesicoureteral reflux (VUR) and thus changing our understanding of it.

I. Gordon, FRCP, FRCR, FRCPaed
Professor of Paediatric Imaging, Institute of Child Health, 30 Guilford Street, London, WC1N 1EH, UK
and
Honorary Consultant Radiologist, Child Health Consultant Radiologist, Great Ormond Street Hospital for Children, London, WC1N 3JH, UK

1.3.2 Isotope Cystography

The VCU is the reference technique for reflux, yet reflux may be seen on one examination and not another. Figure 1.3.1 demonstrates how one may see VUR bilaterally in a child at one moment and a short while later find unilateral VUR under the same physiological conditions, suggesting the evanescent nature of VUR. Both boys and girls find bladder catheterization unpleasant; it is a procedure that may cause both psychological and physical trauma. Any procedure that can search for VUR without a bladder catheter requires very careful scrutiny.

There are at least four different methods for undertaking cystography in children; only the IRC with Tc-99m labeled to mercaptoacetyl triglycine (MAG3) does not require a bladder catheter and is wholly physiological. The IRC should be undertaken in toilet-trained children whenever possible to detect VUR.

1.3.2.1 Direct Radioisotope Cystography

Indications for DIC (Mandell et al. 1997a,b) include female infants (<1 year of age) with a urinary tract infection (UTI) and a normal ultrasound or with a prenatal ultrasound diagnosis of hydronephrosis who postnatally are either normal or who have mild dilatation, and boys (<3 years of age) who require follow-up cystography.

The advantages of the DIC are its high sensitivity for reflux because of continuous monitoring and lower radiation exposure compared to VCU. For the equivalent radiation burden of one VCU, ten DICs can be undertaken in a 1-year-old and 25 DICs in a 5-year-old child. The disadvantage is that bladder catheterization is required and the anatomical de-

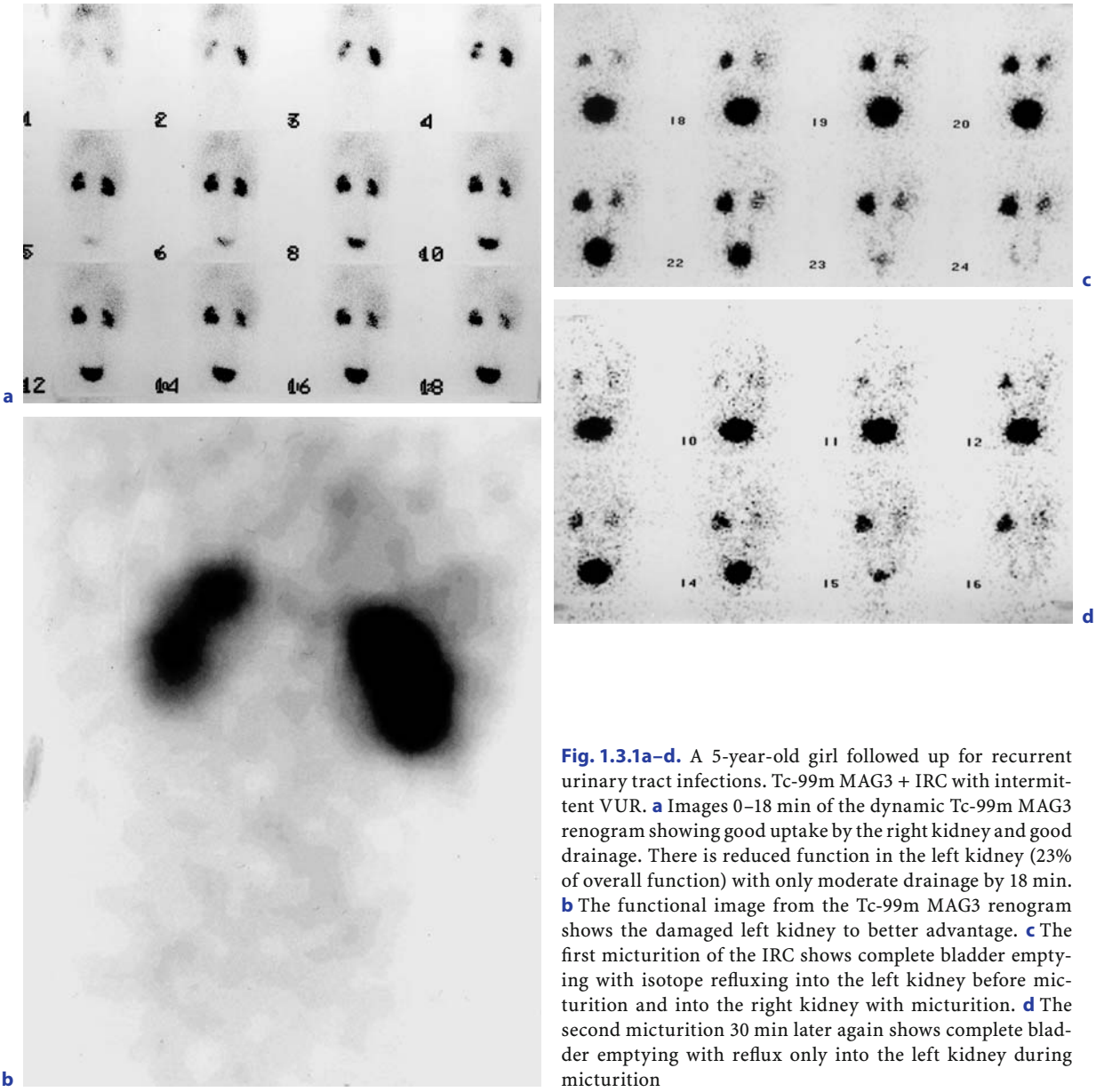

Fig. 1.3.1a–d. A 5-year-old girl followed up for recurrent urinary tract infections. Tc-99m MAG3 + IRC with intermittent VUR. **a** Images 0–18 min of the dynamic Tc-99m MAG3 renogram showing good uptake by the right kidney and good drainage. There is reduced function in the left kidney (23% of overall function) with only moderate drainage by 18 min. **b** The functional image from the Tc-99m MAG3 renogram shows the damaged left kidney to better advantage. **c** The first micturition of the IRC shows complete bladder emptying with isotope refluxing into the left kidney before micturition and into the right kidney with micturition. **d** The second micturition 30 min later again shows complete bladder emptying with reflux only into the left kidney during micturition

tails of the vesicoureteric junction and urethra are poor. The degree of VUR can be estimated in milliliters, but not graded radiologically.

The technique and procedure are similar to conventional VCU (Fig. 1.3.2). Following bladder catheterization, Tc-99m pertechnetate (20 MBq) is instilled followed by warm normal saline until the bladder is full, when micturition should occur. The entire procedure is carried out with double disposable diapers on the infant who is lying on top of the gamma camera linked to a computer system. Both renal areas and the bladder are kept in the field of view. Sedation is rarely if ever required (Kuzmanovska et al. 1996; Treves et al. 1996; Godley et al. 1990).

Conclusion

Because of low radiation burden all follow-up catheter cystograms in young children should be DIC. The main indication is to identify VUR.

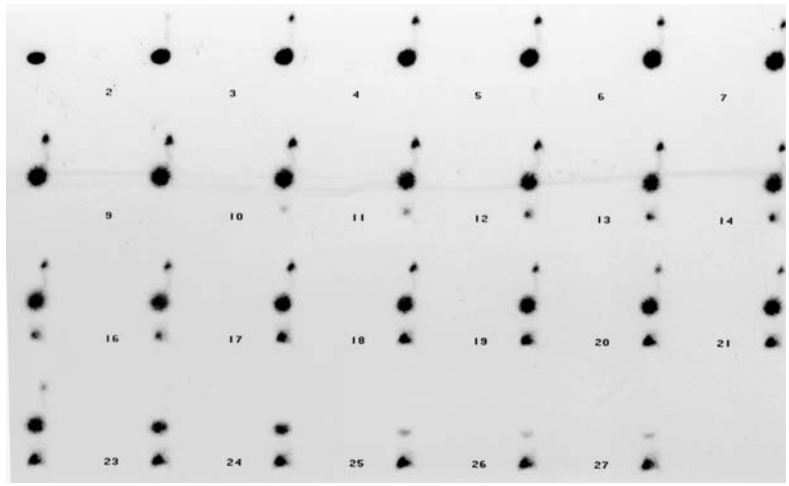

Fig. 1.3.2. Direct isotope cystogram with VUR. A 15-month-old boy with prenatal diagnosis of unilateral hydronephrosis. Postnatally the only abnormality was right VUR on VCU. This follow-up cystogram at 15 months of age shows ongoing right renal reflux in the filling phase of this direct isotope cystogram

1.3.2.2 Indirect Radioisotope Cystography

Indirect radioisotope cystography may be undertaken in any child who is toilet trained (van der Vis Melsen et al. 1989; Canivet et al. 1997). The IRC is done following a dynamic renogram whenever the child wishes to void. All children are adequately hydrated for the renogram and are offered drinks freely following the renogram so that most children do not require encouragement to void. Micturition takes place in front of the gamma camera. If at the end of micturition isotope is still noted in the bladder or kidneys, then the child should be offered more to drink and asked to return to the gamma camera room when he wishes to void again. A quiet room with as few additional people as possible helps for a short successful examination. This is a physiological study that does not require a bladder catheter.

Detection of reflux (VUR). An increase of activity in the kidney during the study indicates VUR. The filling phase of the bladder, studied with VCU or DIC, cannot be studied with IRC. Thus, reflux present only in the filling phase will be missed by IRC. VUR is an intermittent phenomenon for which the incidence varies even using the same examination on different occasions (Fig. 1.3.1). Evaluating any technique for the detection of VUR will remain difficult since there is no absolute reference method. There is agreement that IRC is contributory only when positive, whereas a negative examination cannot exclude VUR. This argument holds true, however, for all cystogram techniques. IRC is a valuable screening technique for the detection of renal reflux and observation of physiological micturition; this is especially true when one is dealing with the difficult or unusual case, e.g., the older girl with recurrent UTI who has a normal ultrasound examination, normal Tc-99m DMSA, but remains symptomatic and may have bladder instability (Figs. 1.3.3, 1.3.4).

Indications for IRC include whenever renal reflux must be excluded in the toilet-trained older child (Figs. 1.3.1, 1.3.3, 1.3.4); ureteric dilatation, again in the toilet-trained older child; older children with known bladder dysfunction (including posterior urethral valve) (Dinneen et al. 1994); and girls with recurrent UTI and normal ultrasound and Tc-99m DMSA scans, in whom the entire nephrourological system can be evaluated.

The strength of IRC lies in the fact that the procedure has a low radiation burden; there is no increase in radiation dose above the routine renogram. Encouraging voiding will in fact reduce the radiation burden since the bladder is the target organ. The Tc-99m MAG3 + IRC provides information about renal function and drainage with a full and empty bladder and also permits assessment of bladder function. When bladder dysfunction is suspected, this is the only physiological cystogram as it does not entail bladder catheterization.

The weakness of IRC includes the need for the child to be toilet-trained. Renal and upper ureteric reflux will be detected, but only the voiding phase of micturition is examined. When there is a high urinary flow rate, as seen after the administration of a diuretic, renal reflux may not be detectable. In the context of hydronephrosis or hydroureter, reflux

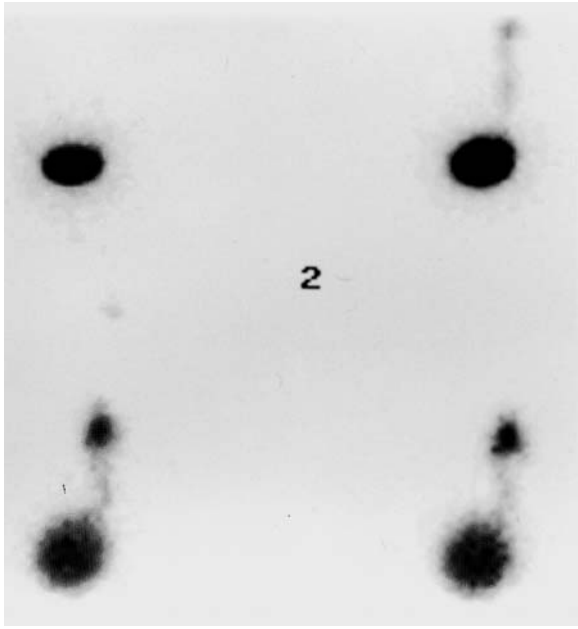

Fig. 1.3.3. IRC recurrent urinary tract infection in a 4-year-old girl. Reflux into right kidney is noted on this indirect radionuclide cystogram despite the fact that there was no micturition. This suggests the diagnosis of an unstable bladder that was confirmed on further investigation

into a dilated system may be difficult to evaluate. Anatomical detail of the vesicoureteric junction and urethra are poor. The presence of a low or ectopic kidney makes the detection of reflux difficult or impossible if the kidney is behind the bladder. Comparison studies between IRC and either VCU or DIC show variable results, with many institutions having a close correlation and others unable to achieve agreement.

Method. After the routine Tc-99m MAG3 study for 20 min, the child is asked to return to the waiting room and called when she wishes to void. Back in the gamma camera room the child voids when she is in front of the camera, which has been turned to a horizontal position. Although boys prefer to stand erect, they should be encouraged to sit with their back to the gamma camera so as to reduce movement to a minimum during micturition. Acquisition should include a 30-s period both before and after micturition. The data should be collected on a computer with a fast frame rate (1 frame/s). The processing includes viewing, regrouping the data into 5-s frames, and both reviewing this data in cine mode as well as drawing regions of interest (ROI) over the bladder and kidneys and generating curves from these ROIs. In addition, a compressed image of the raw data should be created. The diagnosis of VUR should only be made when there is a clear increase

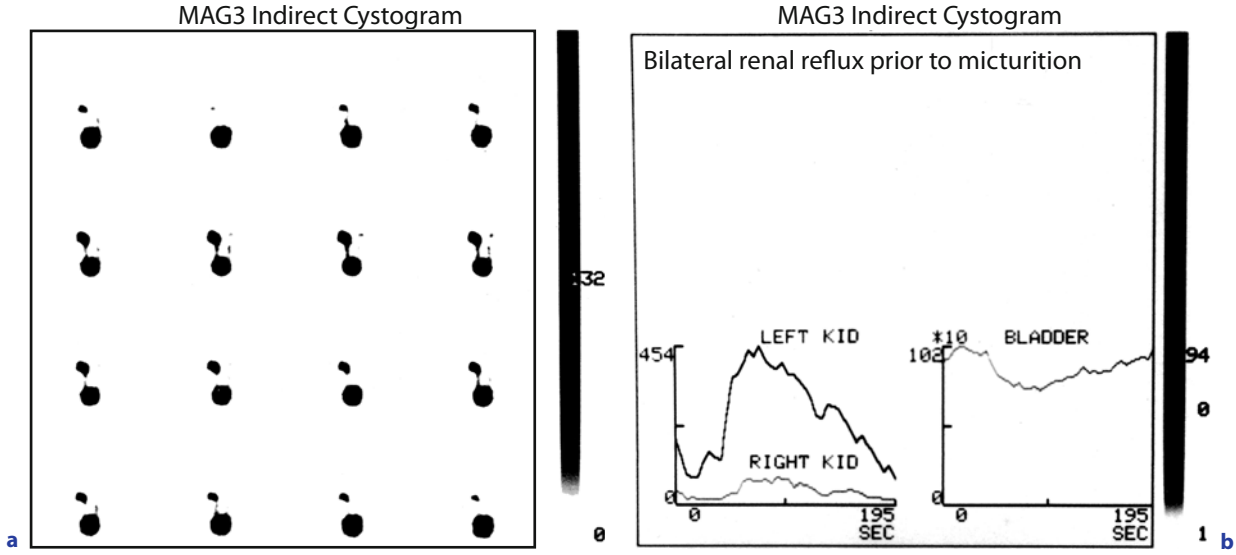

Fig. 1.3.4a,b. Bilateral reflux prior to micturition, first on the left and then on the right. **a** The images are of 5-s duration; the left kidney is seen on the first image, but on the second there is little activity in the kidney. The activity however becomes obvious again by 20 s. **b** The curves show that the reflux is more marked into the left kidney than the right kidney

in activity in the renal areas. If the curves suggest an increase in activity, then this must be seen either on the cine or compressed images or both. Noting only an increase on the curves is not sufficient to diagnose VUR. Movement may be a major cause of false abnormal curves.

There are no contraindications to IRC; however, caution should be exercised in excluding VUR when there is dilatation with poor drainage of the upper tracts. Also in the presence of a pelvic kidney or a low ectopic kidney, the full bladder may obscure the kidney.

Conclusion

Only physiological cystogram is possible. No bladder catheterization is required.
It assesses renal function, bladder function as well as VUR

1.3.3 Dynamic Renography

Although dynamic renography has been used for decades, one must nevertheless ensure that the data are acquired adequately and processed according to well-established guidelines and that the interpretation of the results is based on published supported information wherever possible.

Dynamic renography allows estimation of three parameters of renal function: blood flow to the kidney; renal clearance (Prigent et al. 1999; Rutland 1985; Piepsz et al. 1998), i.e., the extraction of a tracer from the blood, when estimation of relative clearance occurs as in differential renal function (DRF); and the drainage function or excretion from the kidney.

Blood-flow estimation must be undertaken during the first few seconds and is only indicated following renal transplantation in pediatric nephrourology. DRF estimation is best undertaken approximately 1–2 min after tracer injection. After 2 min, there is a possibility that some tracer has left the renal space, therefore invalidating the DRF estimation. Background correction is particularly important in estimation of DRF when there is asymmetrical renal function or decreased overall function. Drainage or disappearance of the tracer from the kidney can simply be estimated by inspecting the renogram curve: an early peak followed by a rapidly descending phase is typical for normal excretion. Delay in excretion is characterized by a continuously ascending curve. Several techniques have been proposed for quantifying the transit of tracer through the kidney. These range from simple descriptive parameters such as the time to reach the maximum of the curve, T_{max}, to more sophisticated parameters, such as deconvolution analysis, output efficiency (OE)/pelvic excretion efficiency (PEE) (Chaiwatanarat et al. 1993; Anderson et al. 1997) or normalized residual activity (NORA) (Piepsz et al. 2000). Sufficient information is provided by the shape of the renogram and the Tmax to discriminate between normal transit (T_{max} around 3 min) or very delayed transit (T_{max} of 20 min). There is no proof that in clinical practice the more sophisticated techniques can improve the information obtained. When dilatation of the collecting system exists, the standard renogram is generally characterized by a continuously rising curve, reflecting poor drainage of the kidney. In this condition, one should administer furosemide (diuretic renography), which increases urinary flow and may distinguish between good and impaired drainage; the data acquired post furosemide must include a series following a change of posture and micturition (see Postmicturition Images, below).

Tracers Used. There are three tracers that rely on tubular extraction–I-123 Hippuran, Tc-99m MAG3 and Tc-99m ethylenedicysteine (EC)–and one tracer dependent on filtration, Tc-99m DTPA. The tracers, reflecting tubular extraction, have a greater renal extraction than Tc-99m DTPA, resulting in a lower background activity and a higher kidney to background ratio than Tc-99m DTPA. In young children, preference must be given to tracers with a high extraction rate, such as Hippuran or Tc-99m MAG3, which provide reasonable images and which allow the DRF to be estimated as early as the end of the first week of life. The tubular agents are preferred for diuretic renography and indirect cystography. Tc-99m DTPA may be useful following renal transplantation when both the blood flow and the formal glomerular filtration rate (GFR) estimation (with blood sample analysis) are required.

The kidney of the young infant is immature, and the renal clearance, even corrected for body surface, progressively increases until approximately 2 years of age. Therefore, renal uptake of tracer is particularly low in infants, with a high background activity.

Indications include all uropathies, which require evaluation of individual renal function at diagnosis and during the different phases of surgi-

cal or conservative treatment and evaluation of the drainage function. Examples include dilatation no matter what the cause (e.g., pelviureteric and ureteric dilatation), bladder dysfunction, complicated duplex kidney, status post trauma, asymmetrical renal function, and reflux nephropathy. When dilatation of the collecting system exists, the standard renogram should be complemented by a diuretic renogram. Other indications include the previously discussed IRC and evaluation of sustained systemic hypertension. If renovascular disease is suspected, then captopril provocation may be used (Taylor et al. 1996) following renal trauma and in the follow-up of renal transplantation. In this case the dose of tracer should be increased, and the acquisition should include a rapid early dynamic phase.

There are no contraindications. However, there are limitations: In the presence of poor renal function, accurate estimation of DRF and/or drainage may not be possible. In the presence of marked hydronephrosis, the interpretation of poor drainage is difficult since this could be due to either partial hold-up or simply because of the reservoir effect of the dilated system. In the presence of calculus obstruction, a renogram may be undertaken, but no furosemide should be administered.

The strengths of dynamic renography lie in the ability to routinely quantify DRF and drainage; serial renography is also reliable. There is a low radiation burden, especially using the agents with tubular extraction.

Methodology includes a well-hydrated child prior to the injection of tracer, which is accomplished by offering fluids freely before the injection. Anesthetic cream should be applied to relieve the discomfort of the injection; this requires a 60-min wait for the cream to have its effect and so provides an opportune time for ensuring good hydration. The maximum recommended doses are: Tc-99m MAG3, 80 MBq; Tc-99m DTPA, 200 MBq. The minimum doses are: Tc-99m MAG3, and Tc-99m DTPA, 20 MBq. The administered doses should be scaled on a body-surface basis. For a 5-year-old using Tc-99m DTPA, the effective dose (ED) is 0.54 to 0.82 mSv, the lower figure relating to a 1-h voiding interval. For Tc-99m MAG3, the corresponding figures are 0.20 and 0.38 mSv, respectively (Stabin et al. 1998; Smith and Gordon 1998).

Images should be acquired with the camera/collimator facing upward in all circumstances except following renal transplantation when the scan is done anteriorly. Placing the child supine reduces movement, and supporting the child with sandbags on either side plus Velcro straps around the child further reduces movement. When possible the child should lie directly on the collimator face. One must ensure that the heart, kidneys and bladder are all included in the field of view. The heart is important if analysis of the renogram will use the curve from the cardiac ROI (see below). The blood-flow phase requires a rapid frame rate (0.5 s/frame for 40 s). A rate of one frame every 10 s or 20 s is suggested for the standard and diuretic renogram. Whatever the processing method used, the DRF estimation is independent of frame time and will be the same using either 10 s or 20 s frames. The duration of study should be a minimum of 20 min.

Diuretic administration should be 1 mg/kg with a maximum dose of 20 mg. There are three variations to the timing of administration (see Table 1.3.1): the F-0 method (furosemide given with the tracer) is gaining popularity, especially in the young child with small veins, since there is only a single IV injection. There is no evidence at the present time to suggest that any one of the timings is better than the other. However, if venous access is difficult, then one single injection is to be recommended. Post-furosemide acquisition parameters should use the same frame rate, zoom factor and matrix size as for the renogram.

Table 1.3.1. Duration of acquisition in relation to the administration of furosemide

Time of diuretic administration	Duration of acquisition		
	Renogram	postdiuretic	PM images within 60 min
F-15	20 min	–	1 min
F0 or F+2	20 min	–	1 min
F+20	20 min	15–20 min	1 min

F-15, furosemide (FA) administered 15 min before injection of radioisotope (IOR); F0, FA given with IOR; F+2, FA 2 min after IOR; F+20, FA 20 min after IOR PM, postmicturition

Postmicturition Images. Since the renogram is obtained with the patient in the supine position, gravity has not had its normal effect. To allow the renogram to be analyzed including the effect of gravity, the infant should be placed erect (on the mother's shoulder for 5 min) or the older child should be sent to the toilet to void. Following the administration of furosemide almost all infants and children will void during this period. The child should return to the gamma camera, and data should be acquired for 1 min in exactly the same way as for the renogram. Indications for the postmicturition (PM) image series include following the administration of a diuretic if upper urinary tract emptying is incomplete and in children with known dilatation in whom the need for a diuretic renogram is unlikely. In this case the PM images may be acquired after the 0–20 min renogram; however, for consistency PM images should be acquired within 60 min after the injection of tracer. Each institution should ensure that there is an attempt to standardize the entire renogram including the time frame. This will allow for comparison with sequential studies as well as comparison between different children. This simple technique excludes the need for bladder catheterization (Gordon et al. 1988; Rossleigh et al. 1993).

To analyze the renogram data from the images, the curves as well as the numerical data derived from the curves must be used together. Three parameters can be estimated: blood flow (only done for renal transplants), DRF, and drainage or washout.

Both renal and background ROIs should be drawn on all acquisition data; background ROIs should be perirenal, including the upper, outer and inferior aspects of the kidney. In the presence of gross pelvic dilatation in the young infant, a complete perirenal background may not be possible since the kidneys extend virtually to the edge of the child. In such circumstances a background ROI above and below the kidney might be the best compromise. Background-corrected curves should be created for each acquisition series and used for analysis.

Images should include a summed image of all the frames during the clearance or uptake phase, i.e., 60–120 s after the peak of the cardiac curve (vascular phase). This image reflects the regional parenchymal function and may allow the detection of regional abnormalities. Although the consensus publication of the International Scientific Committee on Radionuclides in Nephro-Urology on Tc-99m DMSA has shown that Tc-99m DMSA is more appropriate for that purpose, one should not neglect the possibility of detecting parenchymal abnormalities when performing a renographic study. Differential function should be visually assessed on this image and compared to the DRF estimated from the curves to ensure that there is congruity of results. In addition, a series of timed images over the duration of study should be created. The optimum is to combine frames into 1-min images covering the duration of the study, including the PM images. All images, including the postdiuretic and PM images, should be displayed with the same scaling factor. Functional images during the early phase may be useful, especially if one can create an image of pure proximal tubular function using a tubular agent, this may allow focal parenchymal abnormalities to be seen more easily than on simply a summated image. Blood flow estimation is analysis of the images where one looks for appearance of tracer in the kidney relative to the aorta and/or the spleen (Figs. 1.3.5, 1.3.6). Numerical estimation is to quantify the activity in the kidney relative to either the percentage of cardiac output or the activity arrival in the aorta or iliac vessel.

Quantification should include DRF, the relative function of each kidney expressed as a percentage of the sum of the right and left kidneys. It is computed between 60–120 s from the peak of the cardiac (vascular) curve. No renal depth correction is required in children. The International Scientific Committee on Radionuclides in Nephro-Urology has recommended either the integral method or the Patlak-Rutland plot method. The integral method uses the area under the background-corrected renograms, representing the cumulative uptake during the selected time interval (Fig. 1.3.7). The Patlak-Rutland plot method is the mean slope of the ascending portion of the curve plotting the background-corrected kidney ROI counts [R(t)] divided by the cardiac ROI counts [H(t)] as a function of the integral of the cardiac ROI counts divided by [H(t)] (Fig. 1.3.8).

For the estimation of excretion or drainage, numerous methods have been proposed. The simplest method is inspection of the curve: normal excretion (early peak with a rapidly descending curve) as well as slightly delayed excretion is readily distinguished from very abnormal excretion (continuously rising curve). Adequate assessment of the response to the diuretic must include the analysis of the PM images and also take into account the function of the kidney. This can be achieved by express-

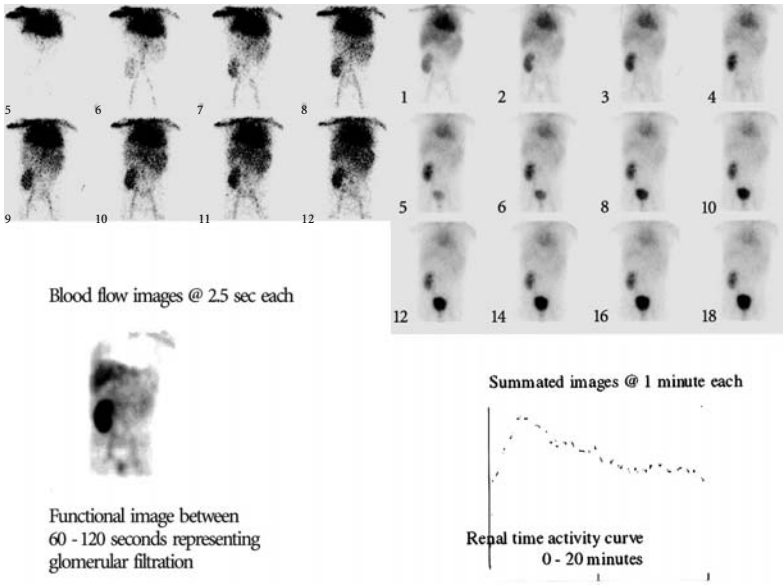

Fig. 1.3.5. Normal Tc-99m DTPA renogram in a 6-year-old boy 4 days after a renal transplant. The eight images at upper left (labeled 5–12) represent the blood flow phase after the bolus injection of tracer. The aorta is just visible on the first frame, but easily identified on the second frame; the kidney is clearly seen on the second frame representing good perfusion. The 12 images at top right are summated images over 18 min; each image represents 1 min. Note how the isotope moves from the renal parenchyma on the early images into the calyces and finally into the pelvis. The image at lower left is the functional image during the period 60–120 s, which, when using Tc-99m DTPA, represents glomerular filtration; this is normal. The renogram curve shows minimal delay in drainage. This is a normal study

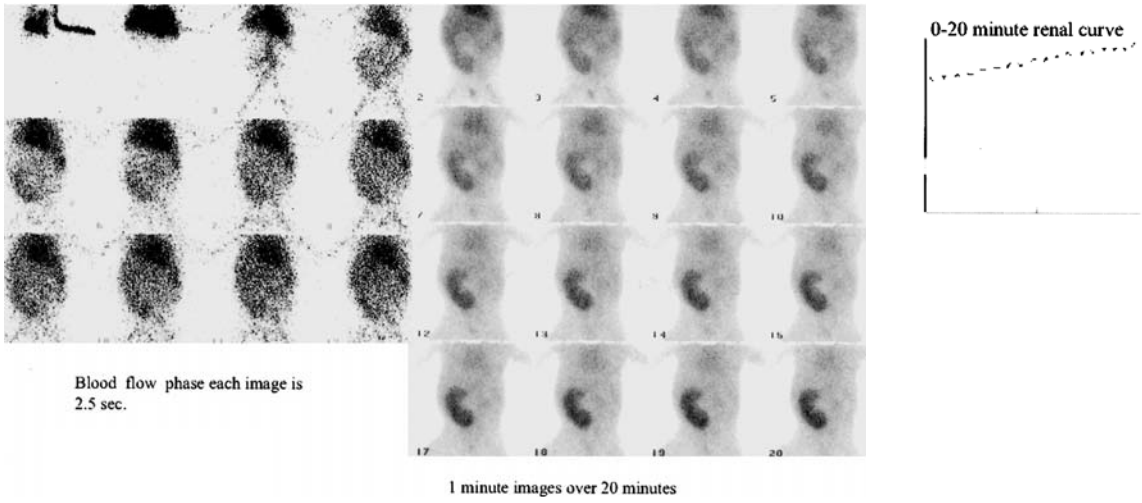

Fig. 1.3.6. Four days after renal cadaveric transplant in a 3-year-old boy with no urine output due to clot obstruction at the lower end of the ureter. The ultrasound examination including power Doppler was normal (not shown). The 12 images on the left represent the blood flow phase after the bolus injection of tracer. The aorta is seen on the third frame; the kidney is seen with difficulty on the fourth and fifth frames, showing that perfusion is present, but reduced. The images on the right are 1-min images over the 20-min study; there is progressive increase in the kidney with no isotope in the bladder by the end of the 20-min period. This is reflected in the progressively rising curve. These features could represent acute tubular necrosis (ATN) or an acute obstruction; however, in this clinical situation where there was hematuria (no clots), a diagnosis of clot obstruction was suspected and proved on antegrade study. In ATN one would expect better perfusion and filtration than is seen in this child. The clinicians were anxious that the cause of the loss of urine output was renal artery and venous pathology. This study not only excluded that possibility, but also suggested the true cause

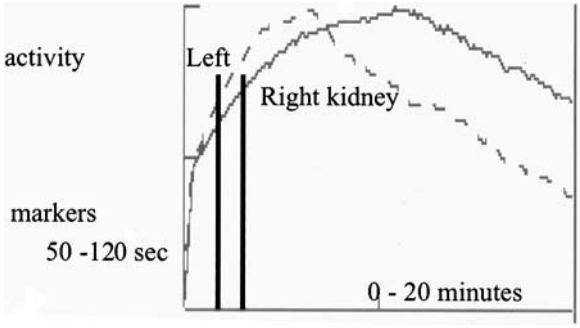

Fig. 1.3.7. Integral technique for estimation of DRF

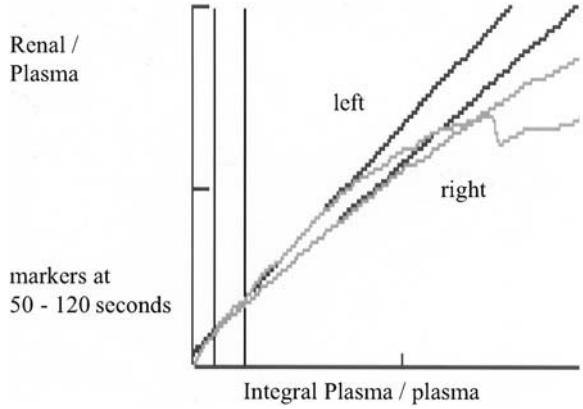

Fig. 1.3.8. Patlak plot technique for estimation of DRF

ing the activity in the PM image as a percentage of the activity taken up at 2–3 min or as a ratio of the radionuclide taken up by the kidney, giving the pelvic excretion efficiency (PEE) (see Fig. 1.3.9). There are, however, no cut-off values available to differentiate between partial and poor emptying. Assessment of the diuretic response must be clearly distinguished from the interpretation of the result. Simple analysis of the postdiuretic curve is inadequate.

Normal DRF values are between 45% and 55% uptake. DRF values within the normal range may be seen when there is bilateral renal damage and/or in the presence of chronic renal failure. Values outside this normal range may be seen when there is an uncomplicated unilateral duplex kidney as well as in unilateral renal damage. The function of an ectopic kidney will be underestimated on dynamic renography: correct evaluation requires a Tc-99m DMSA scan with both posterior and anterior images. Images may show a focal renal defect on early images: dilated calyces and/or renal pelvis and/or a dilated ureter may be evident. Comparison between the renogram and PM images is important to assess the effect of a change of posture and micturition (Fig. 1.3.10).

Adequate hydration is important; this is readily achieved by including the need for good fluid intake in the information letter that every parent receives. Furthermore, since an anesthetic cream is applied to many children and this takes 60 min to be fully effective, there is a second opportunity to encourage oral fluid intake. Infants could receive an additional bottle/breast feed, while older children could be encouraged to drink water or orange juice liberally (250–500 ml). The interpretation of impaired drainage is debated, and its relationship to surgery does not meet universal agreement.

Advantages of Tc-99m MAG3 renography include the ability to quantify DRF reliably, assess parenchymal abnormalities, visualize the collecting systems, and assess drainage. The high extraction by the kidneys from the blood gives a low background and thus facilitates the analysis of the infant's kidneys and also reduces the radiation burden. It allows physiological assessment of the bladder and the collecting systems when an IRC is undertaken. The disadvantages include the fact that the child should lie still for 20 min and that movement makes analysis more difficult. There is controversy in the interpretation of the diuretic response; this is not the fault of the technique, however, but rather shows the difficulty of having an appropriate reference technique to judge infant renal pelvic dilatation.

Role of DTPA Renography in Following Renal Transplantation: A retrospective study evaluated the results of semi-quantitative analysis of and comparison between the images of renal perfusion and filtration on the Tc-99m-DTPA dynamic renal scintigraphy (Sundaraiya et al. in press). These results have been compared to both the report of the renal biopsy at the time and the long-term clinical outcome in children who had biochemical evidence of acute renal dysfunction. A total of 39 renogram studies and biopsies in 31 post-transplant children have shown that if, on Tc-99m DTPA renography, the renal perfusion and filtration are in balance, then the chance of acute rejection is highly unlikely. In proven acute rejection, results were consistent with rejection (reduced perfusion with better filtration) in 11 patients, with no rejection in 3, and 1 patient was equivocal with good perfusion and filtration.

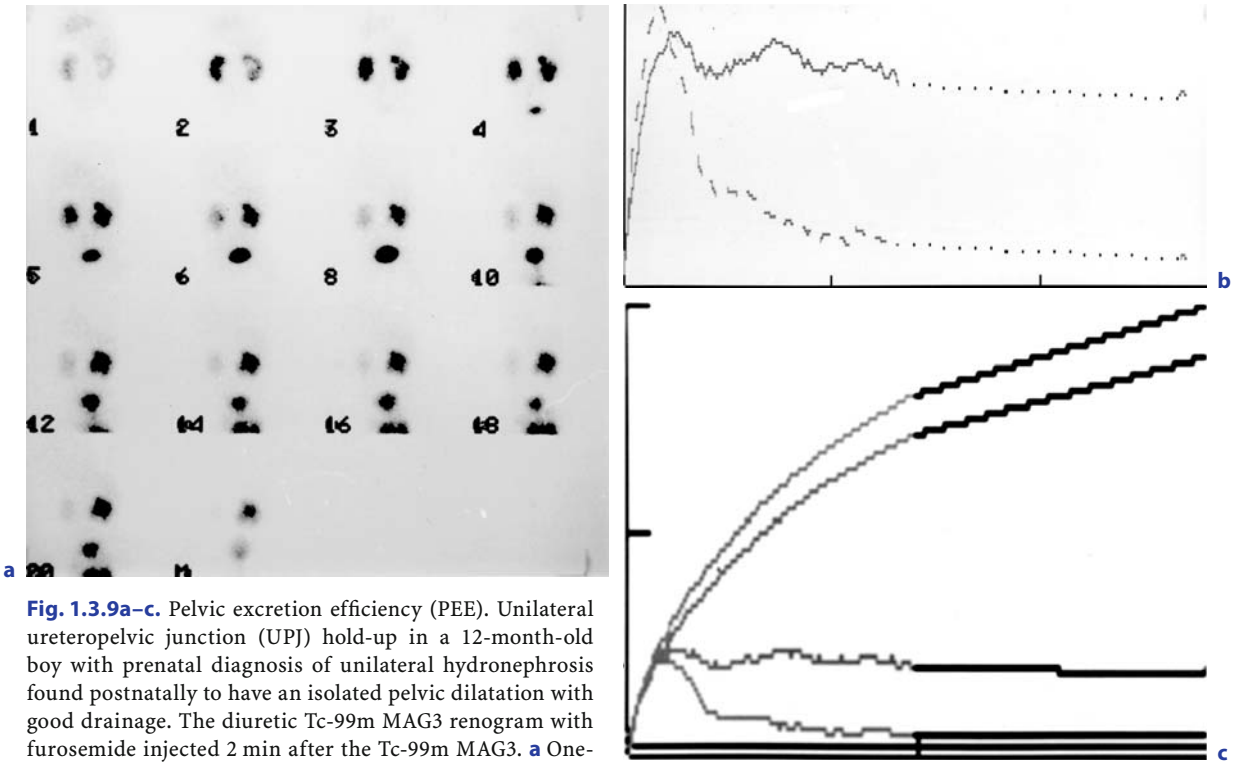

Fig. 1.3.9a–c. Pelvic excretion efficiency (PEE). Unilateral ureteropelvic junction (UPJ) hold-up in a 12-month-old boy with prenatal diagnosis of unilateral hydronephrosis found postnatally to have an isolated pelvic dilatation with good drainage. The diuretic Tc-99m MAG3 renogram with furosemide injected 2 min after the Tc-99m MAG3. **a** One-minute images for the duration of the study including the postmicturition image at 40 min shows good function of both kidneys (differential function left 53%, right 47%), with normal drainage on the left and poor drainage on the right until 20 min, but the postmicturition image shows little isotope in the renal pelvis. **b** The background subtracted renogram curves over the entire study show good uptake by both kidneys and good drainage on the left. The right renal curve is almost flat from approximately 5 min onward. **c** These curves represent the principle of the PEE. The two lower curves represent the actual activity in each kidney over the duration of the study. The upper curves start with the actual curves, but are then extrapolated as if nothing left the kidney for the duration of the study, i.e., as if the kidneys were completely obstructed. The difference between the upper and lower curve for each kidney then represents the amount of isotope, which has come into the kidney and has left the kidney. As seen in these curves there is very good drainage from both kidneys despite the rather flat curve of the right kidney in Figure 1.3.9b

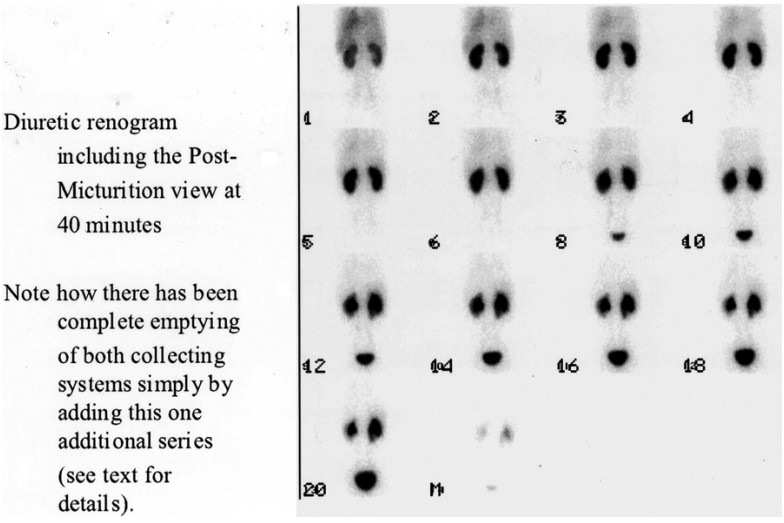

Fig. 1.3.10. Value of postmicturition image series. Tc-99m MAG3 diuretic renogram with consecutive images over 20 min are shown. Both kidneys show prompt uptake of tracer with poor drainage by 20 min. The postmicturition image at 40 min (M) reveals little tracer in the renal pelvis on both sides. Note the bladder is also now empty. This was reflected in the curves and numerical analysis (PEE)

The DRS was able to diagnose rejection in 18 out of 24 children with a clinical outcome of acute and/or chronic rejection (excluding the one patient with uncertain DRS result) and was able to exclude rejection in 12/14 children without clinical rejection giving an overall sensitivity of 76% and specificity of 86%.

Conclusion

Dynamic renography assesses renal blood flow, differential function and drainage. Indications are assessment of pre- and posturological surgery in children. In the presence of dilatation it assesses function and drainage.
Full analysis includes images, numbers and curves.

1.3.4 Static Renal Scan

Technetium-99m DMSA binds to the proximal convoluted tubules, resulting in fixation of the isotope and an unchanging image over many hours with only 10% of the injected dose excreted in the urine. The delayed static images after intravenous injection represent functioning cortical mass and provide an accurate image of renal parenchymal outline.

The main indication for performing Tc-99m DMSA is the detection of cortical abnormalities related to UTI. Compared to ultrasound and intravenous urography, the sensitivity is high in both acute and chronic pyelonephriti Lesions are nonspecific, since similar lesions can be found in renal abscess, cyst, duplex kidney and hydronephrosis. The combination of ultrasound and Tc-99m DMSA allows easy differentiation between these clinical situations. Experimental studies in animals have validated Tc-99m DMSA as an accurate technique for the detection of both acute infection and chronic lesions. The use in the early phase of a UTI (<1 month) will detect acute changes that may resolve. In this situation Tc-99m DMSA is used to identify the kidney involved in the infection. The reason for doing Tc-99m DMSA at a later stage, more than 6 months, is to identify any permanent renal damage (Mandell et al. 1997a,b; Piepsz et al. 1999).

Common indications for Tc-99m DMSA scans include: detection of acute pyelonephritis (Figs. 1.3.11, 1.3.12); renal scars after UTI; detection of abnormalities such as abnormal duplex kidney, small kidney, dysplastic tissue, or ectopic kidney (Fig. 1.3.13); when only one kidney has been identified and doubt exists about the presence of a second (Fig. 1.3.13); in children with gross dilatation (e.g., prune belly syndrome) where assessment of drainage is not possible, but differential renal function (DRF) is required. Confirmation of nonfunctional multicystic kidney, however, since the prognosis is dependent on the other kidney being normal, and of PUJ/mid-ureteric hold is well recognized. A Tc-99m MAG3 diuretic renogram will assess the nonfunctioning multicystic kidney, exclude hold-up in the remaining functioning kidney and expose the infant to the lowest radiation burden.

Preparation and Sedation. Drug sedation is rarely, if ever, needed for Tc-99m DMSA scintigraphy, whatever the age of the patient. A well-adapted environment, an appropriate attitude toward the child, a well-trained technologist for pediatric procedures and involvement of the parents before and during the procedure generally provide effective circumstances to assist in obtaining adequate immobilization of the child during the acquisition. The most difficult age is between 1 and 3 years: in this category of patients, sedation may very occasionally be required. The safest drug is then intranasal or per-rectal midazolam, which will help reduce anxiety.

Precautions. If significant hydronephrosis exists, late images (4–24 h) may be useful, but one must question whether the correct tracer has been chosen. Tubular defects such as the Fanconi syndrome may result in poor renal visualization due to defective binding of the isotope within the tubular cell and consequent high urinary excretion.

Radiopharmaceutical. A dose schedule using a minimal dose of 15 MBq and a maximal dose of 100 MBq scaled on a body surface basis is advised (Piepsz et al. 1990). The tracer should be injected using a fine butterfly needle (caliber 25/27); an anesthetic cream should be applied 60 min before the injection. The radiation burden is approximately 0.9 mSv per examination regardless of the age of the child, providing that the dose is selected according to body surface area.

Image acquisition should begin 2–3 h after tracer injection. Late images are sometimes useful (vide supra). The camera should be collimator-side up,

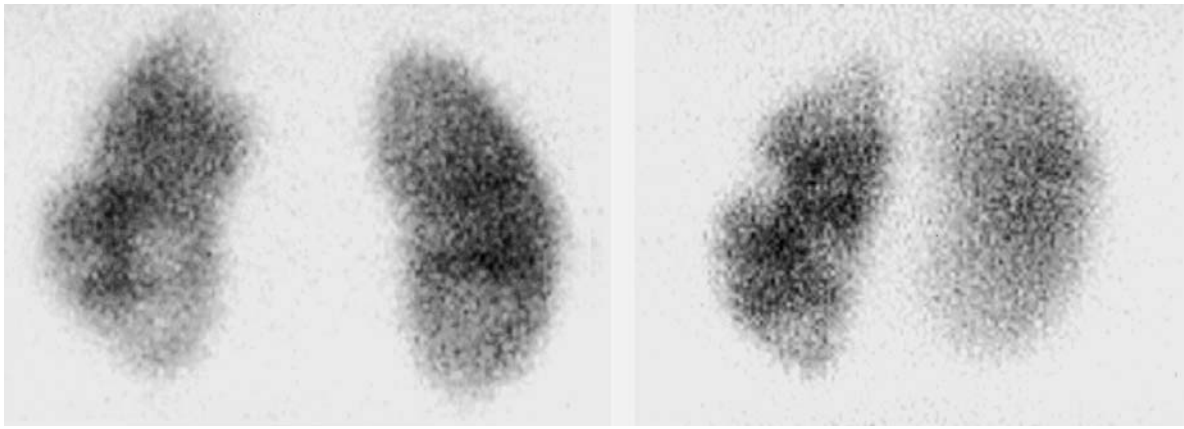

Fig. 1.3.11. Tc-99m DMSA scan on the left in a girl with a urinary tract infection. There is a defect in the acute phase in the left kidney. This 2-year-old girl was severely ill with systemic illness and was found to have a urinary tract infection; the US was normal. The Tc-99m DMSA scan on the right was undertaken 1 week after admission with the diagnosis of urinary tract infection. There are multiple defects in the left kidney that contributed 39% to overall function

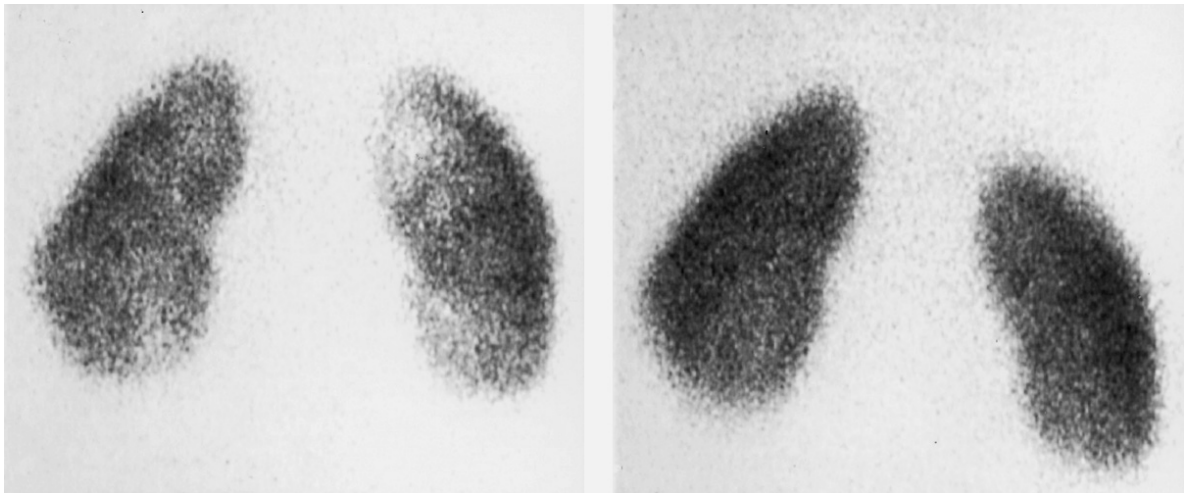

Fig. 1.3.12. Urinary tract infection with defect in acute phase with normal final outcome. This 4-year-old girl was being investigated for a urinary tract infection; the US was normal. The Tc-99m DMSA scan on the left was undertaken 1 week after the diagnosis of the urinary tract infection. There are multiple defects in the right kidney with a defect in the lower pole of the left kidney. The Tc-99m DMSA scan on the right undertaken 6 months later is now normal. Although most defects that return to normal do so within the first 3 months after urinary tract infection, approximately 15% will take up to 6 months to return to normal

using a high- or ultra-high-resolution collimator (Figs. 1.3.14, 1.3.15). Pinhole views (3-mm aperture) may be useful, particularly in infants. The child should be placed supine and posterior since both posterior oblique views are essential. The anterior view is essential for either a horseshoe or ectopic kidney or when hunting for the missing kidney.

The computer acquisition set-up should include a pixel size between 1.8 and 2.5 mm; this can be achieved with a 128×128 plus zoom at acquisition or a 256×256 matrix. At least 300,000 counts or 5 min counting per image is necessary. For pinhole views, the preset count is between 100,000 and 150,000 counts and the preset time around 10 min. An optional additional approach could be to acquire the data in dynamic mode over a given preset time and reframe to a single image, correcting for movement. The same matrix must be used as above.

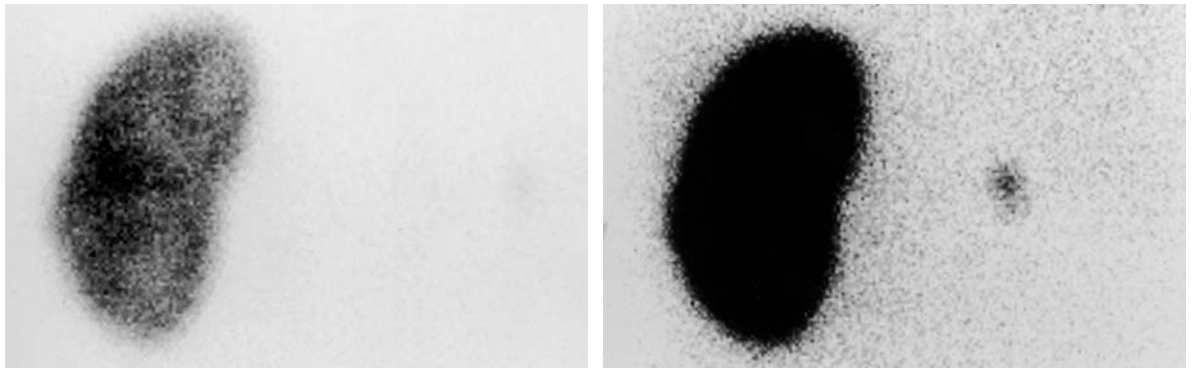

Fig. 1.3.13a,b. Ectopic right kidney. A 5-year-old girl who had been constantly wet since birth. The ultrasound revealed only one kidney and no dilatation. The MRI scan had failed to reveal the ectopic kidney. **a** Tc-99m DMSA scan with normal windowing shows the normal left kidney. Note the clarity of the internal architecture. The small, very poorly functioning right kidney cannot be identified with certainty. **b** The same Tc-99m DMSA scan with the window set very low so that the normal kidney now appears black. The small ectopic right kidney is clearly seen, allowing the surgeon to be confident about which incision to make and where to look for the ectopic kidney, which was removed

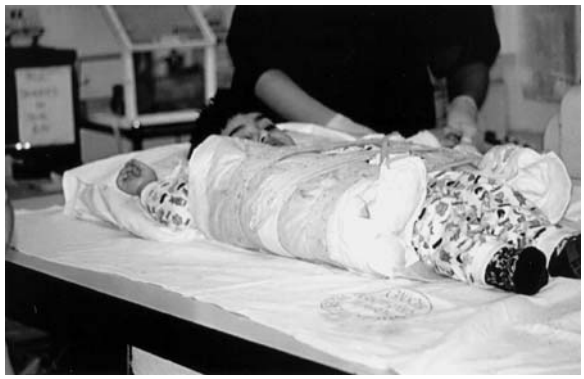

Fig. 1.3.14. Immobilization. The child is lying on the camera face. The bed, which is covered with a sheet, has a hole cut out of the center, allowing the child to lie directly on the camera face. The child has sandbags on either side of the body, and the Velcro straps ensure that the sandbags are firmly attached to the child, thus reducing movement. Sometimes leaving the arms free allows the child to hold a toy or book and so further reduces struggling and movement

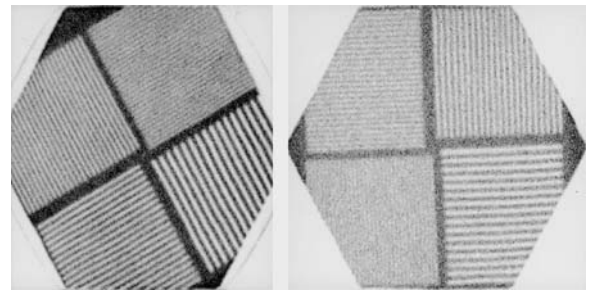

Fig. 1.3.15. Effect of distance on image quality. The two images are of the same line bar phantom showing how one may degrade the image quality by simply increasing the distance between the gamma camera face and the phantom. In the image on the left with the phantom on the camera face, the lines are clearly seen in all four segments. When the phantom is placed on the imaging bed 1 cm above the camera and as close to the camera as possible, the lines are clearly seen in only three segments

SPECT. There is at the present time no consensus about the usefulness of SPECT for Tc-99m DMSA scintigraphy in children. The few publications on investigations in children and the experimental studies have shown little additional benefit of the routine use of SPECT for TC-99m DMSA. When performing SPECT, attention must be paid to the risk of false-positive images and to the necessity of sedation in children. Some institutions also considerably increase the amount of radioactivity given and so increase the radiation burden, which is unacceptable.

Processing. This should include calculation of DRF and an ROI around each kidney, using highly contrasted images, as well as a perirenal ROI for background subtraction. Attenuation correction is required in cases of ectopic or pelvic kidney, and this is best achieved using the geometric mean with the anterior and posterior views.

Interpretation. Normal values of DRF are between 45% and 55% uptake. Values outside this range may be seen when there is an uncomplicated unilateral

duplex kidney. Values within the normal range may be seen with bilateral small kidneys. Pelvic retention, in the case of hydronephrosis, may cause falsely high DRF.

Images. Normal appearances include sharp renal outlines with clear delineation of the cool pyramids from the hot proximal tubules (Fig. 1.3.16). There are many variants, including contours of the kidney that may be round in shape; there is a contrast between the active outer part and the less active inner part. A contour can be flat without suggesting a lesion. The lateral aspect of the superior half of the left kidney can be flattened due to the presence of the spleen. In young children, it is not exceptional for the kidney to appear triangular-shaped, with flattened external sides. A so-called slender kidney, characterized by a short transverse axis in the posterior view, is generally normal and corresponds to a rotated kidney. The transverse axis can be sometimes shorter at one pole (upper or lower) than on the other, giving an aspect sometimes defined as pear-shaped. The pole, and particularly the upper pole, can appear as a pathological hypoactive one, simply because of the contrast with the hyperactive columns of Bertin underlying the pole. The number and size of the columns of Bertin differ from patient to patient (variable thickness of the cortical rim) and may cause false interpretation of the image. Attention should be paid to the presence of fetal lobulation. This may be difficult to distinguish from a scar without the help of other imaging modalities.

When an abnormal pattern is seen the number, size and location of areas of cortical loss should be noted. Loss of the outline may or may not be present. Differentiation between acute lesions, which will improve or disappear, and chronic lesions (scars) is not always possible in the acute phase of a UTI (Figs. 1.3.11, 1.3.12). A polar hypoactive area with an intact renal outline will generally heal; marked localized deformity of the outlines or deformed outlines (volume loss) generally correspond to permanent scar. To assess renal scars after UTI, TC-99m DMSA scintigraphy should be performed at least 6 months after acute infection.

Quality of the images should be checked prior to the child leaving the department. High-quality images have clear renal outlines, and the pyramids are seen as areas of reduced uptake, while the periphery of the kidney and areas with proximal tubules have higher uptake. Movement will cause blurred or double outlines and loss of the internal differentiation.

The advantages of Tc-99m DMSA scans are the absence of bowel gas, the high sensitivity in the detection of parenchymal pathology, and quantification especially for the ectopic kidney; differential renal function is more reliably assessed than with dynamic renogram. The disadvantages include the 2-h wait between injection and scan; each image requires approximately 5 min, and therefore radiographers motivated in pediatrics are necessary. The radiation burden is higher than for dynamic renography, so Tc-99m DMSA is not advocated solely for assessment of DRF. In the presence of dilatation of the renal pelvis, the Tc-99m DMSA may accumulate in the pelvis and result in a falsely high estimation of the function of the hydronephrotic kidney.

In the estimation of DRF there is close correlation between the results of Tc-99m MAG3 and Tc-99m DMSA (Fig. 1.3.17). Correlation between Tc-99m DTPA and Tc-99m DMSA is not as good, but is still clinically acceptable. This means that if only DRF is required then a Tc-99m MAG3 renogram, with the lower radiation burden, should be performed.

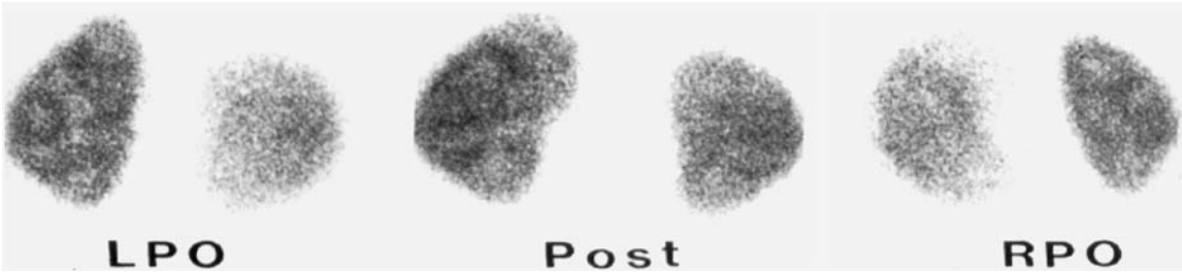

Fig. 1.3.16. Normal Tc-99m DMSA scan. This 3-year-old girl was undergoing investigation for a urinary tract infection. Note the clarity in the outline of both kidneys. The internal architecture is clearly seen in both kidneys. For the right kidney this is better on the right posterior oblique projection (RPO), while for the left kidney this is best seen on the left posterior oblique projection (LPO)

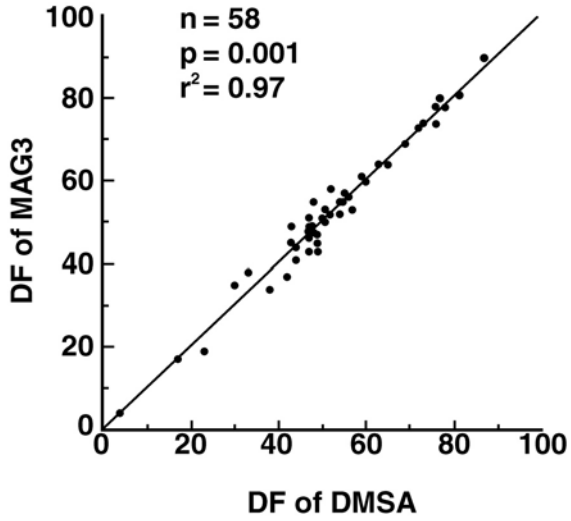

Fig. 1.3.17. Differential renal function using Tc-99m DMSA and Tc-99m MAG3 in the same children. The studies were done within 4 weeks of each other. There is close correlation between the two tracers

Conclusion

High-quality images allow visualization of the internal architecture. The principal indication is to identify focal renal parenchymal defects.

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1.4 Video-Urodynamics

Richard Fotter

The first to describe a combination of urethrocystometry and imaging of the lower urinary tract was Earl Miller (Enhornig et al. 1964, Hinman 1979). Bates et al. (1970) popularized video pressure flow cystourethrography. In the meantime the term video-urodynamics (VUD) has come into general use. Basically, VUD is the combination of voiding cystourethrography (VCU) (with fluoroscopy and video registration or with the digital technique) with pressure/flow/electromyographic studies of the lower urinary tract. Each study can be stored on video or on a PC. Despite statements implying otherwise, it should be underlined that VUD is a relatively simple technique. Recently very sophisticated equipment has become commercially available, but simple equipment can also provide satisfactory information.

The main advantage of VUD is that at any time one can see on the video screen the graphic urodynamic study with a simultaneous fluoroscopic appearance of the bladder and outlet (Fig. 1.4.1). A permanent record of the study, seen on the television monitor, is obtained using a videocassette recording device or a digital recording on a personal computer. Physicians' commentary during the study can be recorded, greatly facilitating the understanding of the study during later playback. Fluoroscopic screening time is generally limited to a total below 40s.

In a first step, bladder and sphincter function are completely evaluated urodynamically during the phases of bladder filling, storage, and voiding. Prior to instrumentation an initial uroflowmetry is performed. The urodynamic study comprises continuous monitoring of rectal pressure, sphincter electromyogram, total bladder pressure, and subtracted bladder pressure (detrusor pressure) during the bladder filling and storage phases. During voiding, the urinary flow rate is monitored.

In a second step the video-urodynamic study itself is performed. Fluoroscopic video-cystourethrography is performed intermittently during the filling and storage phases. Fluoroscopy of voiding demands that micturition be performed in the erect position in older children, and for this a simple funnel-shaped device to fit the female perineum is utilized.

Only when there are problems in catheterizing the bladder is suprapubic filling and pressure measuring performed. Otherwise a urethral approach is used.

Cases requiring video-urodynamic investigations are relatively infrequent in everyday radiologic and urologic practice. A need for video-urodynamic referral centers capable of performing such studies, however, exists.

According to our experience and that of others, VUD is the gold standard for investigating children with neurogenic bladder, where it is available, but it is only a second-step investigation in children with nonneurogenic bladder-sphincter dysfunction. VUD should be performed in cases where the VCU study is indistinct or when complex dysfunctional patterns can be expected from the modified VCU study (e.g., nonneurogenic neurogenic bladder dysfunction), which need comprehensive and complex management.

Conclusion

VUD is the combination of VCU with pressure/flow/electromyographic studies of the lower urinary tract. It is the gold standard for the assessment of children with neurogenic bladder. It is only a second-step study in children with nonneurogenic bladder-sphincter dysfunction.

R. Fotter, MD
Professor and Chairman, Department of Radiology, Head Division of Pediatric Radiology, University Hospital, Medical University Graz, Auenbruggerplatz 34, 8036 Graz, Austria

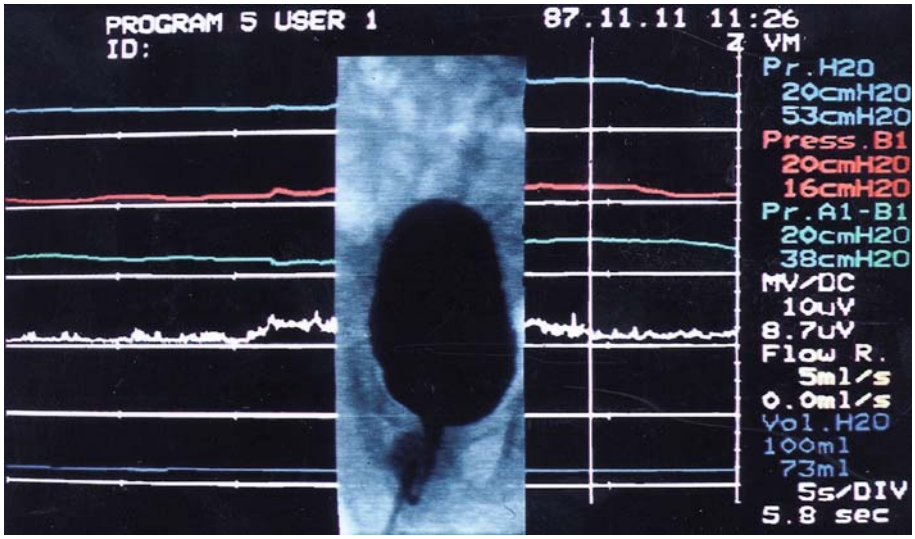

Fig. 1.4.1. Example of a video-urodynamic study. *Blue line* indicates total bladder pressure, *red line* rectal pressure, *green line* subtracted bladder pressure (detrusor pressure), *white line* electromyogram, *dark blue line* urinary flow. *Vertical white line* indicates time of fluoroscopic image

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Urinary Tract Embryology, Anatomy and Anatomical Variants

2

Gabriele Benz-Bohm

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2.1 Embryology

2.1.1 Development of the Kidneys and the Ureters

The normal embryonic development of the human kidney has been studied in detail (Potter 1972). Understanding this process is essential in the evaluation of the various structural malformations of the kidney.

G. Benz-Bohm, MD, Professor
Birresborner Strasse 40, 50935 Cologne, Germany
formerly
Department of Radiology, Division of Pediatric Radiology, University of Cologne, Kerpenerstrasse 62, 50924 Cologne, Germany

During development of the human kidney there are three successive ontogenetic stages: the pronephros, the mesonephros and the metanephros (Fig. 2.1). Although the pronephros and the mesonephros are transitory organs, they are essential for the development of the definitive kidney, the metanephros. All three systems are of mesodermal origin and develop from the nephrogenic cord.

Near the end of the 3rd week after conception, the pronephros begins to form. The proximal ends form nephrostomes, which open into the coelomic cavity, and the distal ends of successive tubules coalesce to form the pronephric ducts. The cephalic segments regress before the caudal parts form and all degenerate by the 5th week. The pronephros appears to be nonfunctional in humans, but is important in giving rise to the mesonephric ducts.

The mesonephros develops in the 4th week after conception, caudal to the last of the pronephric tubules. Whereas the pronephros is a cervical organ, the mesonephros is a thoracic organ. Each mesonephric unit consists of a glomerular structure, a proximal tubule segment that is secretory in nature, and a distal tubule segment that ends in the mesonephric duct. These represent the first true nephron units in renal development. In the female, most of the mesonephros regresses in the 3rd month of gestation with the epoophoron, the paroophoron, and Gartner's duct remaining as vestigial structures. In the male, the mesonephric tubules and the mesonephric duct continue to develop to form the excretory ducts of the male reproductive system.

The definitive kidney is the metanephros and has a dual origin. The glomeruli and tubules arise from a mesenchyme called metanephric blastema in the nephrogenic cord, caudal to the mesonephros. The excretory segments, including the collecting ducts, calyces, pelvis and ureter, develop from a branch of the mesonephric duct called the ureteric bud (Fig. 2.1). This structure arises during the 4th and

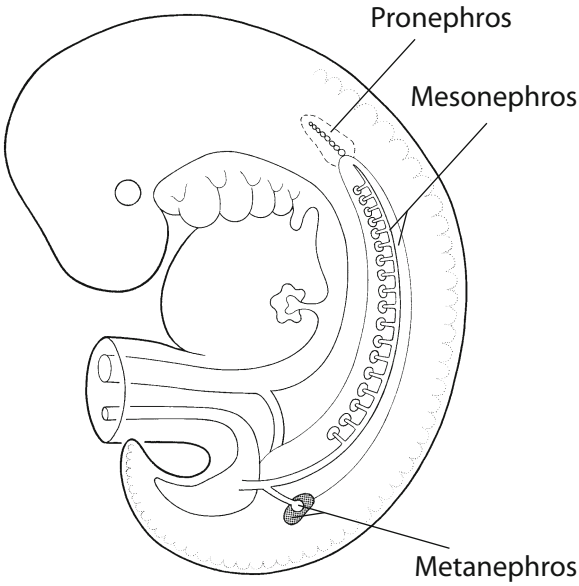


Fig. 2.1. Topography of the pronephros, mesonephros and metanephros

5th weeks and grows dorsally and cephalad until it contacts the nephrogenic cord. The metanephric blastema surrounds the dividing ureteric bud as a condensation of cells. Branches of the ureteric bud must come into contact with the metanephric blastema in order for the kidney to develop properly.

At 7–8 weeks, the first nephrons with well-developed glomeruli are formed from the metanephric blastema. The first three to five generations of branches of the ureteric bud form the renal pelvis. The terminal portions of the next generation of branches remain somewhat constricted and form the infundibula, which connect the calyces with the pelvis. The early calyces are formed at 10 weeks, and by 13–14 weeks the cup-like shape of the calyx is established. It has been estimated that the papillary collecting ducts are developed from the 7th to 11th generations from the original ureteric bud. Rapid branching continues with the formation of collecting tubules until about 14–15 weeks.

Nephron formation begins in about the 8th week in small foci of metanephric blastema adjacent to the ampulla of the ureteric bud. Approximately 1 million nephrons at different stages of maturation are present in the kidney at birth. Although maturation of the nephrons proceeds after birth, no new nephrons are formed. Growth in the kidney continues until adult life, mainly as a result of elongation of the proximal convoluted tubules and loops of Henle and an increase in the size of the interstitium.

The kidneys undergo cephalad migration from their site of origin. The ascent of the kidney occurs due to true migration and also secondary to differential somatic growth of the lumbar portion of the body. They reach their final level by the end of the 8th week of fetal life. During their ascent from the pelvis the kidneys normally undergo medial rotation of roughly 90° around their longitudinal axis before they assume their final position. During ascent, each kidney receives its blood supply from the neighboring vessels. Initially, this is from the middle sacral artery, then the common iliac and inferior mesenteric arteries, and finally the aorta (Clapp and Tisher 1989; Kissane 1983; Moore and Persaud 1998; Netter 1983).

Conclusion

The definitive kidney, the metanephros, has a dual mesoderm origin. The glomeruli and tubules arise from metanephric blastema, the excretory segments from the ureteric bud.

2.1.2 Development of the Urinary Bladder

The cloaca is divided by the urorectal septum into a dorsal rectum and a ventral urogenital sinus (Fig. 2.2). The urogenital sinus is divided into a cranial vesical part that is continuous with the allantois, a middle pelvic part, and a caudal phallic part that grows toward the genital tubercle. The pelvic part becomes the bladder neck and the prostatic part of the male urethra and the entire female urethra. The bladder develops mainly from the vesical part. The trigone region, however, is derived from the caudal ends of the mesonephric ducts. The allantois becomes a thick fibrous cord, the urachus. It extends from the apex of the bladder to the umbilicus. As the bladder enlarges, distal parts of the mesonephric ducts are incorporated into its posterior wall. As the mesonephric ducts are absorbed, the ureters come to open separately into the urinary bladder. The orifices of the ureters move superolaterally–partly by the ascent of the kidneys–and the ureters enter obliquely through the base of the bladder. The orifices of the mesonephric ducts move close together and enter the prostatic part of the urethra as their caudal ends become the ejaculatory ducts. In females, the distal end of the mesonephric ducts degenerate (Moore and Persaud 1998).

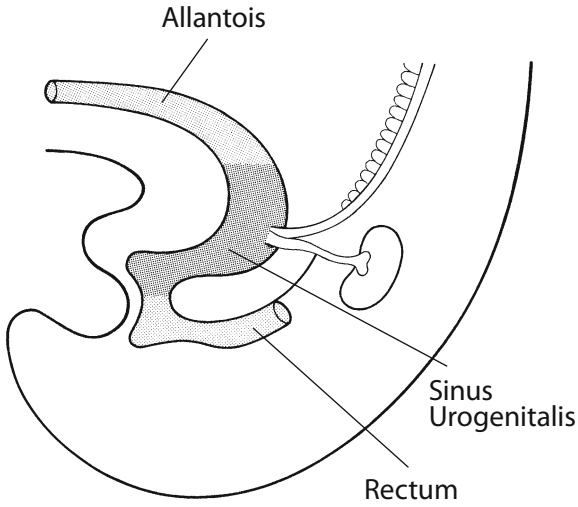


Fig. 2.2. Diagram of urogenital sinus, lateral view

Conclusion

The bladder develops mainly from the vesical part of the urogenital sinus. The trigone region is derived from the caudal end of the mesonephric ducts.

2.1.3 Development of the Urethra

The epithelium of most of the male urethra and the entire female urethra is derived from endoderm of the urogenital sinus. The distal part of the male urethra is derived from the glandular-urethral-plate. This ectodermal plate grows, becomes canalized, and joins the rest of the spongy urethra. Therefore, the epithelium of the terminal part of the urethra is derived from surface ectoderm. The connective tissue and smooth muscle of the urethra in both sexes is derived from the adjacent splanchnic mesenchyme (Moore and Persaud 1998).

Conclusion

The epithelium of most of the male urethra and the entire female urethra is derived from the endoderm of the urogenital sinus. The distal part of the male urethra is derived from an ectodermal plate, called the urethral plate.

2.2 Anatomy and Variants

2.2.1 The Kidneys

2.2.1.1 Position and Anatomical Relationship

The kidneys, bean-shaped organs situated in the retroperitoneum, extend from the 12th thoracic to the 3rd lumbar vertebra, with the right kidney usually slightly more caudal in position in approximately two-thirds of people. The difference in position relative to the spine usually corresponds to the height of one vertebral body (Currarino et al. 1993). The upper pole of each kidney is usually more medial and posterior than the lower pole. The hilum of each kidney is rotated anteriorly on the psoas major muscle, and there is posterior rotation of the convex lateral renal margin – best seen on CT or MRI – near the level of the second lumbar vertebra. The kidney is surrounded by a thin fibrous capsule that is adherent to the pelvis at the hilum, where the vessels pass in or out of the kidney. The posterior surface of the kidney is partly in contact with the diaphragm above the posterior costophrenic sinus. This anatomical relationship explains how a pleural effusion, for example at the level of the posterior costophrenic sinus above the diaphragm, may cause a downward displacement of the kidney, most often left, simulating an adrenal mass. Intraperitoneally, in front of the right kidney and the proximal descending duodenum, is a posterior extension of the infrahepatic recess termed the Morrison pouch, an important space for fluid collection.

The right kidney is slightly less mobile than the left. The degree of mobility usually corresponds to the height of one vertebral body.

2.2.1.2 Shape, Size and Measurement

In the newborn it is possible to recognize the lobes by the presence of grooves surrounding them on the subcapsular surface (Figs. 2.3, 2.4). As the kidney matures, the grooves tend to disappear. They are absent in most adult kidneys, but persistence of fetal lobulation is possible. Campbell (1970) found fetal lobulation at autopsy in 17.6% of children and in 3.9% of adults. It should be recognized as a variant

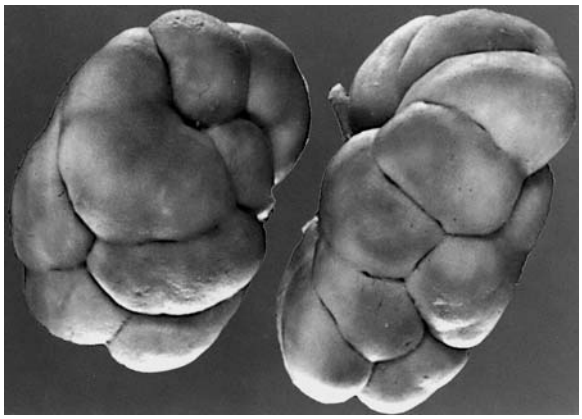


Fig. 2.3. Kidneys from a newborn showing characteristic fetal lobulation by grooves on the surface. Courtesy of the Department of Anatomy, University of Cologne

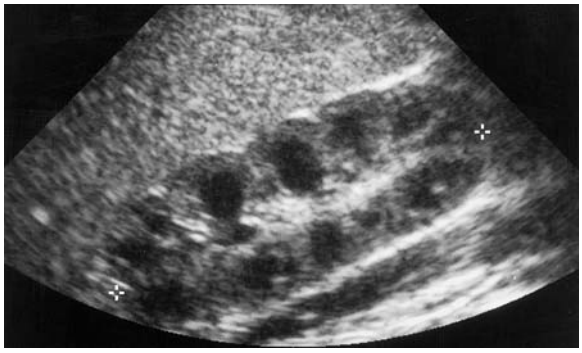


Fig. 2.4. Sonogram of a 2-month-old girl. Sagittal view of the right kidney. Typical sonographic appearance with increased cortical echogenicity, prominent, relatively anechoic pyramids, reduced dense central sinus echoes and grooves on the surface

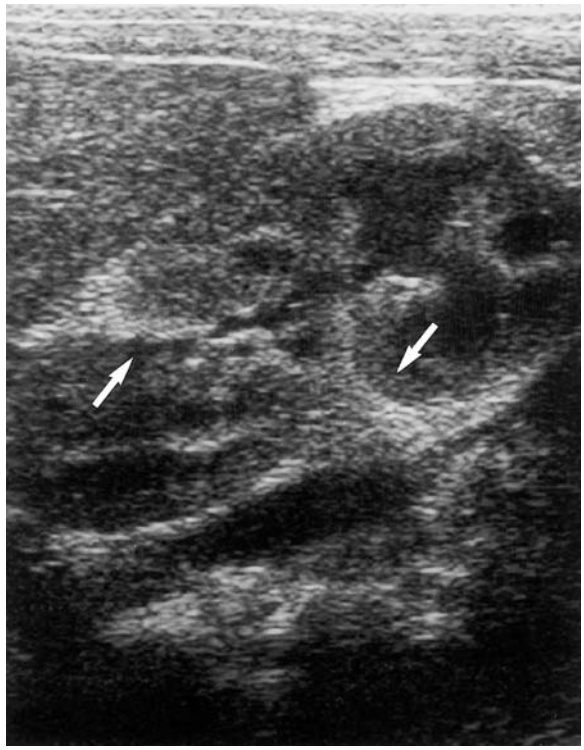


Fig. 2.5. Sonogram of a 9-day-old boy. Parasagittal view of the right kidney. Junctional parenchymal defect (*arrows*) with distinct delineation of superior and inferior renunculi

of normal renal form without clinical importance. Radiographically, this may appear as small notches in the renal margin placed midway between normal-appearing calyces. In contrast, cortical scars correspond to a calyx or group of calyces.

Related to the fetal lobulations is the junctional parenchymal defect (JPD) (Fig. 2.5). This defect consists of a thin triangular echogenic notch in the anterosuperior or posteroinferior aspect of the kidney mimicking a cortical scar. The finding is due to incomplete fusion of two embryonic parenchymatous masses – subkidneys – called renunculi or reniculi and is more common on the right (Yeh et al. 1992; Hoffer et al. 1985; Carter et al. 1985; Dalla Palma and Rossi 1982; Richter and Lierse 1990; Currarino et al. 1993). It is sometimes connected with the hilum of the kidney by an echogenic line called the interrenicular septum (Fig. 2.6) (Hoffer et al. 1985; Richter and Lierse 1990; Currarino et al. 1993).

In infants, the kidney is more rounded and relatively broader than in adults, and its poles are folded into a narrower renal sinus.

The weight and size of the kidney are proportional to body habitus. The two kidneys represent 1/80 and 1/240 of the total body weight in the newborn and in the adult, respectively (Olsson 1986). The left kidney tends to be slightly larger than the right, and the superior pole of each kidney is thicker and rounder than the inferior pole.

Compensatory hypertrophy following unilateral nephrectomy is usually complete within 2 years. Compensatory hypertrophy is more rapid in infants than in children or adults. In a congenitally solitary kidney or in a congenitally functionally solitary kidney, compensatory hypertrophy is not present at birth, but develops rapidly thereafter. Measurement can be made by US or on urographic supine films.

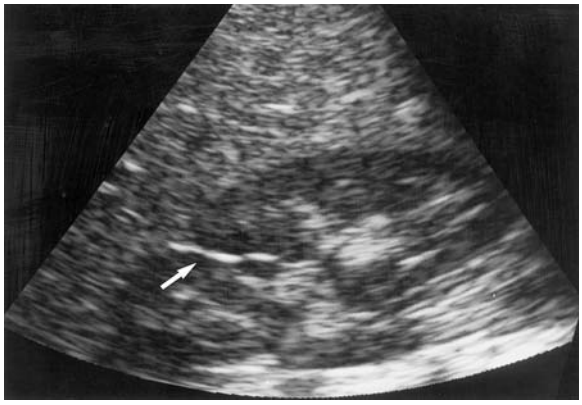


Fig. 2.6. Sonogram of a 10-year-old girl. Sagittal view of the right kidney. Interrenicular septum (*arrow*)

The length of the kidney corresponds to the height of the first four lumbar vertebral bodies with their three interspaces ±1 cm, except for the first 1.5 years of life. At this age the kidneys are relatively larger, corresponding to the height of 4.5 lumbar vertebral bodies, or five vertebral bodies in the newborn. The left kidney is slightly longer than the right. Duplex kidneys are also slightly longer than normal kidneys.

The width of the kidney is approximately 50% of the kidney length and is relatively greater in newborns than in older children. The kidney lengths obtained by US are generally slightly lower than those derived from the urographic films at all ages, being slightly less than 1 cm in the first 5 years and a little more than 1 cm afterwards. The most precise measurement by US is to estimate the kidney volume according to the formula:

$$V = L \times W \times AP \times 0.523$$

where L is the maximal length in longitudinal scan and W and AP are the maximal width and anteroposterior diameter in transverse section (Currarino et al. 1993). These volume standards are correlated with body weight (Deeg et al. 1997).

2.2.1.3 Internal Anatomy

A coronal section of the kidney reveals an outer zone, or cortex, and an inner zone, or medulla. The medulla is composed of 8–18 pyramids that terminate in the renal papillae at the level of the calices. Two or more pyramids may share the same papilla as confluent papillae. The cortex extends into the space between adjacent pyramids as the septa of Bertin. Each half of the septa of Bertin receives its blood supply from a separate artery and each half makes up the lateral margin of adjacent lobes. The septa of Bertin extend downward to the renal sinus, into which they project as ridges. It is along these ridges that the interlobar arteries are arranged. The pyramid with its surrounding cortex makes up a lobe. There are 14 lobes or more per kidney. In the mid-zone of the kidney, the lobes are simple and conform to the description already given, but at the poles they tend to be fused and complex (Fig. 2.7) (Hodson 1978). In these areas, the septa of Bertin project downward for only short distances. The papillae at the poles may also share in this fusion, and a compound papilla may drain as many as three once-separate lobes. This is the type of papilla that allows urine to reflux up (Fig. 2.8) (Ransley 1977; Ransley and Risdon 1975). There are faint striations in the cortex, which are referred to as the medullary rays. They contain the collecting tubules, the thick ascending limbs and the terminal straight parts of the proximal convoluted tubule. The cortex is made up of glomeruli and a large number of tubules, mainly proximal and distal convoluted segments. The medulla is made up of two zones: the inner zone, which is synonymous with the papilla and contains collecting ducts, thin limbs, loops of Henle and vasa recta, and the outer zone, which is made up of the outer and inner stripes. The main component of the outer stripe is the terminal straight part of the proximal convoluted tubules, while the main constituents of the inner stripe are thick ascending limbs and collecting tubules (Fig. 2.9) (Madsen and Tisher 1986).

The specific structural and functional unit of the kidney is the nephron. The nephron consists of the Malpighian corpuscle, glomerulus and Bowman's capsule, connected to an elongated tubule component composed of the proximal tubule, the thin limbs and the distal convoluted tubule. A transitional segment, the connecting tubules, joins the nephron to the collecting duct system.

The cortex and medulla are relatively hypoechoic and are not clearly differentiated by US, except in newborns and infants (see Sect. 2.2.1.5). They are generally well differentiated by MRI and contrast-enhanced CT. They cannot be differentiated by excretory urography, although stasis of contrast material in the pyramids can be detected in some cases.

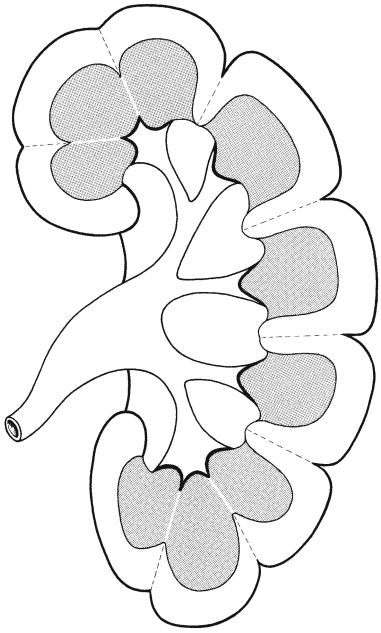


Fig. 2.7. Diagram of lobar architecture in the kidney. In the mid-zone the septa of Bertin reach down to the renal sinus. In the polar regions they are smaller, due to pyramidal fusion

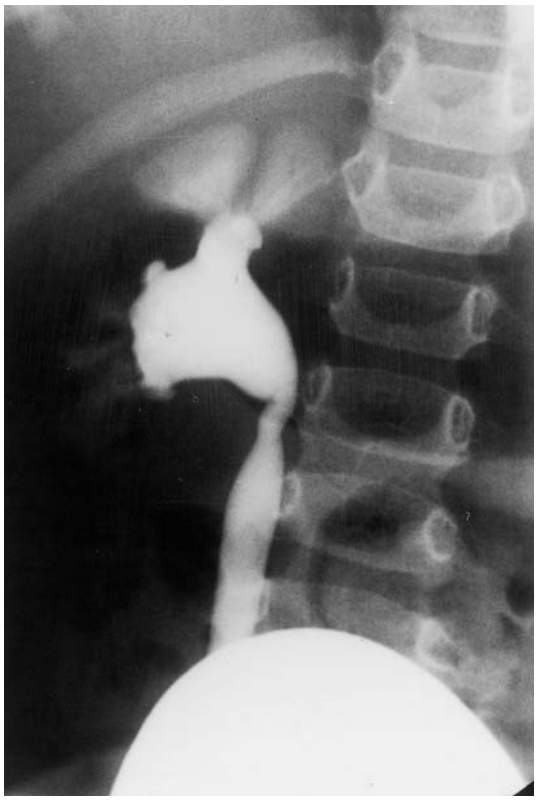


Fig. 2.8. VCU in a 2-year-old girl. Intrarenal reflux predominantly at the upper pole

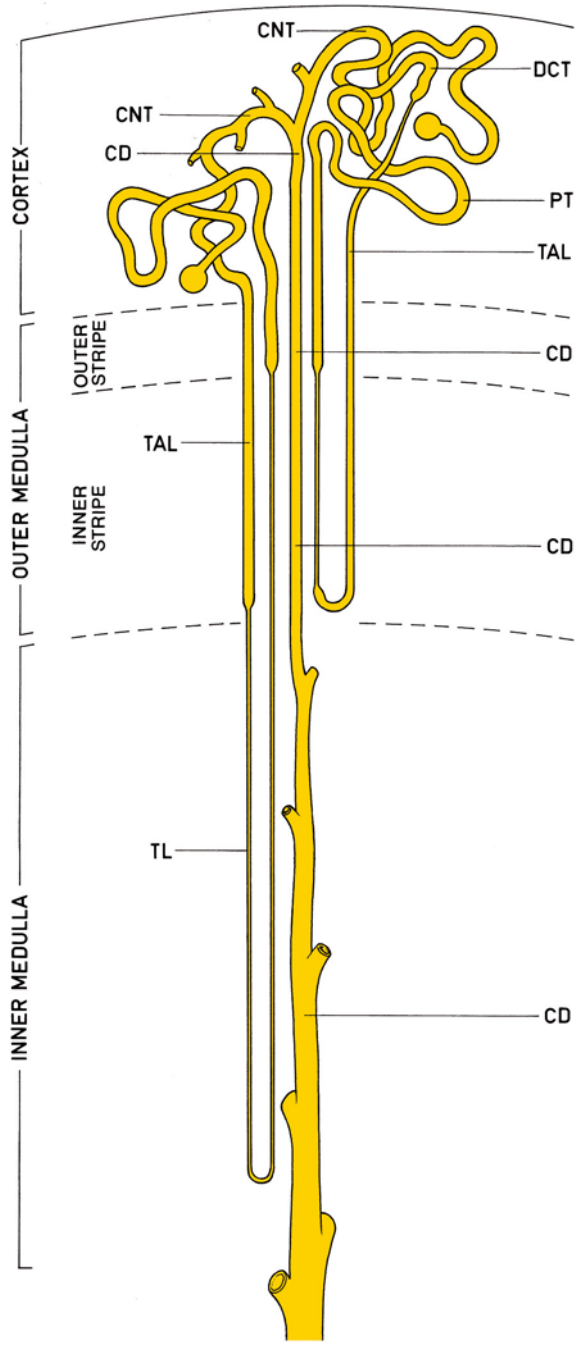


Fig. 2.9. Diagram of the structural organization of the kidney and its relationships to the zones of the kidney. *CD*, collecting duct; *CNT*, connecting tubule; *DCT*, distal convoluted tubule; *PT*, proximal tubule; *TAL*, thick ascending limb; *TL*, thin limb of Henle's loop

2.2.1.4 Blood Supply

For purposes of its vascular supply, each kidney is regarded as made up of five segments: the apical, upper, middle, lower and posterior segments. Each of these is supplied by a segmental artery (Fig. 2.10) (Graves 1954). The main renal artery, as a rule, divides into anterior and posterior parts in the hilum, one passing in front of the pelvis and the other behind. The anterior part generally divides into three segmental branches, the upper, the middle and the lower, to supply the corresponding segments. The posterior part continues backward before giving rise to several branches that supply the posterior segment. The apical segment has a variable blood supply, but the artery usually takes its origin from the proximal part of the upper segmental artery. A common variant is an accessory polar artery that arises in the middle portion of the main renal artery. The kidney may receive aberrant arteries originating from the superior mesenteric, suprarenal, testicular or ovarian arteries. There is no evidence of collateral circulation between these segmental arteries; therefore, ligation of a segmental artery in the belief that it is an accessory vessel will lead to necrosis of the corresponding segment (Clapp and Tisher 1989). The intrarenal veins do not follow a segmental arrangement, and there are free anastomoses of the veins throughout the kidney.

The segmental arteries divide several times, finally forming interlobar arteries, which enter the kidney parenchyma between adjacent renal lobes. They extend forward to the cortex on either side of a renal pyramid. At the junction between the cortex and medulla, the interlobar arteries divide dichotomously into arcuate arteries, which follow a curved course between the cortex and medulla. The arcuate arteries undergo several further divisions. From each of these branches a series of interlobular arteries arise, which finally ascend radially through the cortex. Most of the interlobular arteries terminate within the cortex. Only about five in each kidney, called perforating arteries, reach the surface of the kidney, where they may anastomose with capsular branches derived from the inferior suprarenal, renal and gonadal arteries (Fig. 2.11) (Netter 1983).

The intrarenal veins accompany the arteries. There are two types of interlobular veins draining the cortex. One type originates at the surface of the kidney as stellate veins draining the most superficial parts of the renal cortex. Most interlobular veins are of the second type, which originates in the cortex as a result of the joining of venules from the peritubular plexus. Both types accompany interlobular arteries

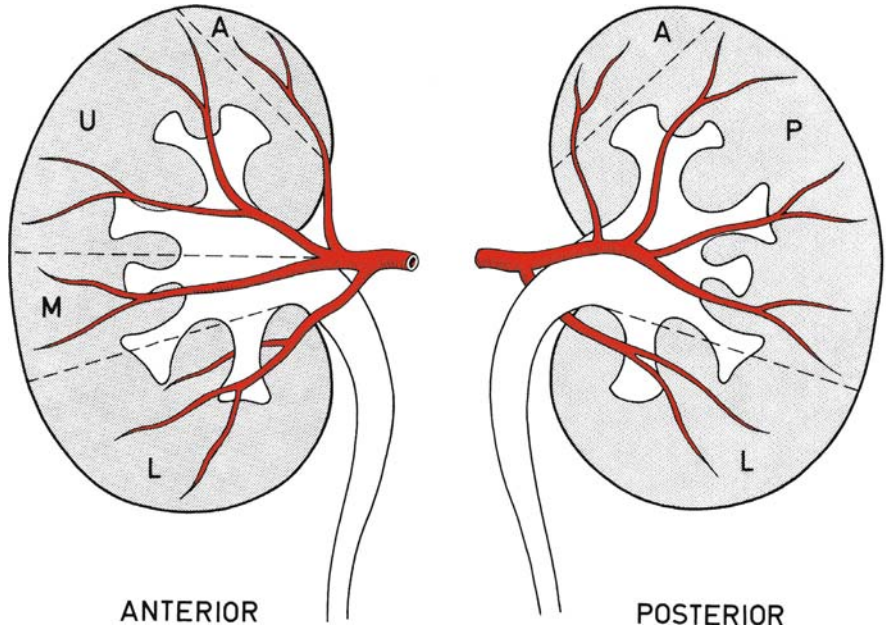


Fig. 2.10. Diagram of the vascular supply of the kidney. Apical (*A*), lower (*L*), middle (*M*), posterior (*P*), upper (U) segment and segmental branches of the main renal artery

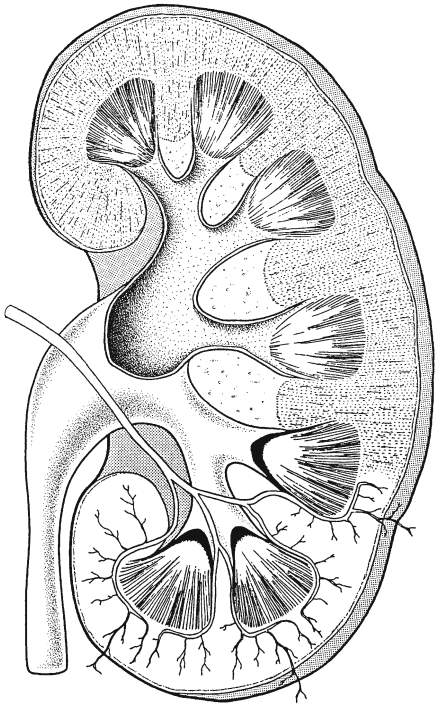


Fig. 2.11. Cut surface of the right kidney in different levels. The lower half with arteria renalis and its branches

and drain in arcuate veins. The arcuate veins join to form interlobar veins. These finally form several veins that join in a simple renal vein (Clapp and Tisher 1989; Heptinstall 1983; Lemley and Kriz 1989).

2.2.1.5 Neonatal Kidney by Ultrasonography

Ultrasonograms of the neonatal kidney are characterized by typical findings (Fig. 2.4):

- The increased cortical echogenicity: the echogenicity is equal to that of the adjacent liver and spleen.
- The medullary pyramids are prominent and relatively anechoic.
- Central sinus echoes are absent or reduced.
- Grooves are on the surface.

Morphometric study provides an anatomic basis for understanding this sonographic appearance (Hricak et al. 1983; Dunnill and Halley 1973; McRory 1978).

- Glomeruli occupy proportionally a much greater volume of the renal cortex during the first 2 months of life than at any later time. The number of glomeruli reaches a maximum at 36 gestational weeks. In the normal kidney, the number of nephrons remains constant from 36 weeks of gestational age to 40 years of age. In the neonatal period, the glomeruli occupy 18% of the volume of the cortex as compared with the mean volume of 8.9% in the adult kidney. Furthermore, in mature neonates, 20% of the loops of Henle are still present within the cortex of the kidney at birth.
- In the neonate the medulla occupies a proportionally larger corticomedullary volume than it does later in life. The hypoechoic appearance of the medulla might also be a relative impression secondary to increased cortical echogenicity.
- A lack or paucity of adipose tissue as determined at gross and microscopic inspection would readily explain the absent or reduced dense central sinus echoes.
- The fetal lobulation is still present.

This sonographic appearance of the neonatal kidney can be seen up to the age of 6 months. By 7 months, the renal parenchyma shows the adult pattern. The central sinus echoes gradually increase with age, and a high-intensity adult pattern is seen in most teenagers (Han and Babcock 1985).

Conclusion

The junctional parenchymal defect should not be mistaken for a renal scar. The segmental arteries have no collateral circulation. The sonographic appearance of the kidneys for the first 6 months differs from that later in life.

2.2.2 The Pelvicalyceal System and the Ureters

The renal pelvis varies in size. The pelvis may lie entirely within the renal sinus–intrarenal pelvis–or almost entirely outside it–extrarenal pelvis. In newborns and small infants, the pelvis is often small and intrarenal and usually points medially instead of downward.

There is a great variation in the configuration of the pelvicalyceal system. The ureteropelvic junction (UPJ) is sometimes sharply defined, sometimes difficult to localize. Filling defects or narrowing at the UPJ without hydronephrosis due to transient contractions or mild, insignificant stenoses are

common findings. A persistence of normal fetal characteristics is sometimes encountered in unobstructed ureters of newborns and infants as mild ureteral elongation and tortuosity, mild widening of the mid-ureter and short kinks or intraluminal mucosal folds in the proximal ureter.

The ureters in children may be highly mobile and can be displaced by distended bowel loops. Because of continuous peristaltic activity, a normal ureter is not commonly seen in its entirety on a single urographic film. The ureter courses within the bladder wall through the bladder musculature and then submucosally to end in the corner of the trigone (Currarino et al. 1993).

2.2.3 The Urinary Bladder

The bladder is divided into the vertex, body and fundus. The trigone is the posterior aspect of the bladder base. This triangular space is formed by the two ureteral orifices superolaterally and by the internal urethral meatus inferiorly in the midline. The trigonal or interureteral ridge, the transverse ridge between the two ureteral orifices, may produce a transverse linear defect in the frontal projection when the bladder is incompletely filled with contrast material.

An incompletely filled bladder in infants occasionally shows a transient unilateral or bilateral herniation of its inferolateral wall into a dilated internal inguinal ring. These bladder "ears" disappear when the bladder is fully distended.

In infants and children the urinary bladder, even when empty, is in the abdomen. It begins to enter the greater pelvis at about 6 years of age, but it does not enter the lesser pelvis and become a pelvic organ until after puberty (Moore 1992).

The bladder neck is the poorly delineated junction between the bladder and urethra at the level of the internal urethral sphincter. At the beginning of voiding the bladder floor descends and becomes funnel-shaped and in continuity with the proximal urethra. At the end of voiding, the bladder base ascends to its normal position. A wide bladder neck and a dilated proximal urethra during voiding (wide bladder neck anomaly and spinning top urethra, respectively) are variants that will be discussed in Chapter 14 on nonneurogenic bladder-sphincter dysfunction (functional disorders of the lower urinary tract).

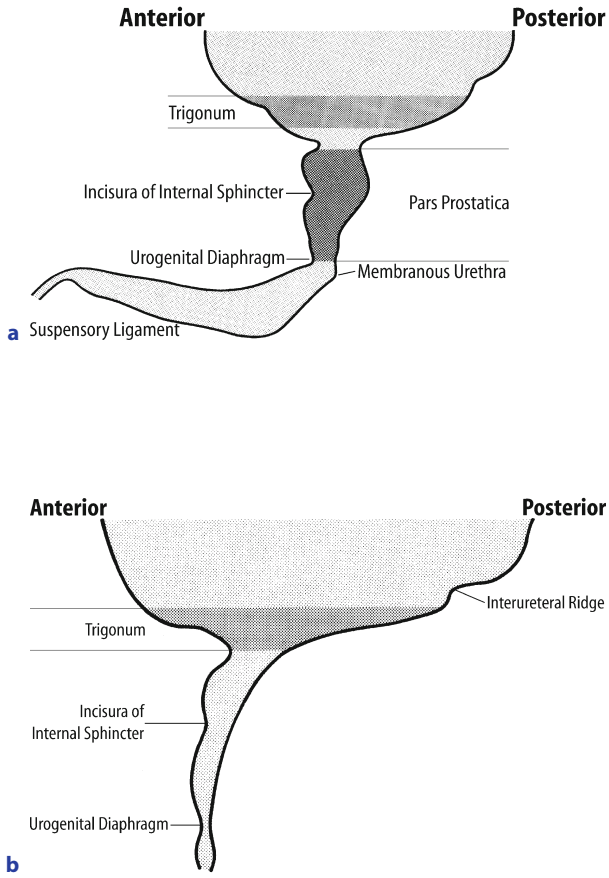
Conclusion

The bladder begins to descend from the abdomen into the pelvis major at about 6 years of age.

2.2.4 The Male Urethra

The male urethra is divided into a posterior and an anterior segment (Fig. 2.12a) (Allen 1970). The posterior urethra is the prostatic urethra, extending from the bladder neck to and through the urogenital diaphragm. This part is surrounded by the prostate and lower by the external urethral sphincter. In the posterior urethra, there are a number of anatomical landmarks: (1) The verumontanum is an oval swelling of approximately 0.5 cm in length. (2) Inferiorly, two thin folds, or fins, can encircle the urethra, completely simulating mild posterior urethral valves. (3) A thin horizontal mucosal fold in the anterior wall of the urethra opposite the verumontanum is called the incisura (Fig. 2.13). (4) At the apex of the verumontanum, a small diverticulum of the urethra corresponds to the prostatic utricle. (5) Numerous openings of the prostatic ducts are on the wall of the posterior urethra; sometimes contrast material refluxes into the prostatic ducts without distal urethral obstruction. (6) Slightly below there are the openings of the two ejaculatory ducts; sometimes reflux also occurs here without a known cause. (7) The urogenital diaphragm normally causes a circumferential narrowing at the distal end of the posterior urethra (Fig. 2.14). Beyond this narrowing is the membranous urethra, a poorly defined zone, tending to be less distensible than the more dilated bulbous portion below it.

The anterior urethra is the cavernous or spongy urethra, divided by the suspensory ligament of the penis into a proximal, bulbar urethra and a distal, pendulous or penile urethra. On the floor of the bulbar urethra are the two openings of the ducts of the Cowper glands. Reflux into these openings during voiding cystourethrography (VCU) in normal children is possible (Fig. 2.14). Throughout the anterior urethra are numerous openings of the urethral glands of Littré and the lacunae of Morgagni, seldom seen radiographically. During VCU in uncircumcised patients, contrast material may accumulate between the glans penis and the prepuce with a typical radiographic pattern.



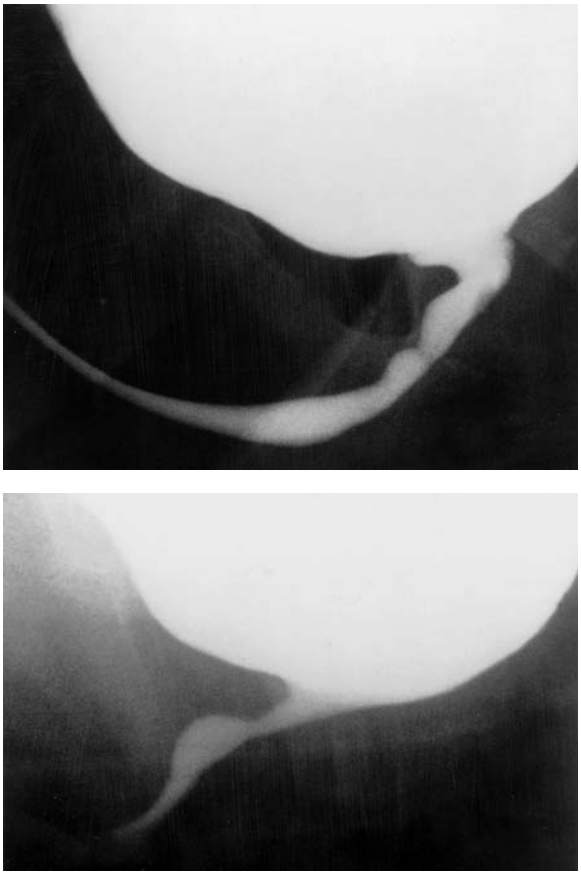


Fig. 2.12a,b. Diagram of urethrogram and urethrogram showing landmarks of normal structures. **a** Male, **b** female

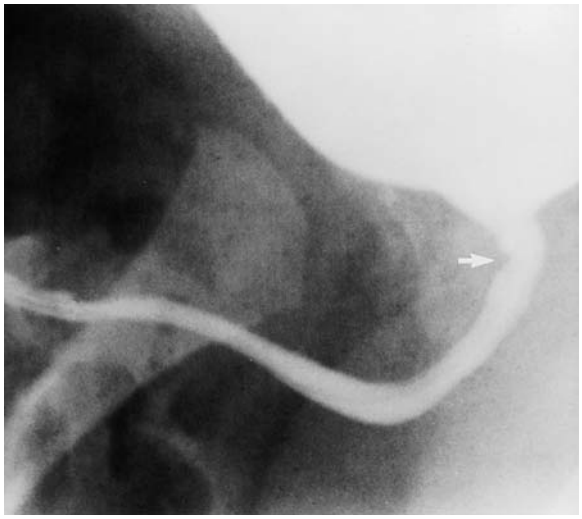


Fig. 2.13. VCU in an 8-week-old boy with a normal urethra. The incisura (*arrow*) in the anterior wall is a common anatomical variant

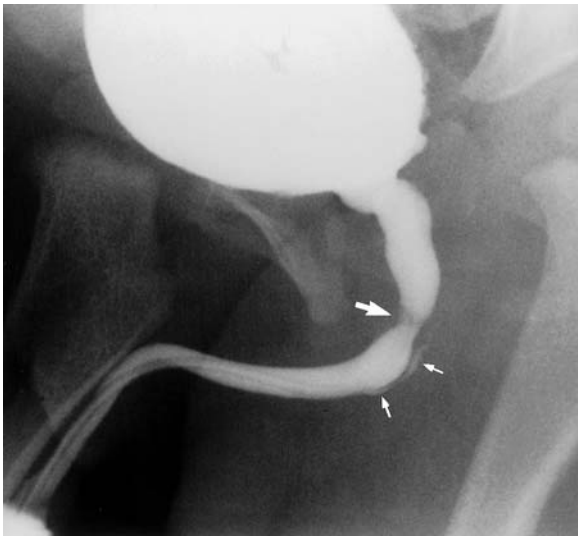


Fig. 2.14. VCU in a 2-year-old boy with a normal urethra. The slight narrowing (*large arrow*) at the junction between the posterior and the anterior urethra corresponds to the urogenital diaphragm. The duct of one Cowper gland is visualized by reflux (*double arrow*)

2.2.5 The Female Urethra

A diagram of the female urethra is shown in Fig. 2.12b (Allen 1970). The female urethra has many variations in its normal appearance, depending on the degree of relaxation of the external urethral sphincter and musculature of the pelvic floor during micturition. Influx of contrast material into the vagina during micturition is a very frequent finding without significance (Fig. 2.15) (Allen 1970; Currarino et al. 1993).

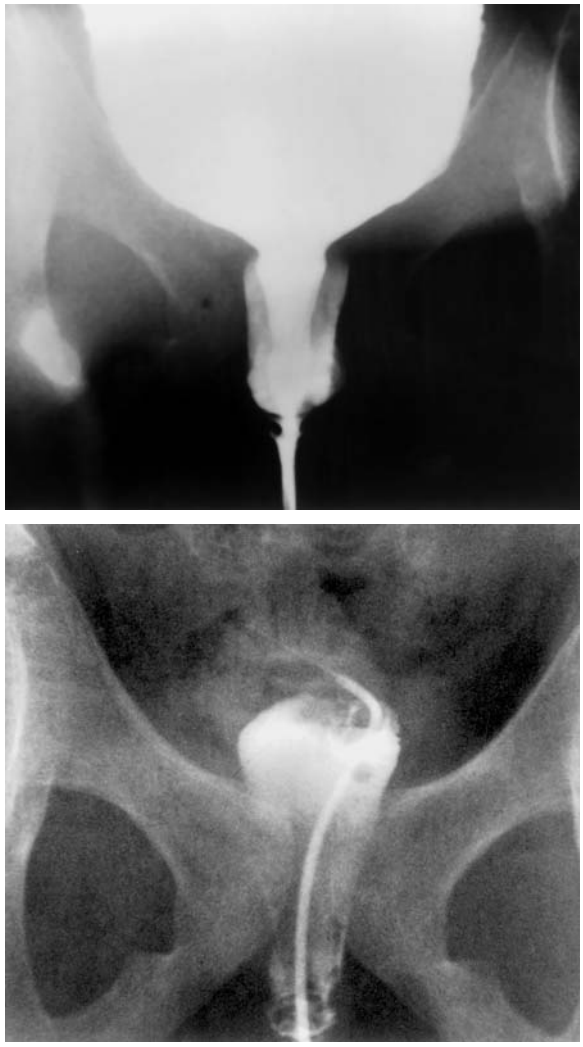


Fig. 2.15a,b. VCU in a 9-year-old-girl. **a** Influx of contrast material into the vagina during micturition. **b** Vaginogram after micturition

Conclusion

The normal male urethra shows variations in caliber in the different segments. The female urethra varies in appearance in VCUs.

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Genetics in Nephrourology

3

Klaus Zerres and Sabine Rudnik-Schöneborn

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K. Zerres, MD
Professor and Chair, Institut für Humangenetik der RWTH Aachen, Pauwelstrasse 30, 52074 Aachen, Germany
S. Rudnik-Schöneborn, MD
Senior Lecturer, Institut für Humangenetik der RWTH Aachen, Pauwelstrasse 30, 52074 Aachen, Germany

3.1 Introduction

Due to the great number of disorders of the urinary tract and the increasing knowledge about the genetics during the last decades, a comprehensive and complete review on hereditary diseases in nephrology and urology is not possible. Enormous efforts have been spent to disclose the underlying basic defects. Very many nephropathies are hereditary and are subject of comprehensive research worldwide. An example for the progress in research is autosomal dominant polycystic kidney disease (ADPKD) but in many other diseases the history can be written in a similar way. With an incidence of about 1:1,000 ADPKD is one of the most common hereditary disorders at all. The first gene was mapped on chromosome 16 in 1985 and identified

in 1994. Including the knowledge of other cystic diseases, experimental in vitro research as well and data of numerous animal models, a common pathogenetic theory of cystogenesis allowed the first causal therapeutic trials within the last years. Much progress in research can be expected within the next years.

Typical steps on the way to the understanding of the pathogenesis or even suggestions for a rational gene therapy in a future vision are: (1) Mapping the gene, e.g. localizing it on one of the possible chromosomes. (2) Cloning the gene, which means disclosing its structure. (3) Analyzing mutations and their clinical consequences (genotype/phenotype correlations). (4) Studying the gene product, protein structure and function. (5) First therapeutic trials based on the understanding of the pathogenesis. It should be kept in mind, however, that even a specific mutation does usually not allow to predict a certain phenotype since specific consequences are often influenced by other genes or exogenous factors acting as modifiers.

The aim of this contribution is to summarize important information on the genetics of urological and nephrological disorders and to describe the current possibilities and limitations in the diagnosis of hereditary renal disorders by use of DNA techniques. Because of the complexity of the topic, some major principles will be outlined.

3.2 Formal Genetics

Many hereditary diseases follow defined modes of inheritance and are caused by mutations in single genes. Gene carriers usually present clinical features according to the modes of inheritance. The clinical picture is often variable which is denoted by the term *variable expressivity*. The related term *incomplete penetrance* describes the fact that not all gene carriers present clinical features. Multifactorial diseases usually have a genetic basis, which is most often polygenic. Exogenous factors, most often unknown, are necessary to lead to a clinical manifestation of the disorder. Recurrence risks in this group are usually given on an empirical basis. The characteristics of the different modes of inheritance are given in Table 3.1. For more details see textbooks of human genetics.

3.3 Molecular Genetics

3.3.1 Inherited Disorders with Localized Genes which have not yet been Identified

With a clinically proven diagnosis in at least one affected family member, a linkage analysis principally allows to predict the disease status at any time in a person at risk without clinical evidence of the disease. Figure 3.1 illustrates the principles of indirect genotype analysis. Because linkage studies are based on indirect conclusion without knowledge about the responsible mutation itself, this method has major limitations. The most important ones are:

3.3.1.1 Exact Clinical Diagnosis in an Affected Family Member is Necessary

It is a widespread misunderstanding that the knowledge of the localization of a gene allows to establish a diagnosis in a single patient with an unclear condition. Linkage studies are resulting in a conclusion about the risk status in persons belonging to a family where specific markers are known to segregate with a disease mutation (Fig. 3.1). In several cases, however, a linkage analysis does allow exclusion of a certain gene to be involved in this specific family, e.g. in case affected and non-affected family members share the same haplotype. If affected subjects share identical haplotypes and do not with non-affected relatives, the conclusion can only be that the results are compatible with linkage to a certain region. In families with a small number of relatives, this conclusion does not prove the involvement of a certain gene in the specific family.

3.3.1.2 Genetic Heterogeneity can Lead to False Results

Genetic heterogeneity of a condition (different genetic entities which usually can phenotypically not be distinguished) can lead to misinterpretation. An impressive example is Alport syndrome with at least three different gene loci. It is estimated that about 80–85% of families follow an X-linked mode of inheritance, however, autosomal modes of inheritance exist. Indirect genotype analysis can lead to

Table 3.1. Characteristics of common modes of inheritance

Mode of inheritance	Characteristics
Autosomal dominant	Usually further first degree family members are affected. In severe diseases spontaneous mutations might occur. The clinical picture is often variable (variable expressivity) and sometimes not evident at all (incomplete penetrance). Risk to children depending on the penetrance up to 50%, usually regardless of gender. Often late onset diseases. Predictive testing in case of known gene and identified mutation possible.
Autosomal recessive	Mostly single patients, siblings affected, generally no further affected family members in other branches. Both parents are gene carriers (heterozygous). Risk for siblings 25%, risk for children usually low (<1%) except in case of parental consanguinity. Clinical picture often severe and similar in siblings. Heterozygosity testing in case of known gene defects generally possible.
X-linked recessive	Usually only boys/males affected, females only rarely and often milder. If mother is a carrier, recurrence risk to affected brothers is 50%, 50% of sisters are carriers. Risk to children of affected males: none, all daughters are gene carriers. About 1/3 of cases of severe diseases represent new mutations in the maternal germ line. Genetic testing in case of known genes possible.
Multifactorial	The genetic basis is often polygenic (involvement of several, mostly unknown genes) in addition to exogenous factors. Risk figures are similar for first degree relatives (siblings, children). They are usually lower than those in monogenic disorders and range between 2 and 10%. The risk increases usually with an increasing number of affected family members and sometimes with the severity of the disease. For more distant family members small risk figures are barely exceeding population risks. Genetic tests are usually not available.

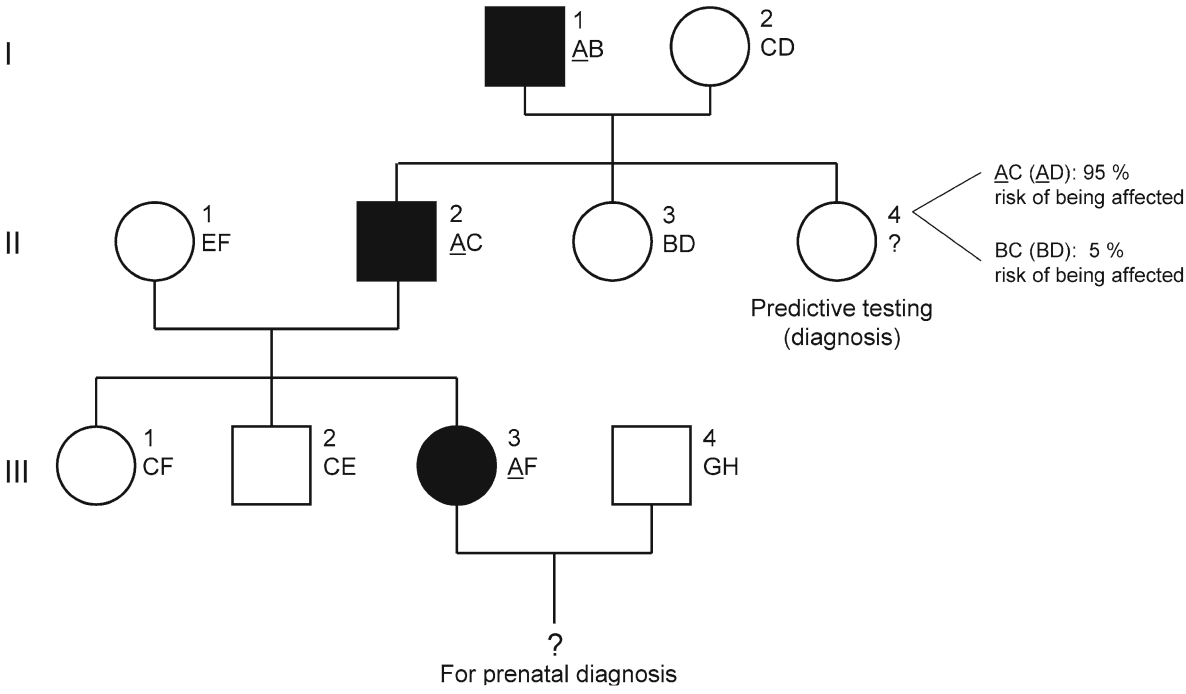

Fig. 3.1. Principle of linkage analysis. A closely linked marker has been analyzed in the family. In accordance with autosomal dominant inheritance the risk of transmitting the responsible mutation is statistically 50%. The diagnosis of an autosomal dominant inherited disease has been made in patient I,1, who transmitted the gene to his son II,2 but not to his daughter II,3, who is not affected. With the knowledge of the marker constellation of the non-affected mother I,2, it can be concluded that the disease is linked with the allele A. In II,4 a predictive diagnosis can be made in presence of marker allele A with a reliability of 95%, in case the marker has a genetic distance of about 5 centiMorgan (cM). If the paternal allele B is present, the risk of being a gene carrier is small (5%). The risk of a misinterpretation is much smaller in those families where closer markers can be used. In the couple III,3 and III,4 principally a prenatal diagnosis can be performed. The fetus carries a high risk (95%) if marker A is transmitted from the mother, in case of transmitting the allele F, the fetus most likely will not be gene carrier

false results under the assumption of the wrong gene locus. Other examples of genetic heterogeneity without clinical difference in single patients are ADPKD, nephrogenic diabetes insipidus and juvenile nephronophthisis. Among the more complex diseases with kidney involvement are tuberous sclerosis, and Bardet-Biedl syndrome with 12 known genes. In small families, a certain localization can neither be proven nor be excluded.

3.3.1.3 The Family has to be Informative

Depending on the individual marker constellation, there can be situations where it might not be possible to identify the at risk haplotype in a family. With the use of a set of flanking or even intragenic and highly polymorphic DNA markers, the majority of families in most nephropathies with known gene loci are informative, allowing to disclose the haplotype at risk. In case of a recombination between the analysed flanking markers, however, a risk estimation can be impossible as well (Fig. 3.2).

3.3.2 Conditions with Known Gene Defects

The situation in conditions where the gene defect is known differs in many aspects from those where only the localization is known. The identification of the responsible mutation in principle does allow a definite diagnosis of the condition without a further investigation or clinical examination. The detection of the mutation in Alport disease for example can replace further clinical or family evaluation. The same applies to the metabolic defects underlying some inherited causes of nephrolithiasis. But even in diseases where a gene is identified, specific problems can limit the practical application:

3.3.2.1 Genetic Complexity of Genes

The structure of many genes is very complex, in a certain percentage of cases it is difficult or even impossible to find the responsible mutation. In X-linked Alport syndrome, for example, more than

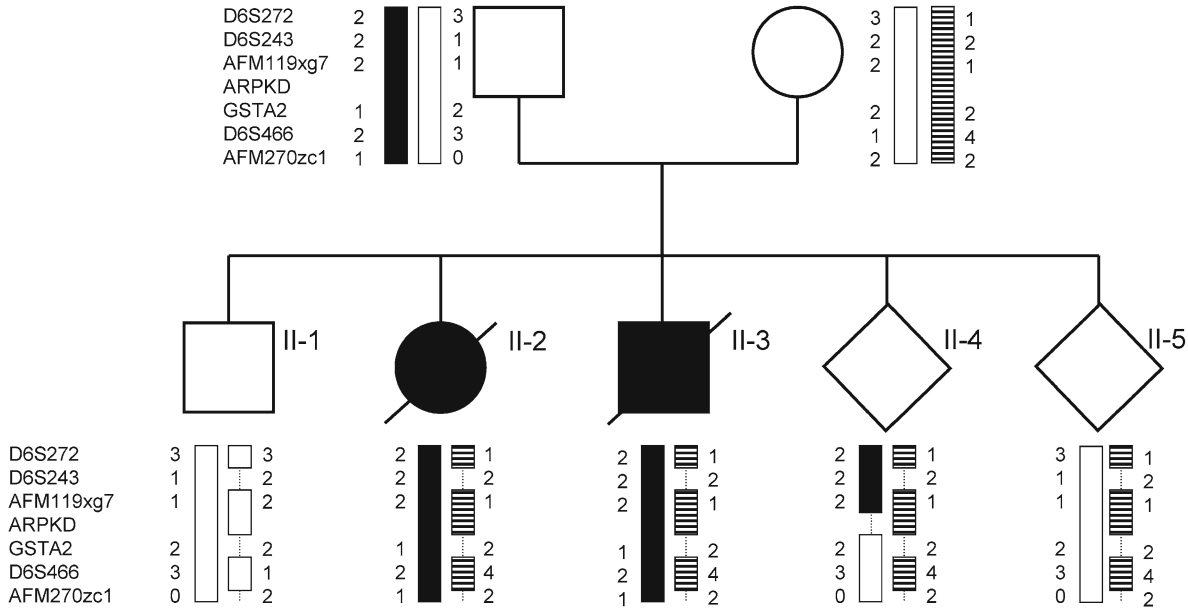

Fig. 3.2. Prenatal diagnosis by means of linkage analysis in a family with autosomal recessive polycystic kidney disease (ARPKD). The diagnosis has been made in the two deceased children II,2 and II,3 pathoanatomically. Both parents demonstrate no renal abnormalities in ultrasound. The haplotypes (chromosomal region) from each individual are shown. The analysis of II,2 and II,3 indicates that the responsible mutations of the disease gene are located on the *black* (paternal) and *hatched* (maternal) haplotypes. The analyzed material of pregnancy II,4 (after chorionic villus biopsy) showed the same maternal haplotype like the affected children indicating that the mother has transmitted the mutation. Between the close flanking markers of the paternal haplotype, however, a recombination took place which did not allow to decide whether the fetus will be affected or not. The fetus II,5 has inherited the affected maternal and the unaffected paternal haplotypes. The fetus therefore will be most likely heterozygous but healthy. The *dotted parts* indicate that these regions are not informative because the mother shows identical alleles for three markers (D6S243, GSTA2 and AFM270)

300 different mutations have been described so far. Another example is ADPKD with the extremely complex PKD1 gene consisting of 46 exons and the existence of many polymorphisms which can be difficult to interpret with regard to their character. As a result some have been classified as "variants of unknown significance". In many diseases DNA mutation analysis is far from being a routine diagnostic method.

3.3.2.2 Genetic Heterogeneity

Similar to the situation in indirect genotype analysis, the detection of a specific mutation can be impossible in case of the existence of more than one gene. Examples have been mentioned above. If a patient turns out to be negative upon mutation analysis of one gene, no diagnostic conclusions can be drawn. However, in patients where a disease causing mutation has been identified in a specific gene, the diagnosis can be clearly established. This information can be used for further family members e.g. predictive testing, heterozygosity testing or even to establish a diagnosis.

3.3.2.3 Genotype-Phenotype Correlation

Another important question which is often forwarded to the medical geneticist is whether the identification of a mutation can predict the individual clinical course. There are diseases where a rough correlation between the type or localization of a mutation and the clinical phenotype exists, often, however, an individual prediction is impossible. A recently described example is again ADPKD with an unusual early manifestation in a child where all family members, including those with a mild onset in adulthood, share the same mutation. It is still unknown which other genetic or non genetic factors may influence the severity of the disease.

3.3.3 Genetic Counseling

Genetic counseling before applying an indirect genotype analysis is essential. According to several guidelines of the German Society for Human Genetics and the Medical Board of Geneticists in Germany, possible limitations of DNA analysis and its consequences should be discussed with the family. Similar guidelines exist in other countries. There are different practical implications of a genotype analysis. The following problems should be mentioned:

3.3.3.1 Prenatal Diagnosis

To demonstrate one of the most important applications of an indirect genotype analysis, one example of a prenatal diagnosis in autosomal recessive polycystic kidney disease (ARPKD) is shown in Figure 3.2. Prenatal prediction is in most cases limited to severe autosomal recessive or X-linked conditions. There is only exceptionally a request for prenatal diagnosis in autosomal dominant conditions. This observation is in accordance with the experience in other autosomal dominant diseases (e.g., Huntington disease, tuberous sclerosis, neurofibromatosis, breast cancer). One reason might be the fact that, given an affected parent, the decision to terminate a pregnancy statistically in 50% of cases is obviously unacceptable. The question of terminating a pregnancy, which is connected with a prenatal diagnosis when early treatment is not available, is always an important issue which has to be discussed in detail with the parents before planning the pregnancy.

3.3.3.2 Predictive Testing

The principle is to predict whether a person in a family with a known inherited disease is most likely a gene carrier and will develop the disease in future, while there are no clinical symptoms when tested. Although in many late onset diseases no prevention is available, the knowledge of a person at risk to be gene carrier can be of importance. Predictive testing differs from any conventional diagnosis and evaluation of clinical symptoms. Predictive testing has enormous consequences for persons at risk. Different aspects have to be discussed with the persons who want to undergo predictive testing. Insurance and occupational problems are only some of the aspects which have to be considered.

Predictive testing in children should be limited to situations when the diagnosis is of any benefit during childhood, e.g. in diseases where a specific preclinical therapy is available. In the majority of diseases this is not the case and a routine clinical examination is sufficient. As soon as there are clinical signs

of the disease, the child than can be regarded as a patient and should be taken under medical care. In late onset diseases, the decision for a genetic testing should be made by the individual at risk.

3.3.3.3 Evaluation of Unspecific Symptoms in Individuals at Risk to Develop a Hereditary Disorder

Especially in late onset diseases, it is sometimes difficult to decide whether non specific symptoms may indicate the beginning of an inherited disorder. An example can be hypertension or the prevalence of "simple" cysts in an individual at risk for ADPKD. In these cases a genotype analysis can give further information whether these symptoms may be regarded as first signs of polycystic kidney disease. It should, however, be emphasized that there is usually no need for a DNA diagnosis in theses cases, as additional clinical evaluations (e.g. renal ultrasound) may definitely clarify the situation. It can be expected that in gene carriers for ADPKD, several cysts can be detected usually up to the age of 20 years which allows to establish the diagnosis.

3.3.3.4 Heterozygosity Testing

In autosomal recessive conditions, heterozygosity testing, which means identification of healthy gene carriers, is only applicable in families with known gene mutation or where specific genetic markers are known to segregate with the responsible gene defect. One example is ARPKD where the gene has been mapped but mutation analysis of the PKHD1 gene may not be successful. The linkage analysis has to include family members which are not affected (Fig. 3.2).

The situation is different in X-linked diseases where indirect genotype analysis can identify female carriers for an X-linked condition, which usually has important implications for family planning and possible prenatal diagnosis. The recurrence risk is 50% for males to be affected. The relevance of being heterozygous for an autosomal recessive disorder, which usually has no consequences for the gene carrier, is often misunderstood and needs a detailed information before testing. The knowledge of the heterozygous state can be relevant for future family planning. It should be emphasized that in those conditions where no gene defect is known, heterozygous testing in the normal population is not possible. The detection of heterozygous gene carriers in relatives of an affected person is therefore often of limited value, as long as no testing can be applied in a spouse. The knowledge of being heterozygous cannot be used for prenatal prediction in a future child if no further risk assessment is available for the couple with unknown carrier status of the spouse.

3.4 Genetics of Important Disorders of the Urogenital System

3.4.1 Renal Agenesis

In most cases renal agenesis can be regarded as a manifestation of a spectrum including hydronephrosis – cortical cysts (Potter type IV) – hypoplastic/dysplastic or multicystic dysplastic kidneys – and renal agenesis depending on the time of the interaction of a disruption (e.g. obstruction). Dysplastic kidneys often vanish during life completely.

After birth of a child with severe Potter phenotype due to bilateral agenesis or dysplasia in up to 10% unilateral agenesis or dysplasia can be found in one parent indicating a genetic basis. Empirical recurrence risks favour mostly multifactorial inheritance with a recurrence risk of about 5% after birth of a child with renal agenesis/dysplasia. In single pedigrees, autosomal dominant or X-linked mode of inheritance seems to be likely with incomplete penetrance and variable expressivity. Specific syndromes have to be ruled out (Table 3.2).

Despite the overall small recurrence risk of renal agenesis careful evaluation of the family history and exclusion of syndromes is essential. Due to the early manifestation during embryogenesis the detection by prenatal ultrasound is reliable.

3.4.2 Cystic Kidney Diseases

While the autosomal dominantly inherited types (ADPKD) (OMIM 601313, 173910) belong to the most common inherited diseases at all, the recessive type (ARPKD) (OMIM 26320) is mainly important among pediatric patients. Although ADPKD is usually a late onset disease with clinical signs in adulthood, and

Table 3.2. Syndromes with renal agenesis (selection)

Syndrome	Major features	Genetics*
Branchio-oto-renal (BOR) syndrome (Melnick Fraser syndrome)	Hearing loss, pinnae anomalies, branchial cleft fistulas, preauricular pits	AD (113650), *EYA1, SIX5*
CHARGE association	Coloboma, heart defect, choanal atresia, mental retardation, genital hypolasia, ear anomalies, growth impairment, deafness	Most often AD new mutations of *CHD7* (214800), rarely of *SEMA3*
Chromosomal disorders	Depending on the cytogenetic changes additional malformations, facial dysmorphism, mental retardation	Most often de novo, in rare cases consequence of a familial translocation
Cryptophthalmos syndrome (Fraser syndrome)	Cryptophthalmia, cleft lip/palate, genital anomalies, atresia of ear cannal, syndactyly	AR (219000): *FRAS1* and *FREM2*
Kallmann syndrome	Hypogonadotropic hypogonadism, anosmia, cryptorchism	AD, AR, X-l (147950) *FGFR1, BROKR2, PROK2*
Rubinstein-Taybi syndrome	Broad thumbs and toes, distinctive facial features, mental retardation, microcephaly, cryptorchism, small phallus	Microdeletion 16p (about 25%), most often de novo, further cases with mutations in *CREBBP, EP300*

*AR: autosomal recessive, AD: autosomal dominant, X-l: X-linked, OMIM number in brackets with the main entry only, italic abbreviation of gene

ARPKD is often diagnosed in newborns or even prenatally, there is a broad clinical overlap. Therefore, family history, including renal ultrasound scans of relatives, is still a major criterion for classification of polycystic kidneys in children. In ADPKD up to now two genes could be identified. While about 85% of patients show 16p linkage indicating mutations in the *PKD1* gene, mutations in the *PKD2* gene are responsible for less than 15%. A third gene locus has so far not been identified, if existing. The *PKD1* gene encodes an integral membrane-protein, polycystin1, which is involved in cell-cell/cell-matrix interaction. Polycystin2, interacting with polycystin1, shows homologous sequences with polycystin1 as well as to one subunit of a calcium channel. The *PKHD1* gene mutated in ARPKD has 66 exons and encodes a large, receptor-like protein of unclear function.

Because of the strong demand for prenatal diagnosis in ARPKD, the haplotype based diagnosis with polymorphic markers is on the background of the complex gene structure still of utmost interest. In contrast to ARPKD there is usually no clear indication for mutation detection in ADPKD. There is nearly no demand for prenatal diagnosis (see also 3.3.3.1). Because it is possible to identify about 95% of gene carriers by renal ultrasound at the age of 20 years and nearly all gene carriers at the age of 30 years, predictive genetic testing by use of DNA analysis is usually not necessary. Due to the complex structure of the *PKD1* gene, mutation detection is not feasible in clinical practice and restricted to selected indications.

Syndromes with cystic kidneys have always to be excluded (Table 3.3). Due to the common combination of liver changes in patients with cystic kidneys the liver morphology is important for clinical classification.

The genetic basis of autosomal dominant glomerulocystic kidney disease has recently been disclosed with mutations in the *HNF1β*-gene which is the gene mutated in MODY type V also denoted as "renal cysts and diabetes syndrome" (OMIM 137920). The renal disease is highly variable and includes renal cysts, glomerular tufts, aberrant nephrogenesis, primitive tubules, irregular collecting systems, oligomeganephronia, enlarged renal pelvis, abnormal calyces, small kidney, single kidney, horseshoe kidney, and hyperuricemic nephropathy. Affected individuals may also have abnormalities of the genital tract, including vaginal aplasia, rudimentary uterus, bicornuate uterus, epididymal cysts, and atresia of the vas deferens.

Table 3.3. Syndromes with cystic kidneys (selection)

Syndrome	Major features	Renal involvement	Genetics
Chromosomal disorders (e.g. trisomy 10p, 13, 17, XYY, triploidy)	According to the chromosomal disorder additional malformations, facial dysmorphism , mental retardation	Different types, often only mild changes	Most often de novo, in rare cases consequence of a familial translocation
von-Hippel-Lindau syndrome	Retinal angiomas, cerebellar hemangioblastomas	Cysts, renal cell carcinoma,	AD with incomplete penetrance and variable expressivity (193300) *VHL* gene
Jeune syndrome (asphyxiating thoracic dystrophy)	Small thorax, polydactyly, rhizomelic limb shortening, trident pelvis, biliary dysgenesis and pancreatic dysplasia	Renal dysplasia, juvenile nephronopthisis, hydroureters, multicystic kidneys	AR (2008500)
Meckel-Gruber syndrome	Occipital encephalocele, polydactyly, cleft lip/palate, microphthalmia, small or ambiguous genitalia, brain anomalies, biliary dysgenesis and pancreatic dysplasia	Renal dysplasia or hypodysplasia, ureteral hypoplasia or aplasia, hypoplastic bladder, urethral agenesis	AR heterogeneous (249000), *MKS1, TMEM67, CEP290*, one further gene locus mapped
Oral-facial-digital syndrome type I	Lobulated tongue, median pseudocleft of lip, cleft palate, hypoplastic alae nasi, digital anomalies, mental impairment	Often late onset polycystic kidney disease	X-l (311200) *CXORF5*
Renal adysplasia (hereditary renal adysplasia HRA)	Anomalies of internal genitalia, occasional anomalies of anus, heart and spine	Renal agenesis, hypodysplasia, dysplasia, ureteral and urethral anomalies	AD (191830)
Short rib polydactyly syndromes type I (Saldino Noonan) and type II (Majewski)	Short ribs and limbs, genital and visceral anomalies, biliary dysgenesis, pancreatic dysplasia	Renal dysplasia, cystic kidneys	AR (263530)
Tuberous sclerosis	Hypopigmentated macules, adenoma sebaceum, retinal and brain tumors, seizures, mental retardation	Renal angiomyolipomas (40–80%), renal dysplasia, cortical cysts, renal vascular anomalies, renal cell carcinomas, polycystic kidney disease	AD (191100) new mutations in about 85% of cases, variable expressivity, incomplete penetrance *TSC1, TSC2* and further gene loci

3.4.3 Hydronephrosis

Familial aggregation of hydronephrosis in families with ureteropelvic junction obstruction has been described in several studies. In many cases hydronephrosis can be regarded as manifestation of a spectrum including hydronephrosis – cortical renal cysts (Potter type IV) – hypoplastic/dysplastic or multicystic kidneys – renal agenesis, depending on the time of the interaction of a disruption (e.g. obstruction). Hydronephrosis can also be a part of more complex genetic syndromes (Table 3.4).

3.4.4 Duplication of Kidneys, Renal Pelvis and Ureters

A genetic basis is well known, many reported families indicate autosomal dominant inheritance with variable expressivity and incomplete penetrance. In about 10% of parents and siblings similar observations can be made, indicating multifactorial inheritance for the majority of cases. According to the general rule of thumb, the recurrence risk doubles with each additionally affected close relative. Isolated duplication anomalies have to be distinguished from genetic syndromes (Table 3.5).

Table 3.4. Syndromes with hydronephrosis (selection)

Syndrome	Major features	Renal involvement	Genetics
Chromosomal disorders (e.g. trisomy 8, 13, 18, 18q-, r(18), XO, triploidy)	According to the chromosomal disorder additional malformations, facial dysmorphism , mental retardation	Different types, often only mild changes	Most often de novo, in rare cases consequence of a familial translocation
Bardet-Biedl syndrome	Obesity, pigmentary retinopathy, polydactyly, hypogenitalism	Ectopic urethra, cystic kidney	AR (209900), heterogeneous with 12 types *BBS1-12* identified
Prune belly syndrome	Deficient abdominal muscles, urinary obstruction/distension, cryptorchism, malrotation of the gut, clubfeet, limb reduction anomalies	Urethral atresia, ureteral duplication, bladder distension, hydronephrosis, renal dysplasia	Mostly sporadic, heterogeneous (100100)
Rubinstein-Taybi syndrome	Broad thumbs and toes, distinctive facial features, mental retardation, microcephaly, cryptorchism, small phallus	Posterior urethral valves, abnormal bladder shape, absent or extra kidney, double renal pelvis	Microdeletion 16p (about 25%), most often de novo (180849), further cases with mutations in *CREBBP, EP300*
Kaufmann-McKusick syndrome	Hydrometrocolpos, transverse vaginal membrane, vaginal septum, postaxial polydactyly, cardiac anomalies, hypospadias	Hydroureter, ureteral duplication, ectopic urethra, urogenital sinus, posterior urethral valves	AR (236700), mutations in Bardet-Biedl type 6 *BBS6* gene

Table 3.5. Syndromes with duplication of kidneys, renal pelvis and ureters (selection)

Syndrome	Major features	Genetics
Branchio-oto-renal (BOR) syndrome (Melnick Fraser syndrome)	Hearing loss, pinnae anomalies, branchial cleft fistulas, preauricular pits,	AD (113650), *EYA1, SIX5*
Chromosomal disorders (e.g. 4p-, 11q-, XO, partial trisomy 3q, trisomy 8 mosaics)	According to the chromosomal disorder additional malformations, facial dysmorphism , mental retardation	Most often de novo, in rare cases consequence of a familial translocation
Nail patella syndrome	Nail hypoplasia, hypoplastic/absent patella	AD (161200) *LMX1B*

Close family members should be screened

3.4.5 Vesicoureteral Reflux (VUR)

Vesicoureteral reflux (VUR, OMIM 193000) is most likely genetically heterogeneous with the majority of cases indicating a multifactorial basis. At least two autosomal loci have been identified with evidence for a further X-linked locus. In single families mutations in the *ROBO2* gene could be identified. In several systematic studies among first degree relatives (children, siblings, parents) about 10%–25% showed VUR depending on the different imaging techniques used. Siblings should be screened.

3.4.6 Hypospadias

The genetic nature of hypospadias has been well known for a long time and has been evaluated in several systematic studies. Empiric risk figures for brothers of affected boys are about 7%, boys of affected fathers probably have a lower risk of about 3.5%. These figures indicate a multifactorial basis of hypospadias in the majority of cases. In line with this assumption is the observation that the risk increases according to the grade of hypospadias. The empirical risk for siblings of grade 1 was 3.5%, for grade 2, 3.9%, and for grade 4,

16.6%. More distant relative have lower risks: about 2% for second degree relatives (uncles, nephews, grandparents) and third degree relatives only 1%. In rare cases autosomal dominant inheritance seems possible. More recently an X-linked type with mutations in the *CXORF6* gene has been described. Rarely, patients with hypospadias showed mutations in the androgen receptor gene responsible for testicular feminization and Kennedy syndrome. Genetic risks in syndromes with hypospadia can be variable (Table 3.6).

3.4.7 Tumors of the Kidney

Renal tumors can occur as part of complex genetic diseases (Table 3.7). Tumors are major manifestations in the two forms of *tuberous sclerosis* and the *von Hippel-Lindau syndrome*. The responsible genes are tumor suppressor genes. The two step hypothesis of Knudson gives an explanation for the great clinical variability.

Table 3.6. Syndromes with hypospadias (selection)

Syndrome	Major features	Genetics
Chromosomal disorders (e.g. 4p-, 13q-, 21q-, triploidy)	According to the chromosomal disorder additional malformations, facial dysmorphism, mental retardation	Most often de novo, in rare cases consequence of a familial translocation
G syndrome, Opitz-Frias syndrome	Stridor, dysphagia, hypospadias, hypertelorism	AD (145410)
Cryptophthalmos syndrome (Fraser syndrome)	Cryptophthalmos, cleft lip/palate, genital anomalies, atresia of ear canal, syndactyly	AR (219000): *FRAS1* and *FREM2*
Rieger syndrome	Hypodontia with malformation of the anterior chamber	AD (180500) *PITX2*
Smith-Lemli-Opitz syndrome	Microcephaly, postaxial polydactyly, ambiguous genitalia, facial dysmorphism, 2–3 toe syndactyly, hypospadias and cryptorchism	AR (270400) *DHCR7*

In hypospadias grade 2–4 the exclusion of a chromosomal disorder is recommended

Table 3.7. Syndromes with tumors (selection)

Syndrome	Major features	Renal involvement	Genetics
Beckwith-Wiedemann syndrome	Exomphalos, macroglossia, gigantism in the neonate	Wilms tumor	Mostly sporadic (50-60% epigenetic imprinting defects), 15% AD with variable expressivity (130650) *(CDKN1C)*, 1-3% paternal duplication of 11p15, 20% uniparental disomy of 11p15
Denys-Drash syndrome	Pseudohermaphroditism, nephropathy	Wilms tumor	AD (194080), *WT1*
Hemihypertrophy	Body asymmetry, organomegaly	In some cases associated with Wilms tumor	Sporadic?
Tuberous sclerosis	Hypopigmentated macules, adenoma sebaceum, retinal and brain tumors, seizures, mental retardation	Renal angiomyoliposmas (40–80%), renal dysplasia, cortical cysts, renal vascular anomalies, renal cell carcinomas, polycystic kidney disease	AD (191100), de novo mutations in about 85% of cases, variable expressivity, incomplete penetrance *TSC1, TSC2* and further gene loci
Wilms tumor, aniridia syndrome	Aniridia	Wilms tumor	Microdeletion 11p13, rare cases of familial translocation

Wilms tumor is only rarely inherited (about 5%) and follows an autosomal dominant pattern in these families. Penetrance is about 60%, i.e. the disease can be transmitted by healthy gene carriers. The involvement of tumor suppressor gene has been shown. The risk for birth of an affected child of a healthy gene carrier (see below) is about 30%. Bilateral and multifocal tumors can always be regarded as heritable. For practical counseling the following risks can be given:

- Risks for children of surviving patient with Wilms tumor: 2–4% in case of unilateral tumor with no further affected family member, 30% in cases with bilateral or multifocal occurrence.
- Risk for children of non affected parents with a family history of Wilms tumor: a) most likely < 1% for second degree relatives of a sporadic patient. b) at least 30% if a parent is a gene carrier (e.g. a sibling of the parent and another child is affected).

A Wilms tumor can occur as part of complex disorder like the WAGR syndrome with Wilms tumor, aniridia, genital malformation and mental retardation. Responsible genes are in close vicinity on chromosome 11 in the region p13 (*WT1*) and p15.5 ($p57^{KIP2}$). Mutation in the $p57^{KIP2}$ gene were found in patients with Beckwith-Wiedemann syndrome, who can exhibit Wilms tumors. Other responsible loci for Wilms tumor have been discussed: 16q (WT3), 17q12–q21 (WT4) and (7p15–p11.2). Wilms tumors can also occur as a feature of Denys-Drash syndrome characterized by nephrotic syndrome and diffuse mesangial sclerosis as well as male hermaphroditism. At the DNA level, mutations in the zink finger coding domains of the WT1 gene on chromosome 11p13 were shown. This is most likely a sporadic disease and only in rare cases consequence of a familial translocation. In cases of Wilms tumor with additional features, especially of the eyes, mutations in the MET gene in patients with familial renal carcinoma were found.

3.5 Genetic Basis of Important Nephropathies

3.5.1 Alport Syndrome (AS)

Alport syndrome is genetically heterogeneous with X-linked (OMIM 301050) and autosomal recessive modes (OMIM 26320) of inheritance. About 85% of cases follow an X-linked pattern and show mutations in the *alpha 5(IV) collagen (COL4A5)* gene. Mutation screening is hampered by a complex genomic region and many different mutations. In practice, mutations can be detected only in about 70–80% of patients with clearly X-linked Alport syndrome. Mutations in other alpha subunits of the type IV collagen are the genetic basis of the rare autosomal recessive Alport syndromes. Benign familial hematuria is a dominant condition with mild features of Alport nephritis; after heterozygous mutations in the *COL4A4* gene were found, it was concluded that benign familial hematuria can be regarded as a heterozygous manifestation of autosomal recessive Alport syndrome.

If the diagnosis of AS is suspected in a patient, a mutation screening in the responsible collagen genes as a basis for genetic classification and counseling has to be discussed. In patients with a proven mutation, no invasive diagnostic means, such as renal biopsy, are necessary.

3.5.2 Bartter Syndrome

This condition is characterized by hypokaliemic metabolic alkalosis, hyperreninism and hyperaldosteronism with normal blood pressure. Three different forms following autosomal recessive inheritance can be distinguished: classical Bartter syndrome, neonatal form (hyperprostaglandin E syndrome) as well as the mild Gitelman syndrome of adolescence and adulthood (OMIM 607364). According to the known pathogenesis of salt-losing, mutations of genes involved in NaCl reabsorption can be detected (classical Bartter syndrome: renal chloride channel *CLCNKB*, neonatal Bartter syndrome: furosomide dependent *NaK2Cl* co-transporter *NKCC2* or renal potassium channel *ROMK*, Gitelman syndrome: thiazide-sensitive NaCl cotransporter). A molecular genetic

diagnosis is useful for a presymptomatic testing of children at risk in order to avoid uncontrolled salt-wasting.

3.5.3 Nephrogenic Diabetes Insipidus

The nephrogenic diabetes insipidus (OMIM 304800, 125800) is characterized by the resistance of the kidney towards the action of vasopressin resulting in the production of large volumes of diluted urine. After previous mapping of the X-linked type, mutations in the vasopressin V2-receptor gene were found. Autosomal recessive or dominant forms are extremely rare and caused by mutations of the water-channel *aquaporin 2* gene (*AQP2*) on chromosome 12q12–q13. A genetic testing has as yet no therapeutic consequences but can be used for prenatal diagnosis, if requested. The molecular disclosure of basic defects is an impressive confirmation of the known pathogenesis of water transport.

3.5.4 Nocturnal Enuresis

Although a positive family history of nocturnal wetting is well-known affecting about 50% of relatives of index patients and indicating major genetic factors in the pathogenesis, mapping of several autosomal dominant genes was surprising, since nocturnal enuresis has often been regarded as a prototype of a classic psychosomatic disorder. Although several gene loci have been identified, no gene has been identified so far (OMIM 600631).

3.5.5 Nephrolithiasis

The genetic basis of an increasing number of conditions leading to hereditary renal stones has been disclosed. The recently detected mutations in a renal chloride channel gene (*CLCN5*) are responsible for the X-linked nephrolithiasis (OMIM 310468) and Dents disease (with Fanconi syndrome) (OMIM 300009). Autosomal recessive cystinuria (OMIM 220100) type I and type II is caused by allelic mutations of the membrane-transporter gene *rBAT* for dibasic amino acids. In type III, mutations in the *SCL7A9-AS* transporter gene could be found. Mutations can only be detected in a small number of patients and cannot be used as a diagnostic tool.

Further genes involved in other conditions responsible for renal stone development among many others could be identified: e.g. osteopetrosis with tubular acidosis type I (xanthinoxidase), hyperoxaluria type I (alanine-glyoxylate-aminotransferase), adenine-phosphoribosyltransferase deficiency (ATRTase), distal tubular acidosis and primary hypomagnesemia.

3.5.6 Juvenile Nephronophthisis/Medullary Cystic Kidney Disease

This disease group is defined by renal cysts at the corticomedullary junction and classified into a recessive form (nephronophthisis) and dominant form (medullary cystic kidney disease) (OMIM 256100 and 174000). Nephronophthisis is genetically heterogeneous, four genes have been mapped and identified (*NPHP1-4*). Additional genes can be expected.

Molecular genetic testing can be used for diagnostic classification, as homozygous deletions can be detected in 85% of patients with *NHPH1* (juvenile type), thus confirming the diagnosis without renal biopsy. The *NPHP1* gene encodes the protein nephrocystin, and *NPHP2* the protein inversin. The responsible *NPHP3* and *NPHP4* genes have also been identified

Manifestations of nephronophthisis with additional signs like congenital hepatic fibrosis, retinitis pigmentosa as well as cerebellar lesions are summarized as Senior-Loken syndrome; mutations could be identified in the *NPHP1, NPHP4* and *NPHP5* genes.

Two genes responsible for autosomal dominant medullary cystic kidney disease, which seems to be rare in Europe, could be mapped on chromosome 1q21 (*MCKD1*) and 16p12 (*MCKD2*). *MCKD2* gene encodes the protein uromodulin (UMOD).

3.5.7 Nephrotic Syndromes

Nephrotic syndrome can also be inherited, following an autosomal recessive or dominant mode in these families. Up to now, the recessive genes responsible for the congenital nephrotic syndrome of the Finnish type (*NPHS1* on chromosome 19q12,

gene product nephrin, OMIM 256300) and the gene involved in the steroid resistent nephrotic syndrome (*NPHS2* on chromosome 1q25, gene product podocin, OMIM 600995) could be identified. Two further genes for the dominant nephrotic syndrome with adult onset and focal segmental glomerulosclerosis (OMIM 603278) could be identified *(ACTN4, TRPCG* and haploinssuficiency for the CD2-associated protein).

The involvement of several genes reflects the heterogeneous pathogenesis of the nephrotic syndromes. Pathoanatomical lesions do not indicate a specific genetic entity. Apart from the congenital nephrotic syndrome of the Finnish type, which rarely occurs in non-Finnish populations, genetic testing is not applicable on a routine basis.

3.5.8 Cystinosis

Patients with cystinosis (OMIM 219800) develop nephritis, cataracts, retinopathy and hypothyreoidism due to an autosomal recessive transport defect of cystin. The responsible gene *CTNS* encodes an integral membrane protein cytinosin.

3.6 The Use of Databases for Information about the Current Status on Molecular Biology of Hereditary Nephropathies

This overview will be outdated as regards the knowledge in molecular biology after publication of this issue. Therefore, the use of databases is important for practitioners as well as for scientists. The most important database about the current development of inherited diseases, which is updated daily, is Victor McKusick's database "online Mendelian inheritance in man" (OMIM) (*http://www.ncbi.nlm.nih.gov/OMIM/*). The entries include current references.

Orphanet is a database dedicated to information on rare diseases and orphan drugs (*http://www.orpha.net/*) and includes a directory of European genetic laboratories.

Addresses of genetic laboratories are also usually published through the national societies of human genetics. In Germany, current laboratories are listed in the database of the Berufsverband deutsche Humangenetik e.V. (http://www.hgqn.org/).

3.7 Conclusion

Molecular techniques have contributed enormous knowledge about the nature of hereditary diseases. Molecular biology provides new insights into basic mechanisms of the nature and classification of hereditary diseases. The understanding of the underlying defects and the pathogenesis of a certain disease may give clues to the development of a future therapy.

The diagnostic facilities also offer new possibilities but it should be realized that DNA diagnosis differs in many aspects from conventional diagnosis and has certain limitations and consequences which requires a careful application.

References

A detailed list of references is not included. Current citations are available in Online Mendelian Inheritance in Man (OMIM): http://www3.ncbi.nlm.nih.gov/OMIM/

Anomalies of Kidney Rotation, Position and Fusion

4

Gabriele Benz-Bohm

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4.1 Anomalies of Rotation

The fetal kidneys undergo a 90° rotation around their longitudinal axis during their ascent from the pelvis before they reach their final position by the end of the 8th week of fetal life (see Sect. 2.1.1) (Moore and Persaud 1998). Campbell (1970) reported only 17 cases of renal malrotation among 32,834 autopsies on adults. The true incidence of malrotation is probably understated because many patients have no clinical symptoms.

Malrotation is most commonly associated with an ectopic (Fig. 4.1) or fused kidney, but may also occur in kidneys that undergo complete ascent. Then the degree of rotation is minimal. The condition may be unilateral or bilateral (Fig. 4.1). The most common type is an incomplete rotation or nonrotation. The renal pelvis is in the anterior position or some variation between the anterior and normal medial position in the adult. Reverse rotation and hyperrotation are other major types of malrotation. In reverse rotation, the renal pelvis rotates laterally and the renal vessels cross the kidney anteriorly to reach the hilum. In hyperrotation, the kidney rotates more than 180°, but less than 360°. The pelvis faces laterally, but the renal vessels are carried posteriorly to the kidney. Malrotation is usually discovered accidentally, during imaging of the kidney. The calyces are often distorted, even without any associated obstruction. It is important to establish the correct diagnosis to exclude other pathological conditions that can produce similar distortion of the kidney. Anomalies of rotation may produce partial ureteropelvic obstruction (Kissane 1983; Ritchey 1992; Currarino et al. 1993).

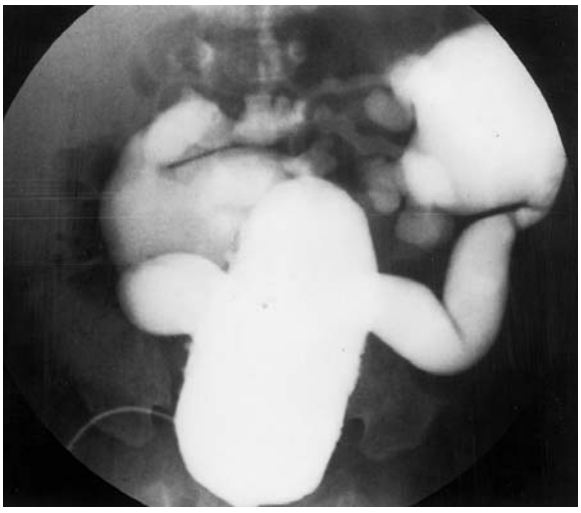

Fig. 4.1. VCU in a 2-year-old boy. Reflux in both lumbar ectopic and malrotated kidneys

G. Benz-Bohm, MD, Professor
Birresborner Strasse 40, 50935 Cologne, Germany
formerly
Department of Radiology, Division of Pediatric Radiology, University of Cologne, Kerpenerstrasse 62, 50924 Cologne, Germany

Conclusion

Malrotation is most commonly associated with an ectopic or fused kidney. Anomalies of rotation may produce partial ureteropelvic obstruction

4.2 Anomalies of Position

4.2.1 Ectopic Kidney

Renal ectopy is the term for a kidney lying outside the renal fossa. As stated in Chapter 2 (Sect. 2.1.1), the kidney migrates cephalad early in gestation to arrive at its normal position. Abnormality of the ureteral bud or metanephric blastema, genetic abnormalities, teratogenic causes, or anomalous vasculature, acting as a barrier to ascent, are reasons for failure of the kidney to complete its ascent (Malek et al. 1971). The incidence of renal ectopy in postmortem studies varies from 1 in 500 (Campbell 1930) to 1 in 1,290 (Thompson and Pace 1937). There is a slight predilection for the left side, and 10% of cases are bilateral (Fig. 4.1).

Simple renal ectopy refers to a kidney that remains in the ipsilateral retroperitoneal space. The most common position is in the pelvis – pelvic or sacral kidney – opposite the sacrum and below the aortic bifurcation. The lumbar or iliac ectopic kidney is one that is fixed above the crest of the ilium, but below the level of L2 and L3. Malrotation frequently accompanies renal ectopy (Fig. 4.1) (Kissane 1983; Daneman and Alton 1991; Ritchey 1992; Currarino et al. 1993).

The differentiation between renal ptosis and renal ectopy can be difficult. In renal ptosis the renal artery arises from the aorta to the normal level and the ureter is of normal length. In renal ectopy the ureter is short, corresponding to the location of the kidney. Renal ptosis results from hypermobility of the kidney in the retroperitoneal space, usually in obese people who have rapidly lost weight. The ptotic kidney can usually be manipulated into its normal position.

4.2.1.1 Diagnosis

The diagnosis of an ectopic kidney can be made by US in most cases. Intravenous urography oblique films may be quite helpful in visualizing the pelvic kidney. Retrograde pyelography can be used to opacify the collecting system in those cases with inadequate excretion of contrast. Since vesicoureteral reflux (VUR) is frequently associated with an ectopic kidney (Fig. 4.1), voiding cystourethrography (VCU) is recommended. The diuretic renogram can distinguish these abnormal pelvicalyceal patterns from ureteropelvic junction obstruction by a high insertion of the ureter on the renal pelvis. More recently, MRI has greatly enhanced the evaluation of these patients. It can also provide information about the vascular supply. The ectopic kidney receives major blood supply from nearby major vessels and are often supplied by multiple vessels (Daneman and Alton 1991; Ritchey 1992).

4.2.1.2 Associated Anomalies

The contralateral kidney may be abnormal in up to 50% of patients (Malek et al. 1971). There is a 10% incidence of contralateral renal agenesis. In up to 70% of children with pelvic kidney there is associated VUR (Kramer and Kelalis 1984). In most cases of renal ectopy the adrenal gland is in normal position. Genital anomalies were found ranging from 15% of males to 75% of females (Thompson and Pace 1937; Downs et al. 1973). Skeletal anomalies occur in up to 50% of children, cardiovascular lesions were found in 9 out of 21 children (Malek et al. 1971) and gastrointestinal abnormalities in one-third of patients (Ritchey 1992).

Conclusion

The diagnosis of an ectopic kidney can be made by US in most cases. VUR is frequently associated. The contralateral kidney may be abnormal in up to 50% of patients.

4.2.2 Thoracic Kidney

Excessive cranial migration of the kidney results in a thoracic kidney or in a superior ectopic kidney (N'Guessen et al. 1984), lying below a thin membranous portion of the diaphragm. An intrathoracic kidney occurs in fewer than 5% of the cases of renal ectopy, with an incidence of 1 in 13,000 autopsies (Campbell 1930). The left side is more commonly

involved, and there is a male predominance. Occasionally, the condition can be bilateral (N'Guessen et al. 1984). In the supradiaphragmatic kidney, the ureter and hilar vessels enter through the foramen of Bochdalek. In general, the thoracic kidney functions normally, and most patients are asymptomatic. The thoracic kidney is often detected on a routine chest radiograph as a suspected mass (Ritchey 1992).

Conclusion

The thoracic kidney is often detected on a routine chest radiograph as a suspected mass.

4.3 Anomalies of Fusion

During the ascent of the kidneys they cross the umbilical arteries. Malposition of the umbilical arteries may cause the developing nephrogenic blastemas to come together. Fusion of the nephrogenic masses in the midline would result in a horseshoe kidney. This occurs early in embryogenesis, before rotation is complete, and therefore malrotation is present in all cases (Fig. 4.2c,d) (Ritchey 1992).

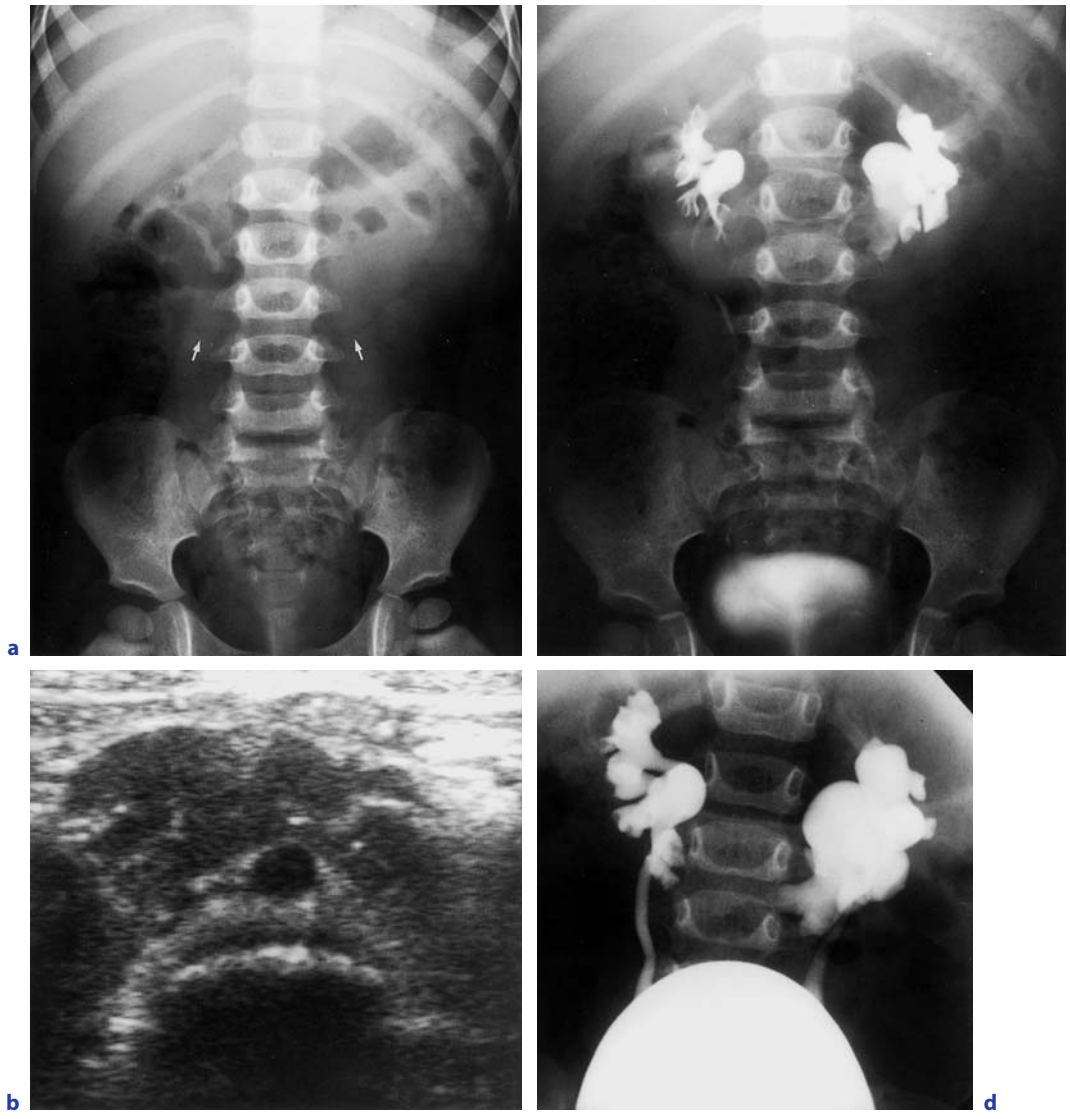

Fig. 4.2a–d. Typical appearance of horseshoe kidney in a 19-month-old girl: **a** on a plain radiograph; **b** on US; **c** on intravenous urography; **d** on VCU by reflux

4.3.1 Horseshoe Kidney

Horseshoe kidney is the most common type of renal fusion and one of the most frequent renal anomalies. It is usually characterized by fusion of the lower poles across the midline by an isthmus lying anterior, seldom posterior, to the aorta and inferior vena cava (Dajani 1966). Occasionally the lower poles are connected only by fibrous bands. The horseshoe kidney is usually positioned low in the abdomen with the isthmus lying just below the junction of the inferior mesenteric artery and aorta. The incidence varies from 1 in 400 (Glenn 1959) to 1 in 1,800 (Campbell 1970). The abnormality is more common in males.

4.3.1.1 Diagnosis

The diagnosis of horseshoe kidney may be suspected from a plain radiograph of the abdomen, if one can visualize the renal outlines in their abnormal position (Fig. 4.2a). The diagnosis can be confirmed by a variety of imaging techniques, including renal ultrasonography (Fig. 4.2b), intravenous urography (Fig. 4.2c), CT or MRI (Fig. 4.3). The radiographic appearance of a horseshoe kidney is frequently altered by associated abnormalities such as hydronephrosis and/or diminished renal function. In the majority of cases, there are multiple renal vessels. The blood to the isthmus is often supplied by a separate vessel. This may arise from the aorta, the common iliac or inferior mesenteric arteries. Before any surgery, it may be necessary to assess the function of the isthmus by radionuclide imaging of the kidneys (Kissane 1983; Ritchey 1992).

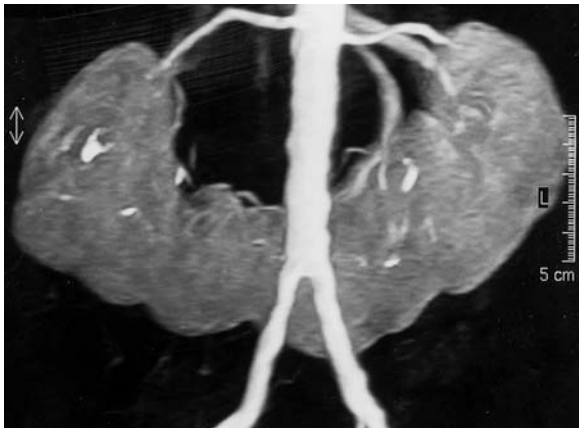

Fig. 4.3. Horseshoe kidney detected on MRI in an adult

4.3.1.2 Associated Anomalies

The incidence of associated anomalies is much higher if the horseshoe kidney is discovered in the newborn period. In postmortem examinations of 99 infants with horseshoe kidneys, 78% had malformations of other organ systems such as the central nervous system, the gastrointestinal tract, and the skeletal and cardiovascular system (Zondek and Zondek 1964). One-third of patients with horseshoe kidney had at least one other abnormality (Boatman et al. 1972). Several well-known syndromes are associated with fused kidney. Trisomy 18 has an incidence of 21% (Warkany et al. 1966; Boatman et al. 1972). In US studies, Lippe et al. (1988) noted horseshoe kidneys in 7% of patients with Turner's syndrome. In patients with neural tube defects, there is also an increased incidence of horseshoe kidneys (Whitaker and Hunt 1987). Nearly one-third of patients with a horseshoe kidney remain undiagnosed throughout life (Glenn 1959; Pitts and Muecke 1975).

Ureteropelvic junction obstruction by a high ureteral insertion or an anomalous renal vessel is the most common cause of hydronephrosis, which occurs in 30% of patients diagnosed during life. Urolithiasis develops in 20% of patients with a horseshoe kidney. Stasis secondary to hydronephrosis, but with metabolic factors are also the reasons (Evans and Resnick 1981).

In all children with a horseshoe kidney, VUR should be excluded. The upper urinary tract dilatation may be secondary to VUR (Fig. 4.2d). More than 100 renal malignancies have been reported in patients with horseshoe kidney (Buntley 1976). The risk of developing a Wilms' tumor increases sevenfold in patients with a horseshoe kidney (Mesrobian et al. 1985).

Conclusion

Horseshoe kidney is the most common type of renal fusion. Hydronephrosis, urolithiasis, and VUR are associated anomalies and effects. The risk of Wilms' tumor is increased sevenfold.

4.3.2 Crossed Renal Ectopia

Crossed renal ectopia is the second most common fusion anomaly after horseshoe kidney, with an incidence of 1 in 7,000 autopsies (Abeshouse and Bhisitkul 1959). The crossed ectopic kidney lies on the opposite side from the ureteral insertion of the bladder. There are four varieties of renal crossed ectopia (Fig. 4.4) (McDonald and McClellan 1957; Abeshouse and Bhisitkul 1959). Crossed renal ectopia with fusion occurs in 85%, without fusion in less than 10%; solitary crossed renal ectopia and bilateral crossed renal ectopia are rare (Kakei et al. 1976). Crossing from left to right occurs more frequently than right to left, and there is a slight male predominance. There are six variations in the crossed renal ectopia with fusion (Fig. 4.5) (McDonald and McClellan 1957; Abeshouse and Bhisitkul 1959). The most common form is the unilateral fused type with inferior ectopia, in which the upper pole of the crossed kidney is fused to the lower pole of the normally positioned kidney. The renal pelves remain in their

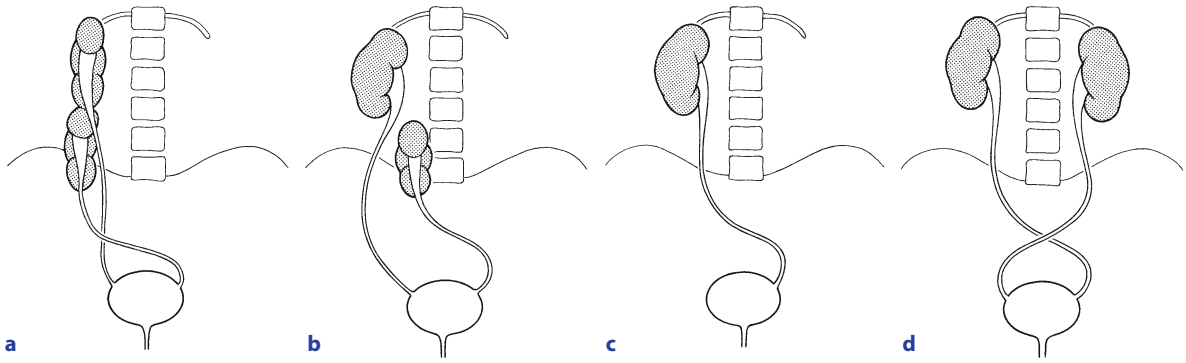

Fig. 4.4a–d. Four types of crossed renal ectopia: **a** with fusion; **b** without fusion; **c** solitary; **d** bilateral

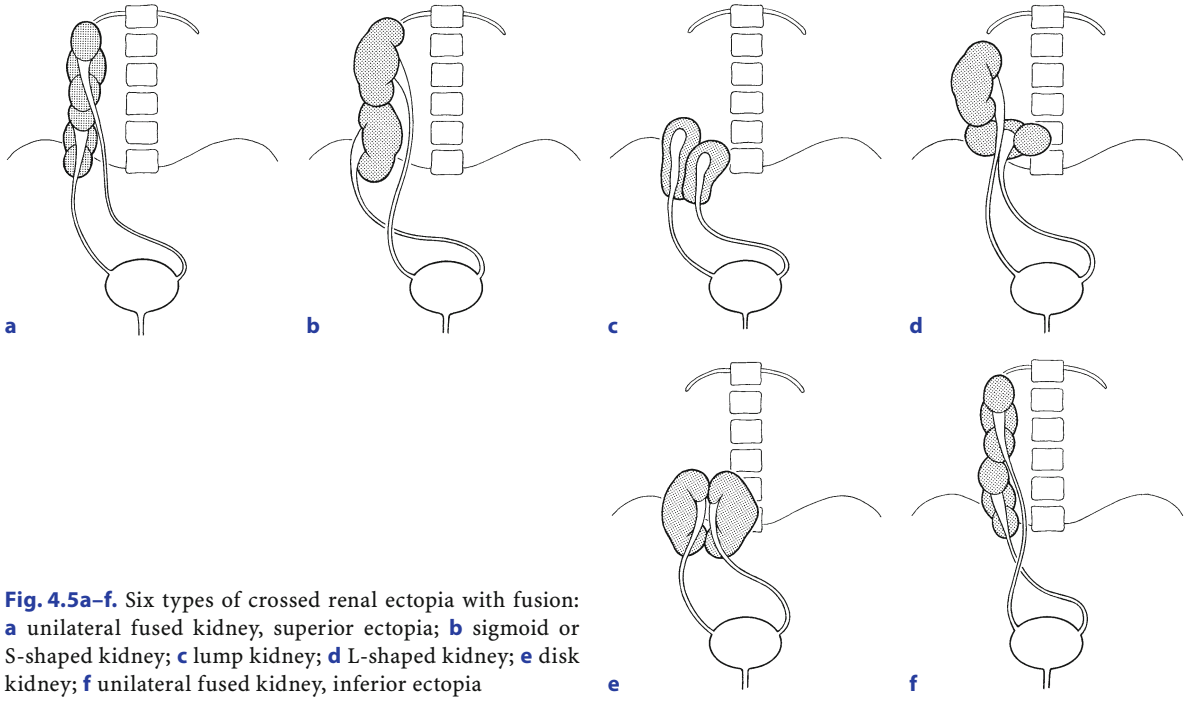

Fig. 4.5a–f. Six types of crossed renal ectopia with fusion: **a** unilateral fused kidney, superior ectopia; **b** sigmoid or S-shaped kidney; **c** lump kidney; **d** L-shaped kidney; **e** disk kidney; **f** unilateral fused kidney, inferior ectopia

anterior position, representing a failure to complete rotation. The second most common type is the sigmoid or S-shaped kidney with inferior ectopia. Both kidneys have completed their rotation so that the two renal pelves face in opposite directions. The other four types of fusion are less common. In the lump or cake kidney and in the disk kidney, the two kidneys are extensively fused. In the L-shaped kidney, the crossed kidney is in the transverse position. The superior ectopic kidney lies superior to the normal kidney (Kissane 1983; Ritchey 1992; Currarino et al. 1993).

4.3.2.1 Diagnosis

Generally it is difficult to distinguish between crossed renal ectopy with fusion and crossed renal ectopy without fusion by US (Fig. 4.6a) or by excretory urography. In contrast, CT and MRI are able to establish the correct diagnosis. MRI in particular can also provide information about the vascular supply, which is quite variable. Multiple anomalous branches to both kidneys are possible, arising from the aorta or from the common iliac artery. A crossing renal artery to supply the crossed kidney is very rare (Rubinstein et al. 1976).

4.3.2.2 Associated Anomalies

The most common associated abnormality is that of VUR (Fig. 4.6b) (Kramer and Kelalis 1984). Therefore, VCU should be performed in all of these patients. Skeletal anomalies, imperforate anus, and cardiovascular anomalies have an increased incidence (Abeshouse and Bhisitkul 1959). Patients with solitary crossed ectopy have a higher incidence of genital abnormalities, probably related to the renal agenesis (Kakei et al. 1976).

Conclusion

Crossed renal ectopia occurs with fusion in 85%, without fusion in less than 10%. MRI is the best diagnostic imaging. VUR is the most common associated abnormality.

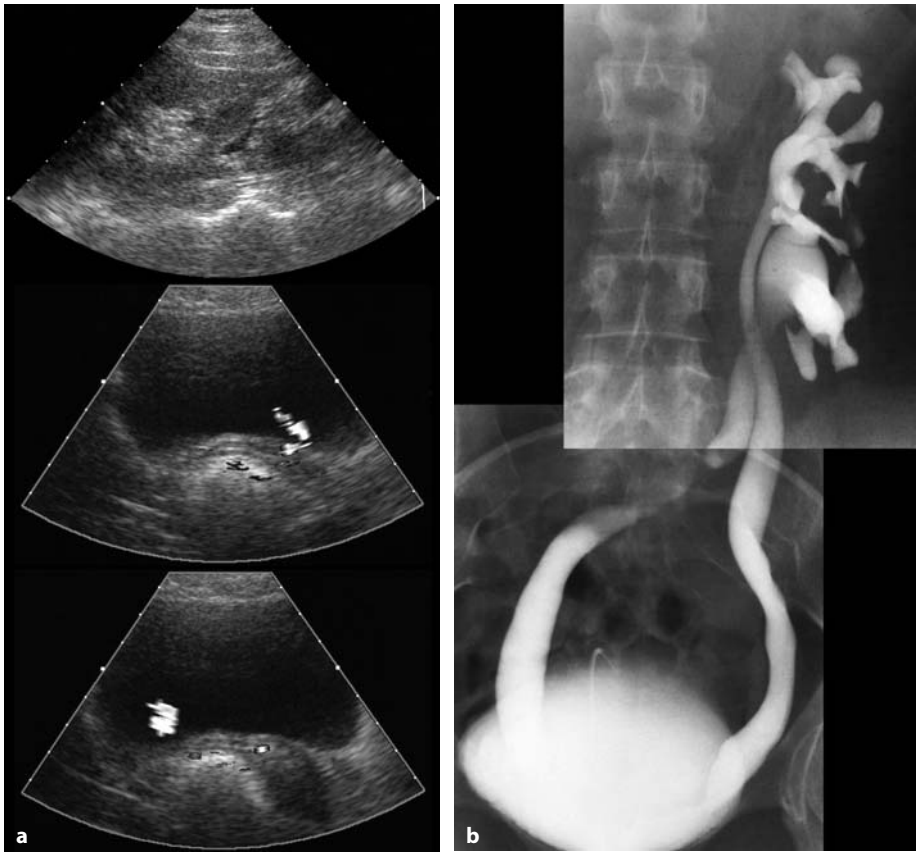

Fig. 4.6a,b. Crossed renal ectopia in a 14-year-old girl: **a** left-sided kidneys with correct position of the ureterovesical junctions on US: crossed ectopia with fusion is suspected; **b** VCU: bilateral VUR grade III

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Anomalies of the Renal Pelvis and Ureter

5

Fred E. Avni, Michelle Hall, Frank Collier, and Claude Schulman

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F. E. Avni, MD, PhD
Department of Medical Imaging, Erasme Hospital, 808 Route de Lennik, 1070 Brussels, Belgium
M. Hall, MD
Department of Nephrology, University Children's Hospital Queen Fabiola, Avenue JJ Crocq 15, 1020 Brussels, Belgium
F. Collier, MD
Department of Urology, University Children's Hospital Queen Fabiola, Avenue JJ Crocq 15, 1020 Brussels, Belgium
C. Schulman, MD, PhD
Department of Urology, Erasme Hospital, 808 Route de Lennik, 1070 Brussels, Belgium

5.1 Introduction

Congenital anomalies may involve any level of the collecting system; the most usual presentation is urinary tract dilatation that may already be detected during fetal life. The role of imaging is to determine the origin of the dilatation, i.e., obstructive versus non-obstructive (Table 5.1 lists the causes of urinary tract dilatation). Other useful information includes the level of the obstruction and its impact on renal function. All these data are important in order to determine the best therapeutic approach.

Two imaging techniques have been classically used in order to demonstrate the morphology of the collecting system: ultrasound (US) and intravenous urography (IVU). Newer techniques have merged these last years: computed tomography (CT) and MR urography; their aim is to complete the information brought by US and to replace IVU. In many indications, the newer techniques have progres-

sively replaced the older ones. The work-up of most anomalies has to be completed by voiding cystourethrography (VCU) and functional isotope studies.

Table 5.1. Causes of urinary tract dilatations

Congenital etiologies
Ureteropelvic junction obstruction
Ureterovesical junction obstruction
Vesicoureteric reflux (grades III–V)
Nonobstructive nonrefluxing megaureter
Duplex collecting system
Posterior urethral valves
Megacalycosis
Pelvi-infundibular stenosis
Secondary etiologies
Tumoral involvement
Extrinsic compression
Retroperitoneal fibrosis
Constipation
Megabladder
Lithiasis

5.2 Imaging the Pelvis and Ureter

Historically, IVU was the first imaging technique that allowed the visualization of the collecting system; after iodinated contrast injection, the pyelocalyceal system, the ureter and the bladder opacify, and this allows a morphological evaluation of the collecting system. The best results are obtained when the collecting system is not too dilated and when good renal function is maintained. This technique is rapidly disappearing because of its drawbacks; it is an irradiating technique, and iodinated contrast material has to be injected. Also, if the renal function has deteriorated, opacification will not be optimal and the information provided will be insufficient (Almen and Mattson 1995; Hilton and Kaplan 1995).

In pediatric uronephrology, US has maintained a central position; whatever the anomaly, it will be performed first and will determine the subsequent work up. US is very efficient for the demonstration of dilatation of the urinary tract and the level of obstruction; yet, the method cannot differentiate between obstructive and nonobstructive dilatation. Also, the degree of dilatation is influenced by the state of hydration of the patient; therefore, some teams advocate the use of furosemide and measurement of the resistive index in order to diagnose obstruction. Another interest of US is that the technique also provides information on the renal parenchyma (Chopra and Teele 1980; Patriquin 1991; Gilbert et al. 1993; Haller and Cohen 1987; Bude et al. 1992; Bude et al. 1994; Palmer 2006).

CT has proved informative in many pathological or doubtful situations involving the pyelocalyceal and ureteral system; it may demonstrate the connections of atypical cystic parenchymal lesions with the collecting system, and it may determine the primitive or secondary origin of an obstruction. CT completes the information given by US; if necessary 2D or 3D reconstructions or urographic images post-contrast injection may also be obtained. The technique is irradiating, and therefore its use must be well thought-out and cautious (Berdon 1991; Hilton and Kaplan 1995; Palmer 2006).

These last years, the use of MR urography has been gaining popularity for the visualization of the urinary tract, both the parenchyma and collecting system. Its best indications are the morphological assessment of the very dilated urinary tract, ectopic ureteral insertion, and assessment of renal parenchymal damage. The combination of hydrographic sequences and gadolinium-enhanced sequences provides information on both morphology and (indirect) function. In the near future, further studies will determine whether MR imaging can be considered as an "all in one" examination and will replace both IVU and isotopes (Roy et al. 1998; Borthne et al. 1999; Wille 2003; Jones 2004; Rohrschneider 2003; Boss 2006; Nolte-Ernstig et al. 1998).

Till then, the best functional evaluation of renal function and of the degree of renal obstruction is obtained by isotope studies with furosemide injection (Berdon 1991; Roarke and Sandler 1998; Piepz and Ham 2006; Palmer 2006). Other techniques such as ascending pyelography have almost completely been abandoned.

Conclusion

US is the central imaging technique for the visualization of a dilated collecting system. Morphology of the urinary tract is best assessed by MR imaging or CT (IVU is more and more abandoned). Function is best assessed by isotope studies.

5.3 Anomalies of the Pelvis and Ureter in Single and Bifid Collecting Systems

5.3.1 Calyceal Diverticulum

A calyceal diverticulum is an eventration of a calyx into the renal parenchyma that is filled with urine. Most of the diverticula are small and asymptomatic. Complications include the development of milk of calcium and lithiasis and rarely hematuria; infection is unusual. The relation between diverticulum and isolated renal cyst is unclear. The diverticulum is usually detected by US as an isolated cystic structure. However, the connection with the pyelocalyceal system is usually not visualized on US; it can be demonstrated on IVU or on CT (Fig. 5.1). Treatment is necessary only when complications such as hemorrhage or lithiasis occur (Siegel and McAllister 1979; Wulfsohn 1980; Ulchaker et al. 1996).

5.3.2 Hydrocalyx, Fraley's Syndrome and Infundibular Stenosis

Hydrocalyx refers to a dilatation limited to one or more calyces in the absence of renal pelvis dilatation. The condition may be congenital or acquired. Congenital hydrocalyx results from a stenosis of the infundibulum draining the calyx into the renal pelvis. The narrowing induces a (cystic) dilatation of one of the calyces (Fig. 5.2). When more than one calyx is involved, the condition is also referred to as infundibular stenosis. On IVU, the cystic-appearing calyces are connected to the renal pelvis by contrast-filled tubular channels. MR imaging is also able to demonstrate the anomaly. The most extensive form of the disease is infundo-pelvic stenosis, in which a small pelvis may also be associated (Figs. 5.3–5.5). The condition may also be acquired secondarily to infection (tuberculosis) or lithiasis (Kelalis and Malek 1981; Lucaya et al. 1984; Bodner et al. 1987; Uhlenhuth et al. 1990).

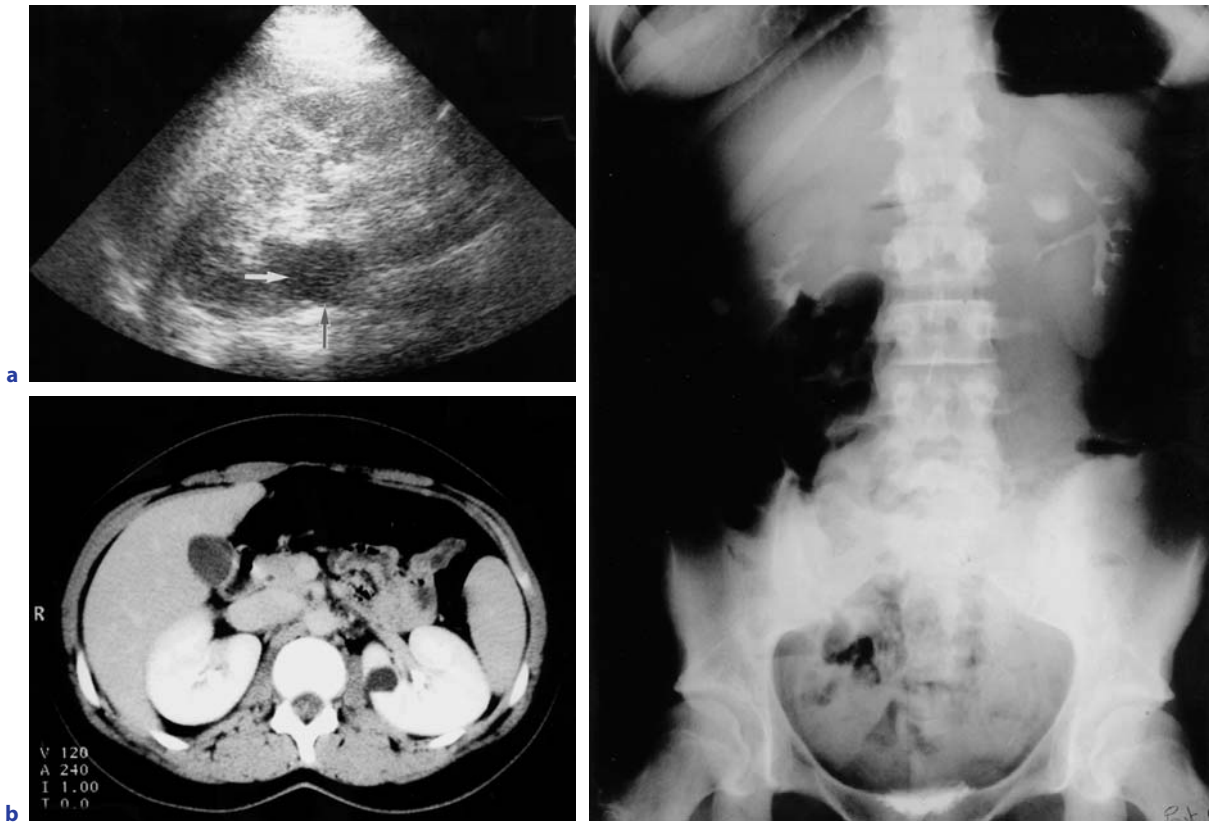
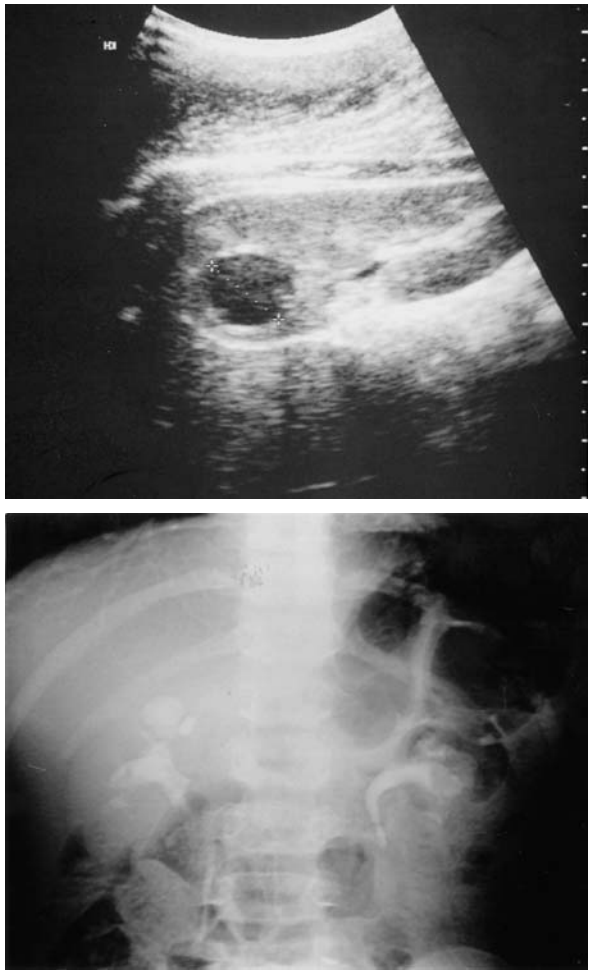
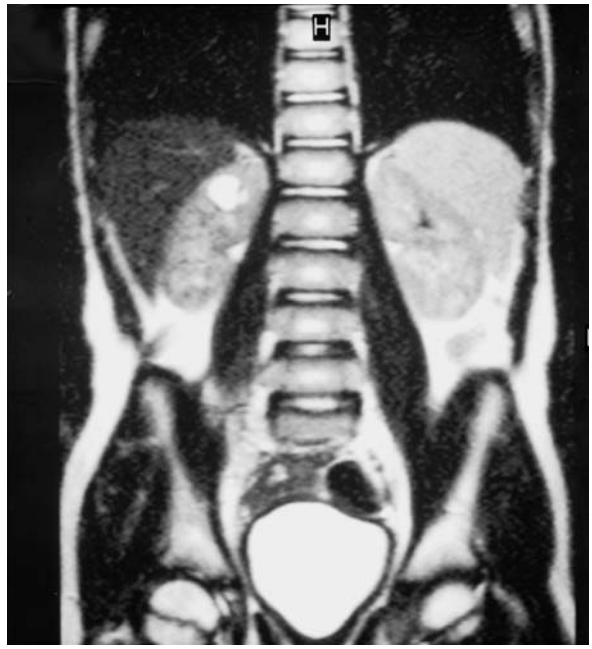


Fig. 5.1a–c. Calyceal diverticulum. **a** US: sagittal scan of the left kidney; a hypoechoic mass is visualized posteriorly (*arrows*). **b** CT scan after contrast enhancement: the cystic structure seen in the left kidney contains a fluid/contrast level suggesting a connection with the pyelocalyceal system. **c** IVU: the calyceal diverticulum is clearly opacified



a

b



c

Fig. 5.2a–c. Hydrocalyx. **a** US: cystic mass (between crosses) at the upper pole of the right kidney. **b** IVU: typical appearance of the right hydrocalyx. **c** MR: T2-weighted coronal view demonstrating the right hydrocalyx

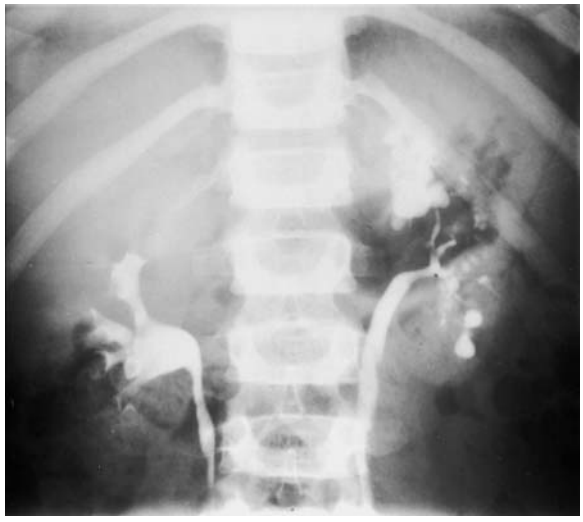


Fig. 5.3. Pelvi-infundibular stenosis of the left kidney. On the IVU, only the upper calyceal system has an unusual but dilated aspect (courtesy of JF Chateil MD)

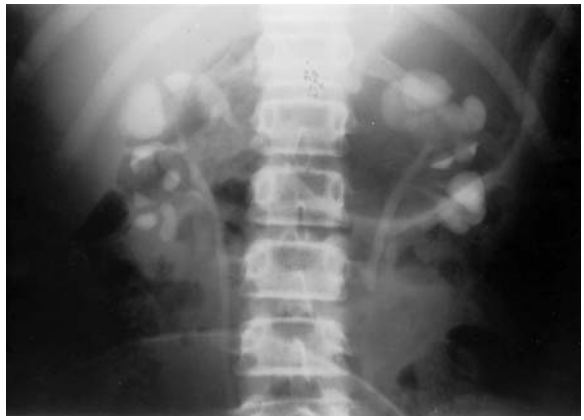


Fig. 5.4. Bilateral pelvi-infundibular stenosis (courtesy of JF Chateil MD)

Fig. 5.5. MR imaging of bilateral infundibulopelvic stenosis. T2-weighted sequence. The anomaly is associated with a right megaureter and with a segmental ureteral cystic dilatation to the left ureter

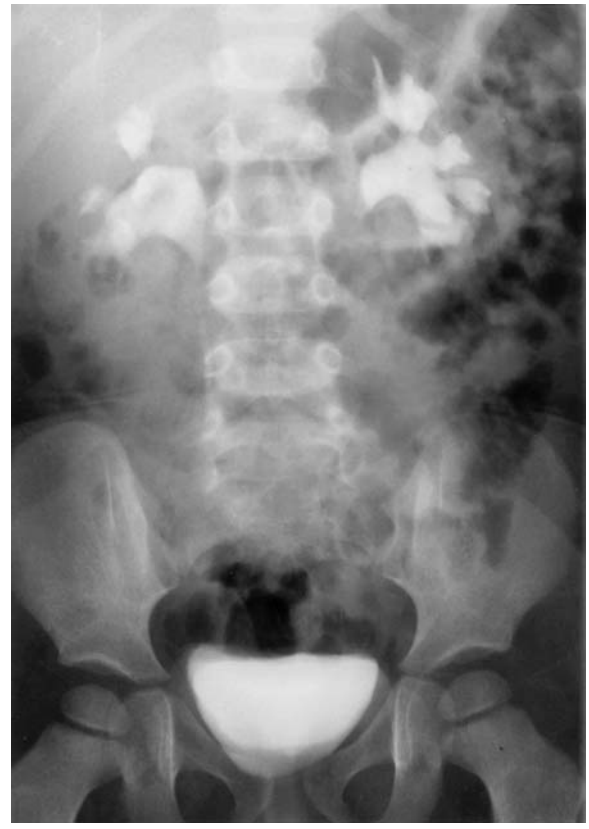
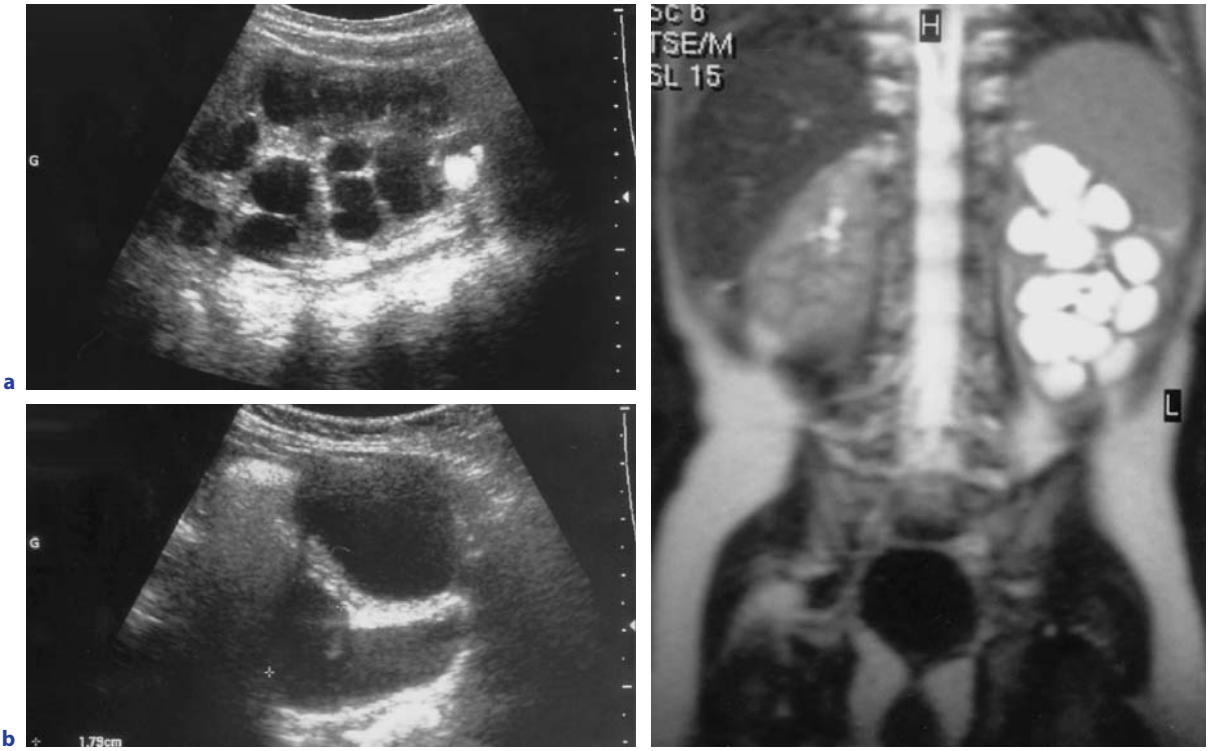


Fig. 5.6. Fraley's syndrome. On the IVU, there is an extrinsic compression of the upper right calyx

The dilatation of the calyx may be secondary to extrinsic compression by a vessel (the so-called Fraley syndrome) (Fig. 5.6), to scarring following inflammatory or infectious processes (tuberculosis), and to obstruction by a lithiasis or a blood clot (Bodner et al. 1987).

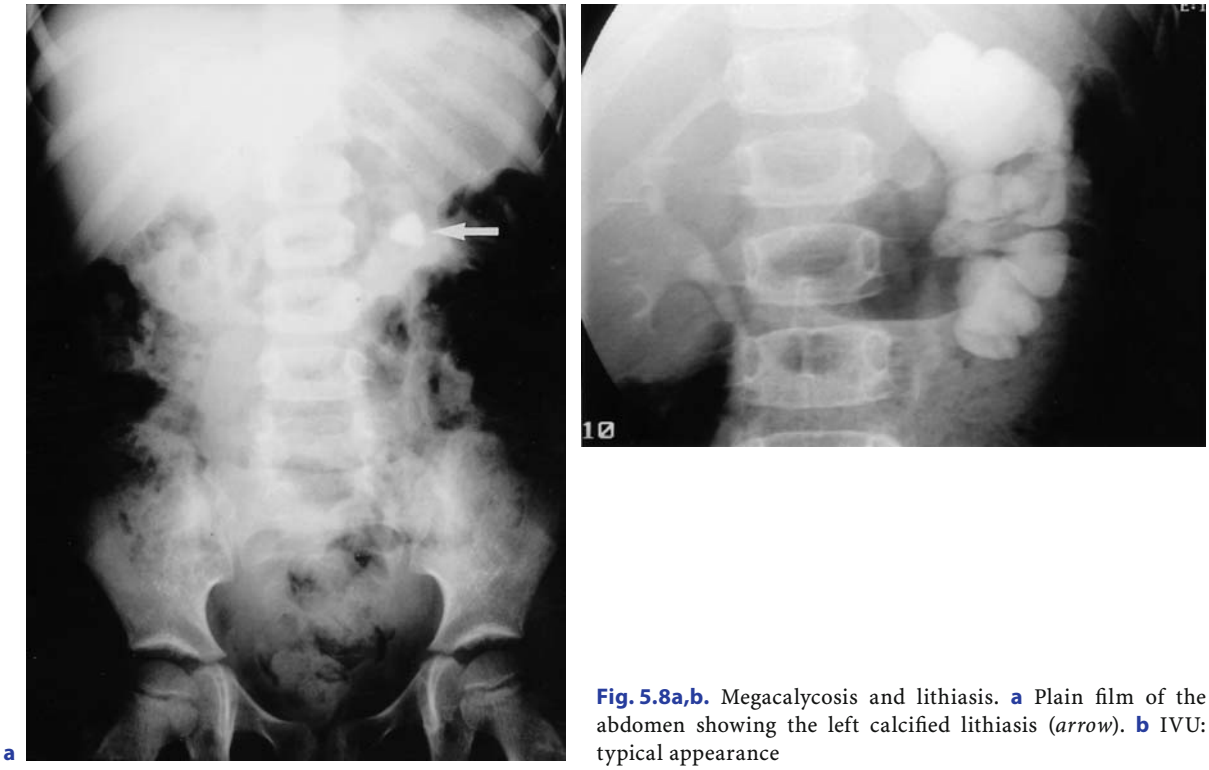
5.3.3 Megacalycosis

Mega(poly)calycosis is characterized by the presence of 12–20 dilated calyces in the absence of obstruction and is probably related to or associated with a developmental hypoplasia of the medullary pyramids. The condition is difficult to diagnose on US and better evaluated on IVU or MR imaging (Figs. 5.7, 5.8). The small renal pelvis is easier to demonstrate, and the dilated numerous calyces are easier to count by these techniques. Megacalycosis may typically also be associated with a primary megaureter (Kozakiewich and Lebowitz 1974; Holthusen and Lundius 1984; Vargas and Lebowitz 1986; Mandell et al. 1986). Complications include the development of lithiasis (Figs. 5.7, 5.8).



a b c

Fig. 5.7a–c. Megacalycosis and megaureter. **a** US: sagittal scan of the left kidney. Unusual cystic dilatation of all the calyces. A lithiasis is visible at the lower pole. **b** US of the pelvis showing an associated dilated ureter (1.8 cm between crosses). **c** MR urography: typical megacalycosis of the left kidney



a b

Fig. 5.8a,b. Megacalycosis and lithiasis. **a** Plain film of the abdomen showing the left calcified lithiasis (*arrow*). **b** IVU: typical appearance

5.3.4 Ureteropelvic Obstruction

5.3.4.1 Diagnosis of Obstruction

Dilatation of the urinary tract may occur secondary to obstruction and/or vesicoureteric reflux (VUR) or as a primary process (like non-obstructive megaureter). The main objective of all the imaging techniques will be to diagnose among all the cases those that might require surgical correction in order to preserve or improve function. The antenatal diagnosis and postnatal follow-up of fetal uropathies have brought lots of new information on the natural history of obstructive or pseudo-obstructive uropathies. Unfortunately, no clear-cut conclusions can be drawn from these many examples. There are still controversies concerning the diagnosis of obstruction and the yield of early surgery (Mandell et al. 1990; Wiener et al. 1995; Peters 1995).

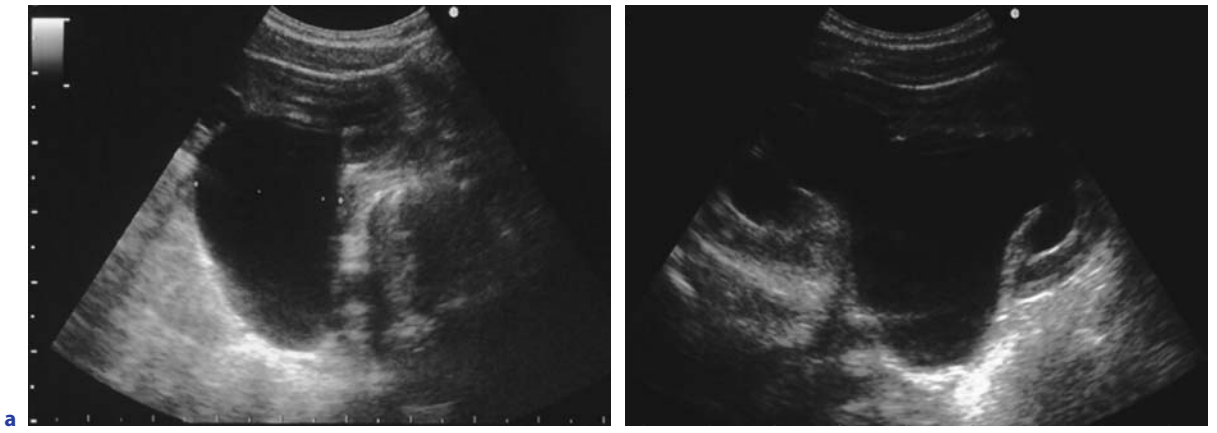
The first step towards the detection of obstruction is US (Fig. 5.9), the main landmark being the demonstration of dilatation of the urinary tract. Dilatation is best evaluated on an anteroposterior measurement of the renal pelvis on a transverse scan of the kidney. In the newborn, a pelvic diameter greater than 7 mm is considered abnormal; in older children, a diameter higher than 10 mm should be considered abnormal. The following step in the work-up of a uropathy is VCU. Once VUR is excluded, it becomes more probable that the urinary tract dilatation is secondary to obstruction. It is noteworthy that VUR and obstruction may coexist in the same collecting system (Fernbach 1992; Maizels et al. 1992; Tsai et al. 1989; Stocks et al. 1996).

The best method to evaluate and to quantify obstruction is the radio-isotope study (diuretic radionuclide renogram). Two aspects of renal function are assessed: renal clearance and excretion of the tracer. Estimation of relative clearance (differential renal function) requires the measurement of GFR by injection of chromium isotope-ethylnediamine-tetraacetic acid (Cr-EDTA) using a simple plasma sample technique. The most accurate method for evaluation of GFR is based on the plasma disappearance curve after a single bolus injection of a glomerular tracer.

The second parameter that may be obtained from a renographic curve is the evaluation of tracer molecule transport through the entire nephron, known as the transit time. A normal transit time (approximately 3 min) excludes renal obstruction. Abnormal transit time indicates urine statis. It is not possible on the basis of a prolonged transit time to differentiate obstruction from simple dilatation of the collecting system.

Tubular tracers with a high extraction such as iodine 123-hippurate, ^{99m}Tc-mercaptotriglycine (^{99m}Tc-MAG3), or ^{99m}Tc-ethylene dicysteine are recommended. The response depends on the rate of tracer extraction. Postmicturition images should be acquired.

The response to intravenous injection of furosemide provides additional information in cases of renal statis. In cases of nonobstructive dilatation, the retained radioactivity in the UT is washed out rapidly by increased urine flow, whereas renal emptying is slow or nonexistent in the case of obstruc-



a b

Fig. 5.9a,b. US of urinary tract dilatation (UPJ obstruction). **a** Transverse and **b** sagittal scan of the left kidney

tion. However, the degree of washout depends on the degree of uptake of the tracer by the kidney. Poor response to furosemide may be observed in kidneys with impaired renal function in the absence of any obstruction (Fig. 5.10, 5.11) (Chung et al. 1993; Piepz and Han 2006).

During the first months of life, the response to furosemide is often equivocal despite the absence of obstruction because of the low extraction (low clearance values). In the presence of a full bladder, drainage from the kidney may be delayed even in the normal individual.

The interpretation of drainage in the presence of marked hydronephrosis is more difficult. Only good drainage is easily defined. The definitions of obstruction and risk factors of renal deterioration are still controversial (Piepz et al. 2001; Gordon et al. 2001).

Consequently, other imaging methods have been used or have been developed. For many years, IVU has been used for the diagnosis of urinary tract obstruction. Signs of obstruction include the demonstration of dilatation and delayed filling of the collecting system (Fig. 5.12a). On imaging, especially on IVU, the dilatation of the renal pelvis and calyces contrasts with a non-dilated ureter; furthermore, due to the obstruction, the ureter may not always be visible. A prone film of the abdomen may help to visualize the junction. Furosemide injection may be needed in order to confirm doubtful cases.

Yet, as it is an irradiating technique and the quality of information provided depends upon the age of the patient, intestinal bowel distension, and renal function, it is less and less performed (Barnewolt 1998).

Many hopes were placed on US for the diagnosis of obstruction. Various grading systems have been described in order to categorize the urinary tract dilatation (Maizels et al. 1992). However, besides diagnosing urinary tract dilatation, conventional US alone does not provide information on renal function or the degree of obstruction. Therefore, several authors have proposed Doppler analysis of the renal arteries with calculation of the resistive index after furosemide injection. In case of obstruction, the resistive index tends to be greater than 85%. The first results are promising, but the use of the technique in newborns and small infants is more difficult and less reproducible (Fig. 5.13) (Bude et al. 1994; Gilbert et al. 1993; Yagci et al. 1999; Patti et

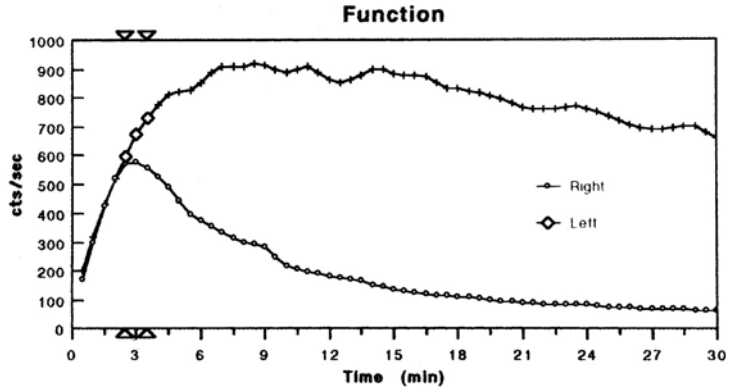


Fig. 5.10. Isotope study of a left urinary tract obstruction (MAG3 + CrEdta + furosemide). Typical obstructive pattern

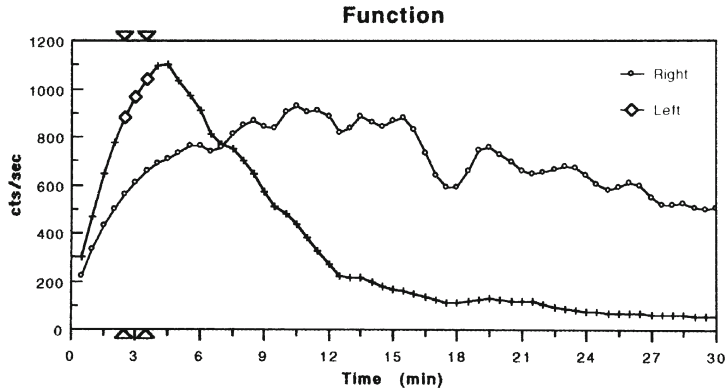


Fig. 5.11. Isotope study: intermediate pattern of a right urinary tract obstruction

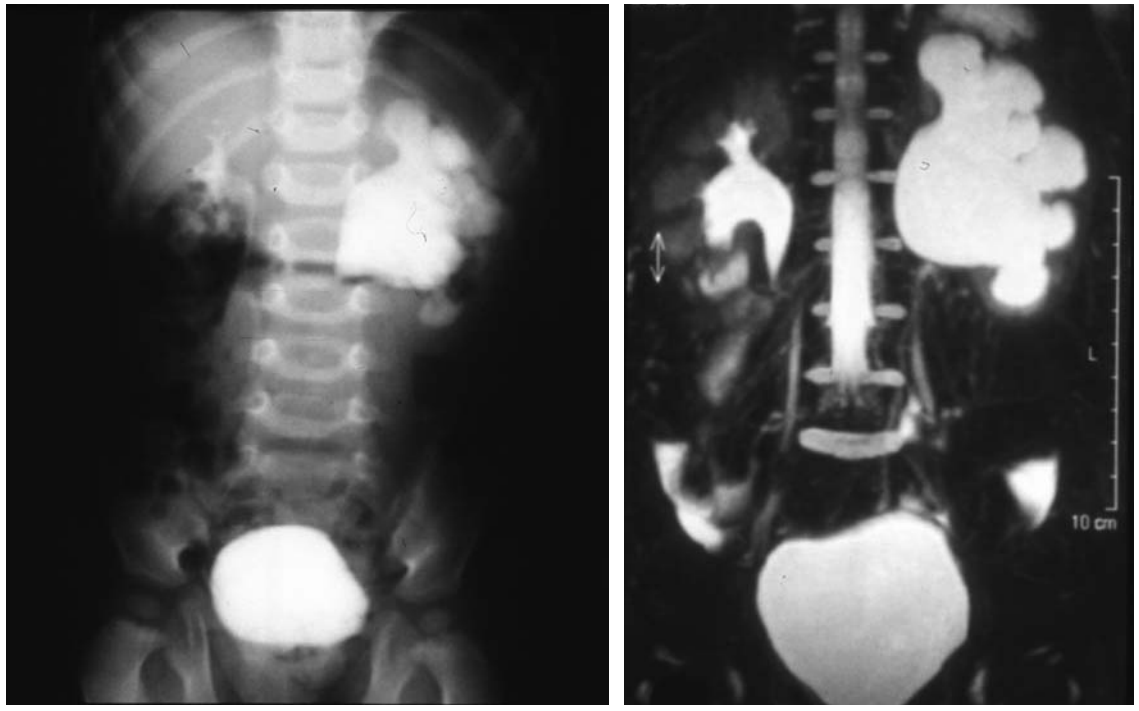


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Fig. 5.12a,b. Left UPJ obstruction. **a** IVU: typical dilatation of the collecting system. **b** MR urography. T2-weighted sequences. Both ureters are visualized and normal

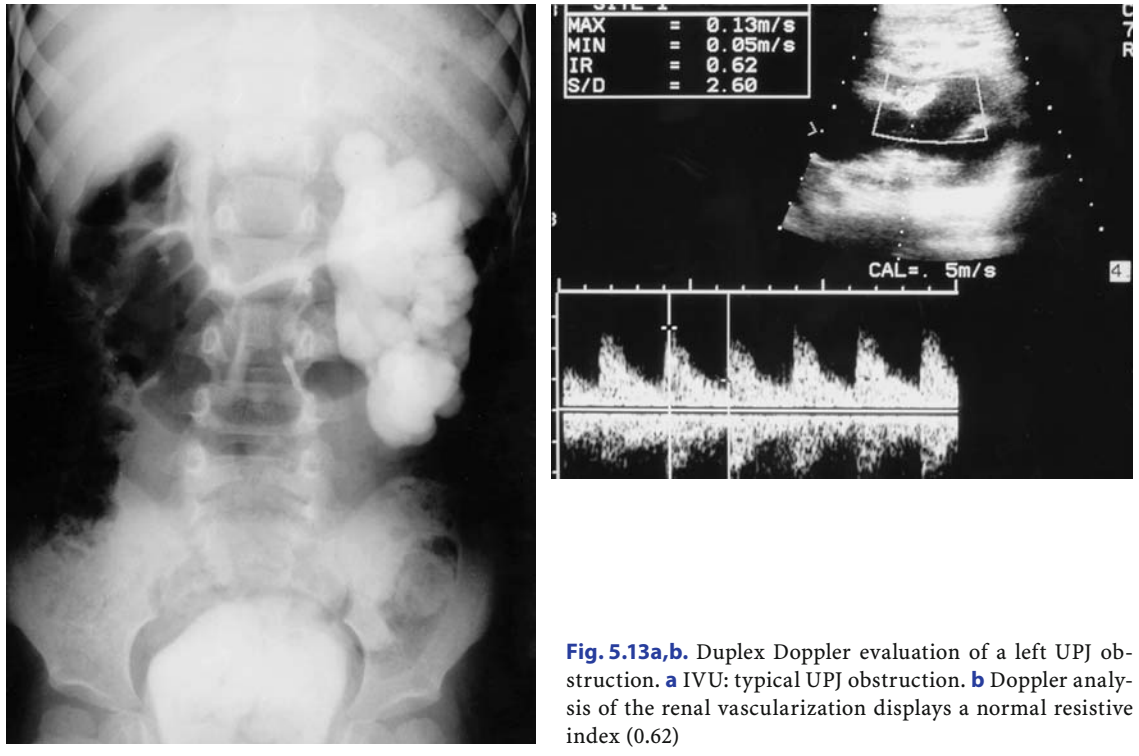

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Fig. 5.13a,b. Duplex Doppler evaluation of a left UPJ obstruction. **a** IVU: typical UPJ obstruction. **b** Doppler analysis of the renal vascularization displays a normal resistive index (0.62)

al. 2000). Infants and neonates tend to have a physiologically higher resistive index.

The Whitaker test or pressure measurements after urinary tract nephrostomy are used with some success in selected cases (Peters 1995). It necessitates sedation and the placement of a nephrostomy tube. It can therefore not be used in every case.

More recently, MR urography has been used in patients with obstructive uropathy. After contrast injection, early angiographic phases can be obtained and curves of gadolinium uptake can be drawn in a similar way to isotopes (Figs. 5.12b, 5.14). The results seem promising, although there is a need to standardize the conditions of the examination. Also, correlation between renal function and parenchymal enhancement after gadolinium injection has to be demonstrated (Regan et al. 1996; Nolte-Ernstig et al. 1998; Boss et al. 2006).

4.3.4.2 Etiology of Ureteropelvic Junction Obstruction

Ureteropelvic junction obstruction (UPJ) represents the leading cause of dilatation of the urinary tract (about 35%–40% of the cases). Its origin is not always understood or can be interpreted as multifactorial. UPJ obstruction can result from anatomic anomalies or abnormal peristalsis. At surgery, muscular discontinuity or extrinsic compression of the UPJ due to vessels or ureteral kinks can be found. MR imaging can very nicely display the crossing vessel (Fig. 5.15) (Calder et al. 2007; Koff et al. 1986; Frauschner et al. 1999).

5.3.4.3 Clinical Presentations

Nowadays, since the widespread use of obstetrical US, most cases of UPJ obstruction are detected in utero or in the direct neonatal period in asymptomatic patients. Rarely, the condition is revealed after the palpation of an abdominal mass, hematuria or urinary tract infection. Interestingly, despite antenatal diagnosis, cases of UPJ obstruction are still detected later in childhood. In older children, symptoms leading to the diagnosis include, among others, hematuria following an abdominal trauma, nausea, failure to thrive, and flank pain (Cendron 1994).

5.3.4.4 Particular Forms of UPJ Obstruction

5.3.4.4.1 Giant UPJ Obstruction

Giant UPJ obstruction is usually detected in the newborn after an antenatal diagnosis (Fig. 5.16). A flank mass is often palpated, and gastrointestinal discomfort is present. Pelvic dilatation is huge, extending from the diaphragm up to the bladder and across the midline. Besides MR imaging, it is difficult for imaging procedures to identify the type of uropathy.

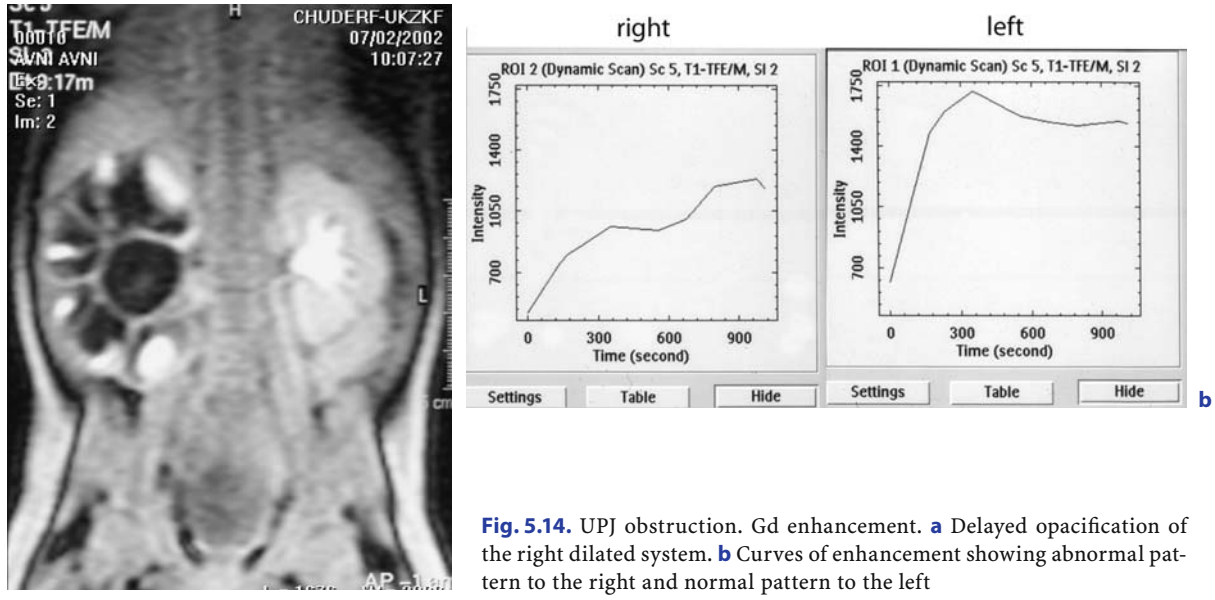

Fig. 5.14. UPJ obstruction. Gd enhancement. **a** Delayed opacification of the right dilated system. **b** Curves of enhancement showing abnormal pattern to the right and normal pattern to the left

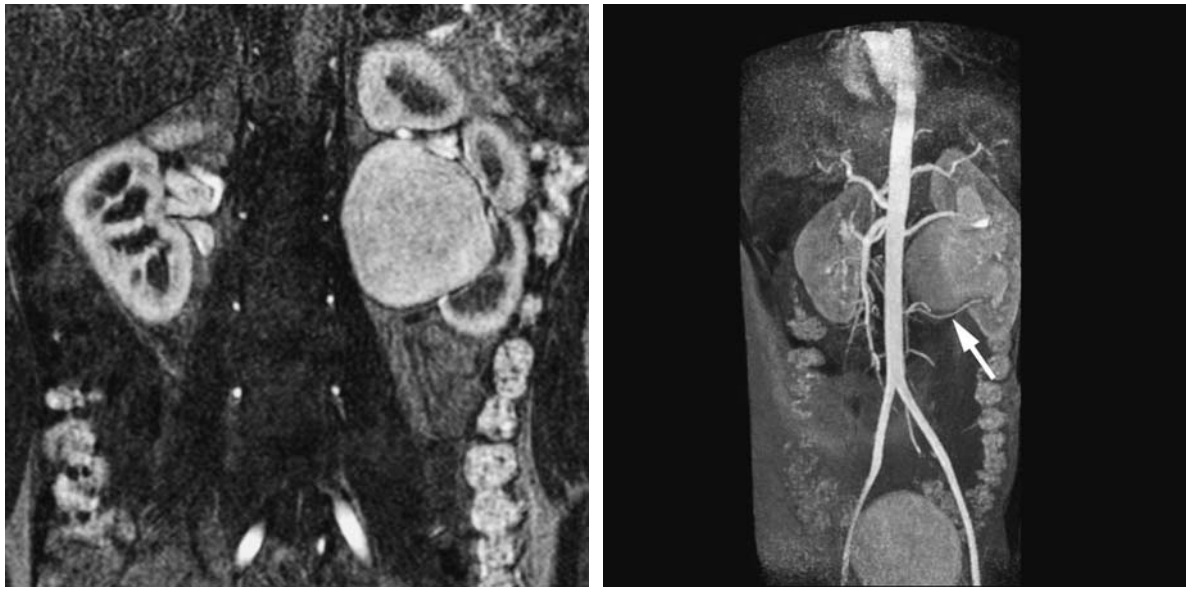

Fig. 5.15a,b. UPJ obstruction. **a** T1-weighted sequence + Gd enhancement. Typical left UPJ. **b** MR angiography displays the crossing vessel (*arrow*) (courtesy of JN Dacher, MD, PhD)

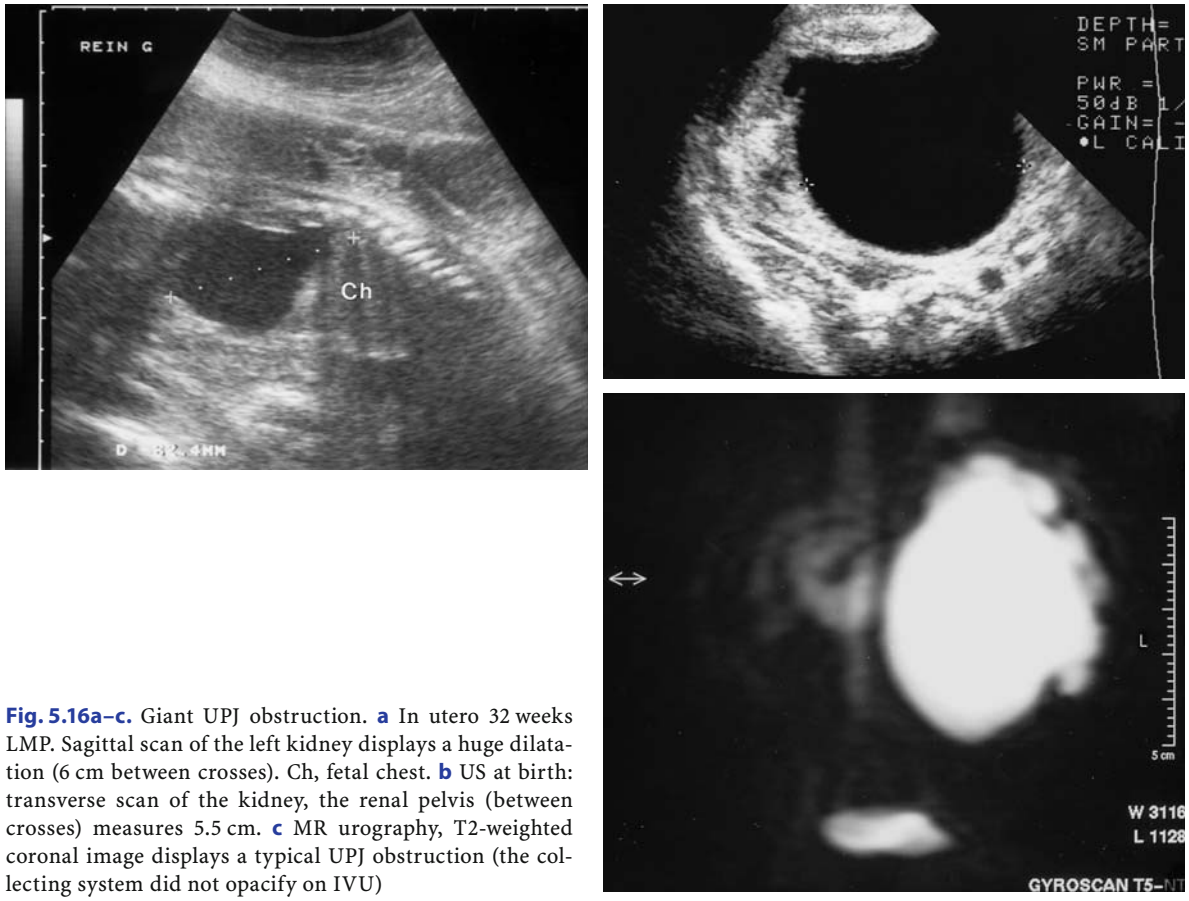

Fig. 5.16a–c. Giant UPJ obstruction. **a** In utero 32 weeks LMP. Sagittal scan of the left kidney displays a huge dilatation (6 cm between crosses). Ch, fetal chest. **b** US at birth: transverse scan of the kidney, the renal pelvis (between crosses) measures 5.5 cm. **c** MR urography, T2-weighted coronal image displays a typical UPJ obstruction (the collecting system did not opacify on IVU)

The kidney functions poorly and the condition usually necessitates a nephrectomy. The condition may mimic a giant multicystic dysplastic kidney.

5.3.4.4.2 UPJ Obstruction and VUR

See Chapter 11 (Lebowitz and Blickman 1983; Bomalski et al. 1997).

5.3.4.4.3 UPJ Obstruction and Ureterovesical Junction Obstruction (UVJ)

Both UPJ and UVJ obstruction may coexist. UVJ obstruction may evolve unrecognized, especially on IVU, up to the surgical correction of the UPJ obstruction (Fig. 5.17); only thereafter will the lower obstruction be detected and eventually corrected. The condition might be easier to diagnose on MR urography (McGrath et al. 1987).

5.3.4.4.4 UPJ Obstruction and Lithiasis

Any condition favoring urinary stasis may induce the development of lithiasis (Fig. 5.18) (Kraus et al. 1999) (see Chap. 20).

5.3.4.4.5 UPJ Obstruction and Horseshoe Kidney

Horseshoe kidney may present UPJ obstruction due to the crossing between the vessels and the ureters. This usually involves one of the collecting systems (Fig. 5.19).

5.3.4.4.6 UPJ Obstruction and Urinoma

An urinoma may complicate a UPJ obstruction. This type of complication may occur already in utero. It is more common with posterior urethral valves and acts like a protecting mechanism against obstruction (Avni et al. 1987; Genes and Vachon 1989).

5.3.4.4.7 Intermittent UPJ

Intermittent UPJ obstruction is a condition where stable conditions alternate with acute dilatation of the collecting system. During an acute phenomenon, the patient experiences pain, nausea and vomiting (Dietl's crisis). The clue to the diagnosis is thickening of the pelvic wall on US during convalescence (Tsai 2006).

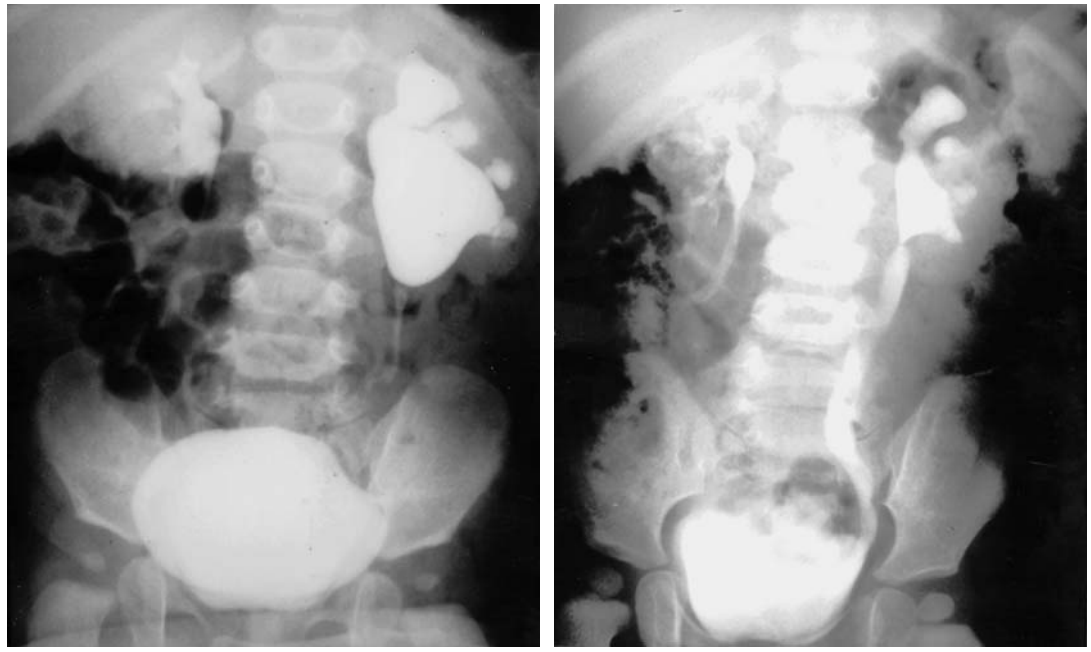

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Fig. 5.17a,b. UPJ and UVJ obstruction. **a** IVU before pyeloplasty. **b** IVU after pyeloplasty: the dilated ureter is now visible

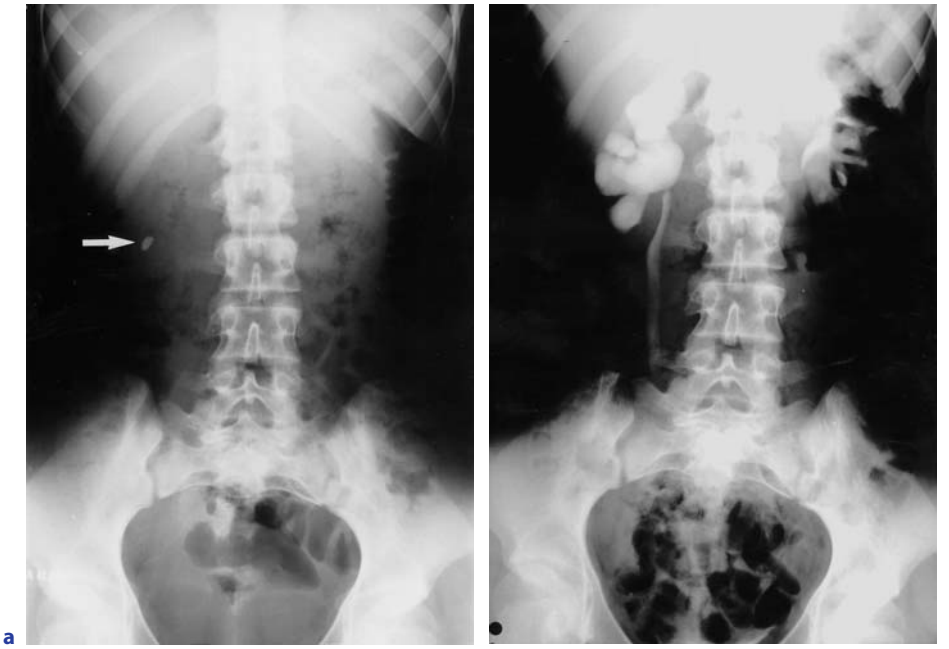


Fig. 5.18a,b. UPJ obstruction and lithiasis. **a** Plain film of the abdomen; right calcified lithiasis (*arrow*). **b** IVU: UPJ obstruction; the lithiasis is in the inferior calyx

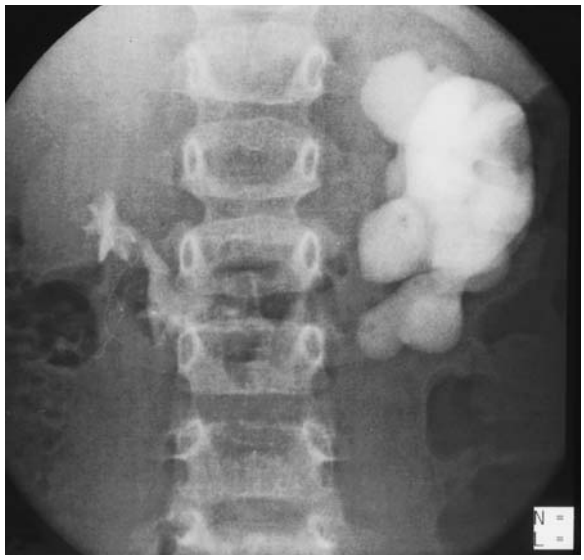


Fig. 5.19. UPJ obstruction and horseshoe kidney. Left side UPJ obstruction on the IVU

5.3.4.5
Differential Diagnosis of UPJ Obstruction

Differential diagnosis of UPJ obstruction should include multicystic dysplastic kidney (MDK), infundibular stenosis, and UVJ obstruction. This differential diagnosis is easy in most cases. In MDK, no renal parenchyma is seen, there are cysts of variable sizes, and there are no connections between the cysts. In infundibular stenosis, the calyces are very dilated, usually more than the renal pelvis. Finally, in UVJ obstruction, the ureter is dilated (Felson and Cussen 1975).

5.3.4.6
The Natural History and Treatment of Neonatal UPJ Obstruction

The postnatal follow-up of fetal hydronephrosis has shown that more than half of the cases of hydronephrosis resolve spontaneously in utero or after birth. This evidence has led to a more conservative approach towards all uropathies and among them UPJ obstruction. On the other hand, many urologists stress the fact that early surgery would improve renal function, while others publish opposite conclusions, although they agree that pyeloplasty is safe in early life.

It seems reasonable to follow these patients during their first year of life with US and isotope studies and to propose surgery if any complication occurs, if renal function diminishes, or if there is evidence of contralateral renal hypertrophy (Koff et al. 1994; Koff and Peller 1995; Koff and Campbell 1994; Ransley et al. 1990; Duckett 1993).

5.3.4.7 Progression of Obstruction

It has rarely been shown that patients with normal kidneys in early life present a true UPJ obstruction later in childhood, necessitating surgical correction (Noe and Magill 1987; Rickwood and Godiwalla 1997; Flaschner et al. 1993).

Conclusion

UPJ obstruction is the leading cause of a urinary tract dilatation. More and more cases are diagnosed with antenatal diagnosis. The confirmation of the obstruction and the best timing for surgery remain controversial.

5.3.5 Megaureter and Hydroureter

Ureteral dilatation, or hydroureter, is a frequent cause of a dilatation of the fetal urinary tract. Under normal conditions, on fetal or postnatal US, the normal ureter is not visualized. Once it is visible (Fig. 5.20), a urinary tract dilatation is present and must be investigated (Keller and Weiss 1993). The presence of a dilated ureter may correspond to primary megaureter (MU), to refluxing MU (see Chap. 11), to nonobstructive nonrefluxing hydroureter, or to secondary hydroureter. The various imaging techniques will be necessary in order to differentiate between these entities.

5.3.5.1 Primary Megaureter

Primary MU corresponds to an obstructive dilatation of the ureter above an adynamic ureteral segment at the ureterovesical junction (Dixon et al. 1994; Lee et al. 1992). The degree of dilatation is variable; typically, on IVU the ureter is predominantly dilated up to the ureterovesical junction, and the dilatation persists on the post-voiding upright view (Fig. 5.21). The adynamic segment may or may not opacify. There may also be a ballooning of the distal ureter. These characteristics also appear on MR urography studies (Fig. 5.22). The degree of associated pelvicalyceal dilatation varies, and it may even sometimes be absent. As mentioned, more and more cases are diagnosed during fetal life and evaluated after birth. MU tends to resolve spontaneously in a large percentage, and therefore a conservative attitude has been proposed. The patients are put under prophylactic antibiotic therapy and followed clinically and by US for several years. Surgery is elected if any complication occurs or if renal function deteriorates (Keating and Retik 1990; Peters 1989; Avni et al. 1992; Wilcox and Mouriquand 1998; Baskin et al. 1994; Liu et al. 1994).

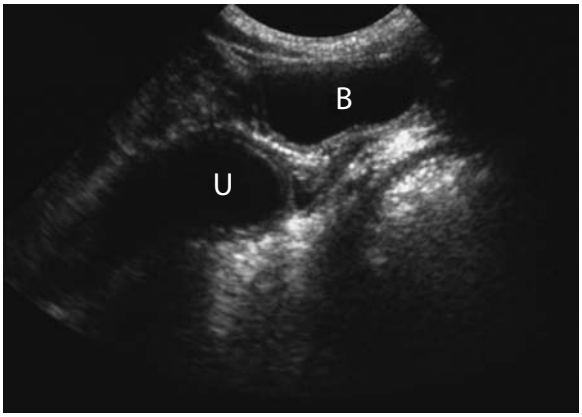


Fig. 5.20. Hydroureter: Ultrasound. Left sagittal scan. A dilated ureter (*U*) is visible behind the bladder (*B*)

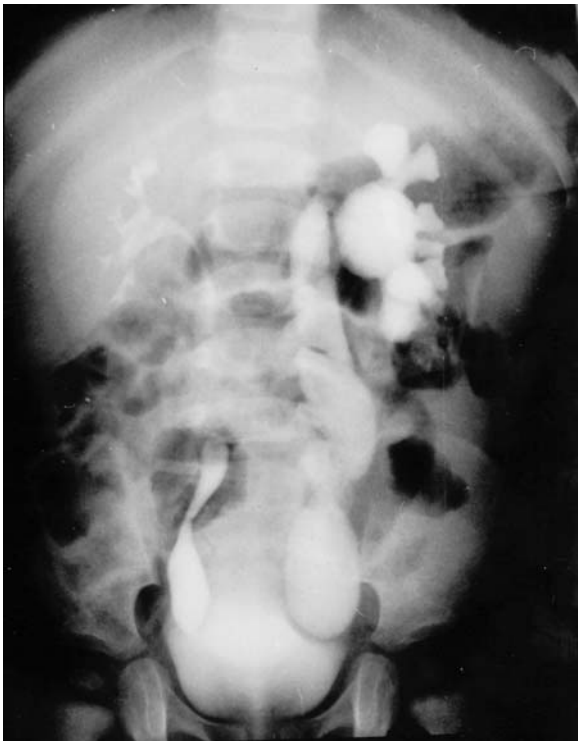


Fig. 5.21. Primary obstructive megaureter. Typical appearance of the UVJ on IVU

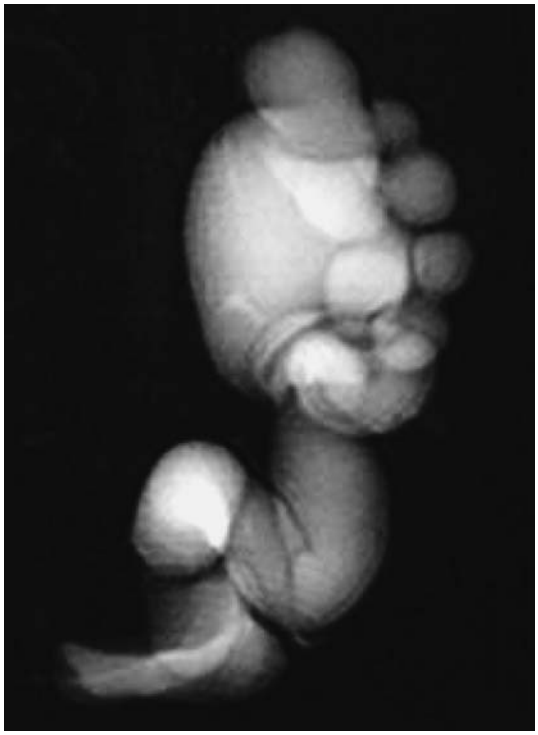


Fig. 5.22. Primary left megaureter on MR urography (courtesy of JN Dacher, MD)

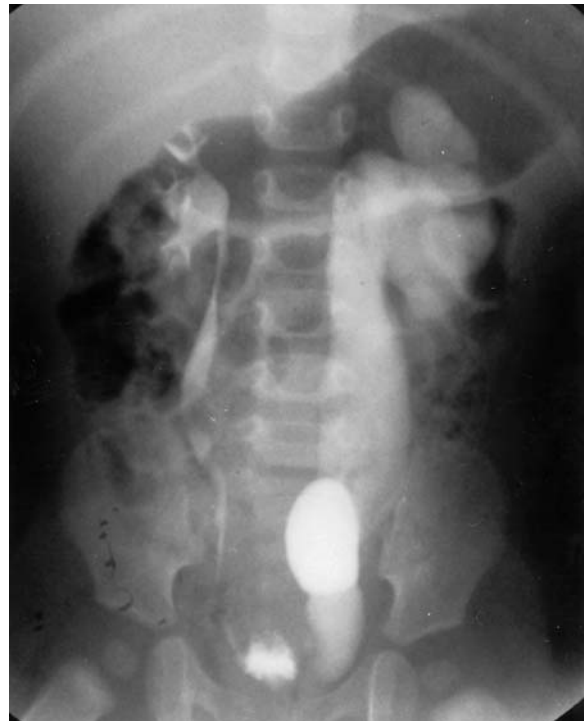


Fig. 5.23. Coexisting UVJ obstruction and VUR: post-void film of a VCU; there is bilateral VUR. On the left, VUR has occurred in a dilated collecting system

5.3.5.2 Refluxing Megaureter

MU and VUR may coexist (Fig. 5.23) (see Chap. 11). Treatment should include both ureteral modeling and antireflux reimplantation (Blickman and Lebowitz 1984).

5.3.5.3 Nonrefluxing Nonobstructive Megaureter

In this condition no VUR is found on VCU and no adynamic segment is demonstrated. This condition may represent the evolution and sequelae of an antenatal dilatation (Rickwood et al. 1992).

5.3.5.4 Secondary Hydroureter

5.3.5.4.1 Intrinsic Causes

Ureteral dilatation may occur secondarily to ureteral valves, midureteral or distal stenosis, or due to ureteral diverticula (Figs. 5.24, 5.25) (Sant et al. 1985; Young and Lebowitz 1986; Maizels and Stephens 1980; Cope and Snow 1991; Pinter et al. 1997). Valves should be differentiated from pseudovalves corresponding to the persistence of a fetal pattern that is transitory and nonobstructive (Fig. 5.26).

5.3.5.4.2 Extrinsic Causes

Retrocaval ureter causes a typical medial displacement of the right lumbar ureter that is appreciated on IVU (Fig. 5.27), but best demonstrated on CT. Ischiatic or crural herniation of the ureter may also occur; the ureter will display an unusual lateral and anterior course (Fig. 5.28). Retroperitoneal tumoral processes and genitourinary pelvic tumors may determine displacement and secondary obstruction of the ureters (Fig. 5.29). A distended bladder also induces ureteral and pyelocalyceal dilatation, and, therefore, the size of the collecting system must be controlled after micturition. In severe cases constipation may displace and distend the ureters

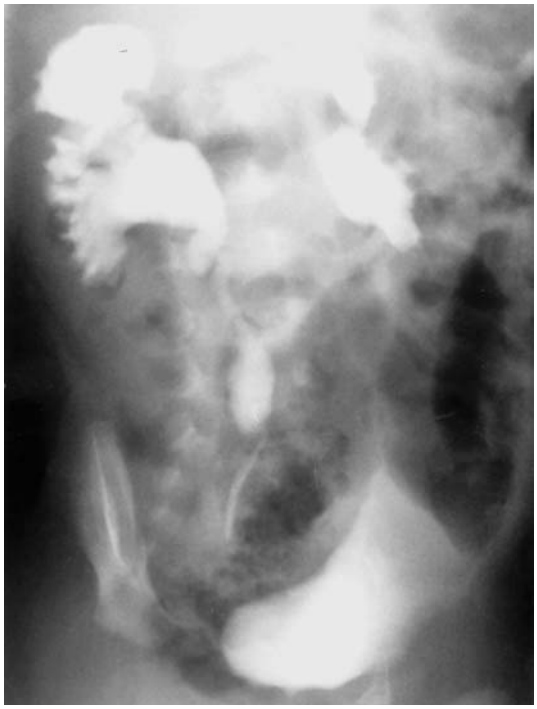


Fig. 5.24. IVU of a right mid-ureteral stenosis (oblique view)

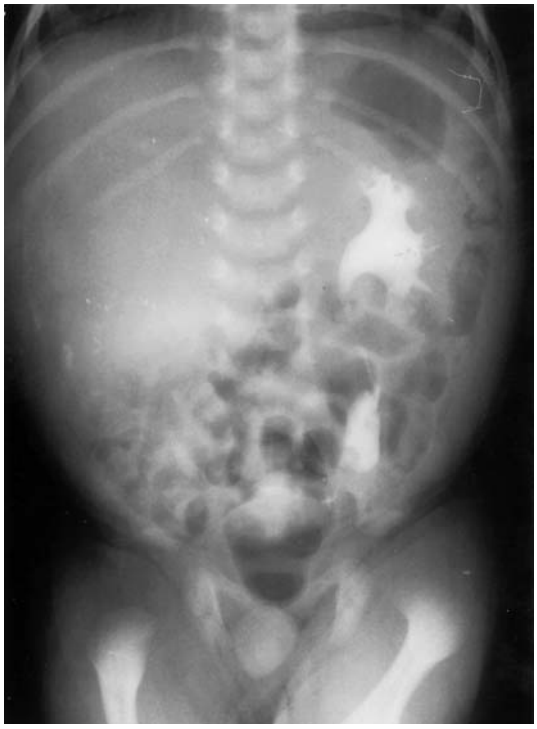


Fig. 5.25. Left ureteral diverticulum (coexisting mild right UPJ obstruction)

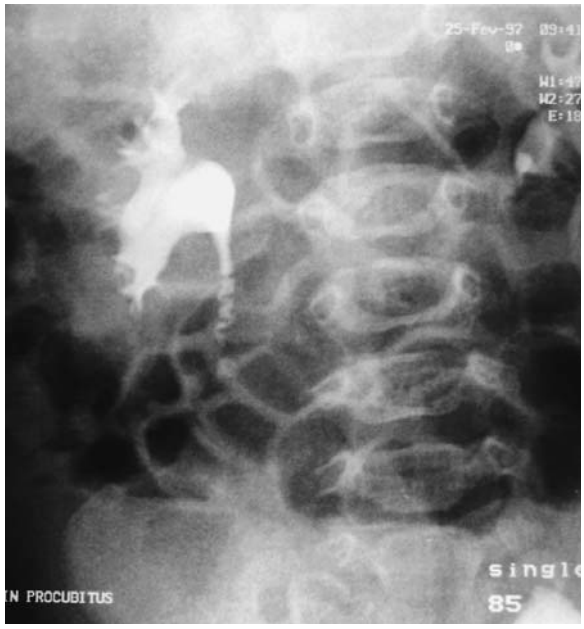


Fig. 5.26. Persisting fetal ureter determining pseudovalves on the proximal ureter (30-s view of an IVU)

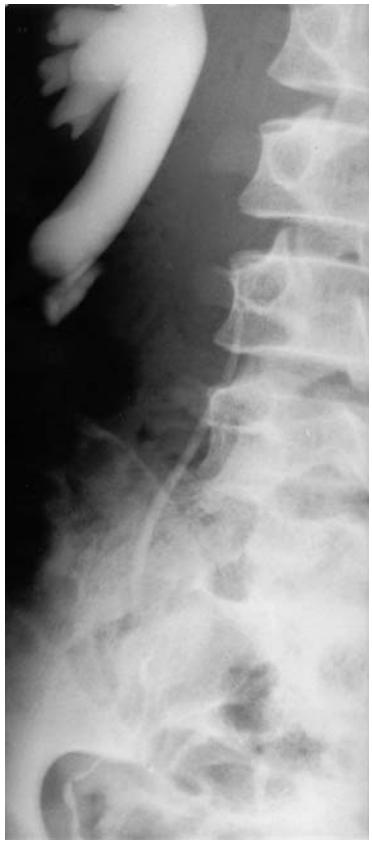


Fig. 5.27. Retrocaval ureter with a typical course on IVU (oblique view) (courtesy of U. Willi, MD)

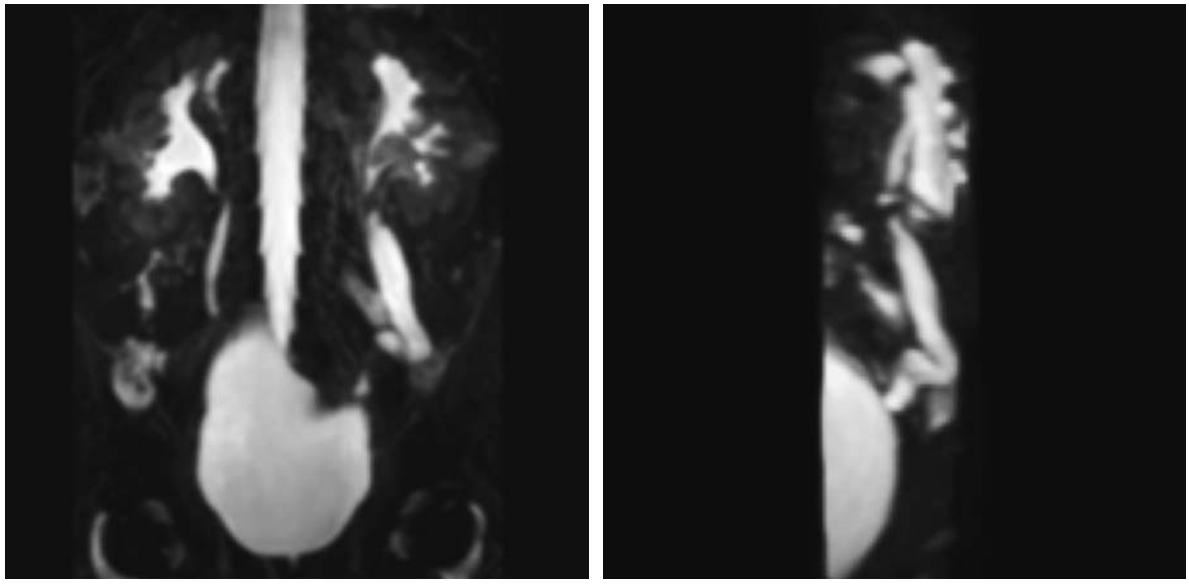


Fig. 5.28a,b. Crural hernia of a left megaureter. MR imaging T2-weighted sequence. **a** Upright AP view. **b** Lateral view showing the anterior course of the ureter

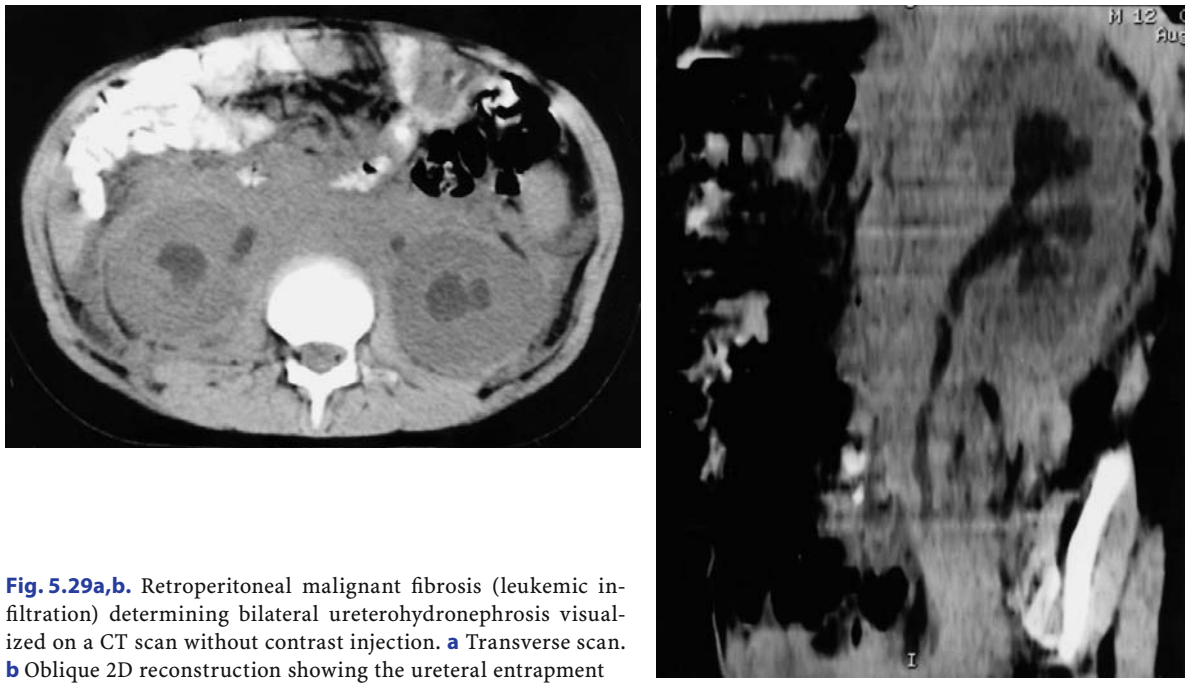


Fig. 5.29a,b. Retroperitoneal malignant fibrosis (leukemic infiltration) determining bilateral ureterohydronephrosis visualized on a CT scan without contrast injection. **a** Transverse scan. **b** Oblique 2D reconstruction showing the ureteral entrapment

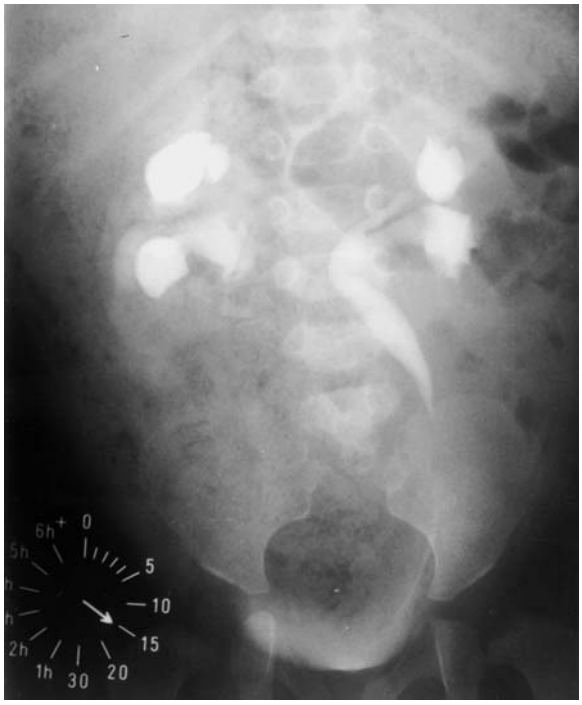


Fig. 5.30. Ureterohydronephrosis induced by fecaloma (patient with caudal regression syndrome and dysplastic kidneys)

(Fig. 5.30). Lithiasis, hematoma or, rarely, tumors induce ureteral dilatation, and the work-up must be adapted according to the potential diagnosis (Young and Lebowitz 1986; Lautin et al. 1988; Herbetko and Hyde 1990; Oyen et al. 1987; Padovani et al. 1984; Sherman et al. 1988).

5.3.5.5 The Natural History of Primary Megaureter

See Chapter 13.

5.3.6 Ureteral Wall Lesions and Look-Alike

Ureteral wall lesions most often correspond to inflammatory and infectious lesions. They are best visualized on IVU where they appear as filling defects (cystic ureteritis) or striations (ureteritis) (see Chap. 15). Differential diagnosis should include hematoma and varices (Williamson et al. 1986; Avni et al. 1988; Galakhoff et al. 1986; Matsumoto 1986; Padovani et al. 1984).

5.3.7 Ectopic Ureter

Ureteral ectopia may be associated with single or duplex collecting systems (see below). Ureteral ectopia with a single system is much rarer than in the duplex kidney. Unilateral ectopia is more common in boys, whereas bilateral ectopia is more frequent in girls. It is usually associated with poorly functioning dysplastic kidney(s); the kidney may even correspond to a multicystic dysplastic kidney (Blane et al. 1992). The ectopic ureter may drain into the rectum, the posterior urethra, or the vas deferens in boys (Fig. 5.31). It drains into the urethra, the vagina, or the uterus in girls, it may drain into the rectum, or a Gartner duct cyst (Sheih et al. 1996). VUR into the ectopic ureter may appear during cycling VCU.

The anomaly is best demonstrated on MR urography or on contrast-enhanced CT. Poorly functioning kidneys are difficult to characterize on IVU, and the

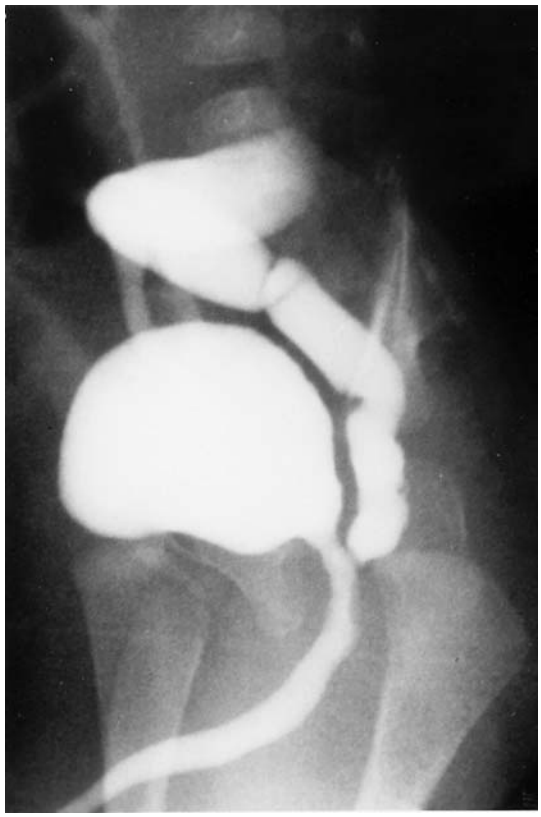


Fig. 5.31. VUR into an ectopic ureter inserting into the posterior urethra (patient with pelvic horseshoe kidney)

inferior ectopic insertion may be difficult to localize precisely by US (Borer et al. 1998; Wyly and Lebowitz 1984; Pantuck et al. 1996; Gharagoloo and Lebowitz 1995; Braveman and Lebowitz 1991; Avni et al. 1997).

5.3.8 Ureterocele

Ureterocele (ucele) represents cystic dilatation of the intravesical segment of the ureter. It is more common with duplex kidneys. When it is associated with a single system, the ucele is commonly intravesical. An ectopic ucele may also be associated with a multicystic dysplastic kidney (Fig. 5.32). On US, the ucele appears as a cystic structure within the bladder that is connected with the ureter (Fig. 5.33); the upper urinary tract is not necessarily obstructed or dilated. On IVU, after injection, the ucele appears as a filling defect within the bladder, especially on early films, and it opacifies progressively (Fig. 5.34).

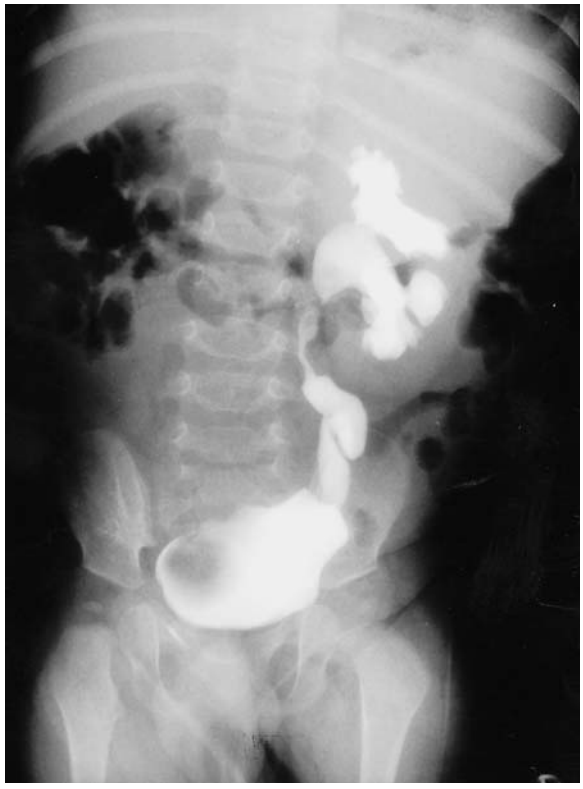


Fig. 5.32. Right side ureterocele associated with a multicystic dysplastic kidney; mild dilatation of the left collecting system (30-s view of an IVU)

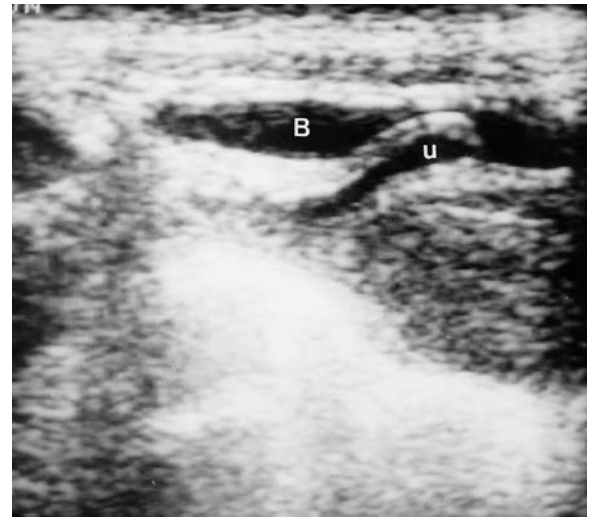


Fig. 5.33. US of a single system ureterocele (*u*) protruding into the bladder (*B*) on a left parasagittal scan

The treatment is similar to that for ucele in duplex kidneys depending on the degree of secondary obstruction (Gonzales 1992). It is worth noting that a ucele may be associated with a multicystic dysplastic kidney.

5.3.9 Bifid Collecting Systems

Bifid collecting systems correspond to incomplete duplication of the ureter; the ureters may meet at any level between the UPJ and the UVJ. US cannot differentiate the complete from the incomplete duplex kidney. The condition is best evaluated by IVU or MR urography (Fig. 5.35). An obstruction may occur at the lower pole collecting system or at the meeting point of the two ureters. Ureteroureteral or pyelopyelic reflux (yo-yo reflux) is also typical for this condition (Fig. 5.36) (see Chap. 11) (Joseph et al. 1989; Tressider et al. 1970; Gonzales 1992).

Conclusion

Primary MU has a typical appearance best demonstrated on IVU and MRI. A hydroureter may or may not be secondary to obstruction and associated with VUR.

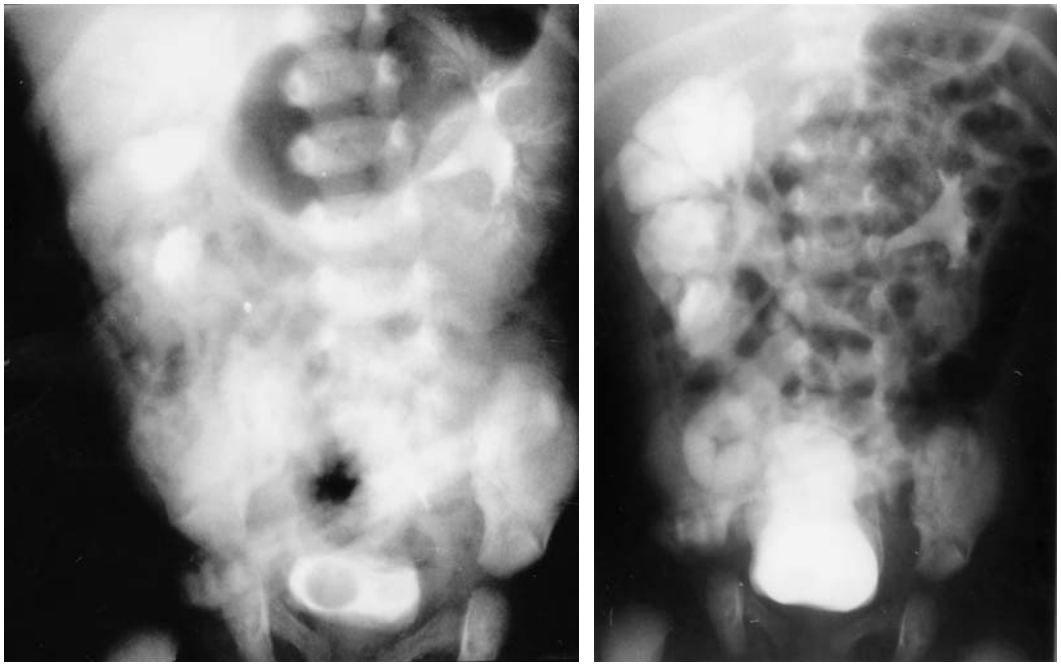


Fig. 5.34a,b. IVU of a right single system ureterocele. **a** Early film showing a filling defect within the bladder that corresponds to the ureterocele without contrast. **b** On a late 45-min view the entire system is now opacified

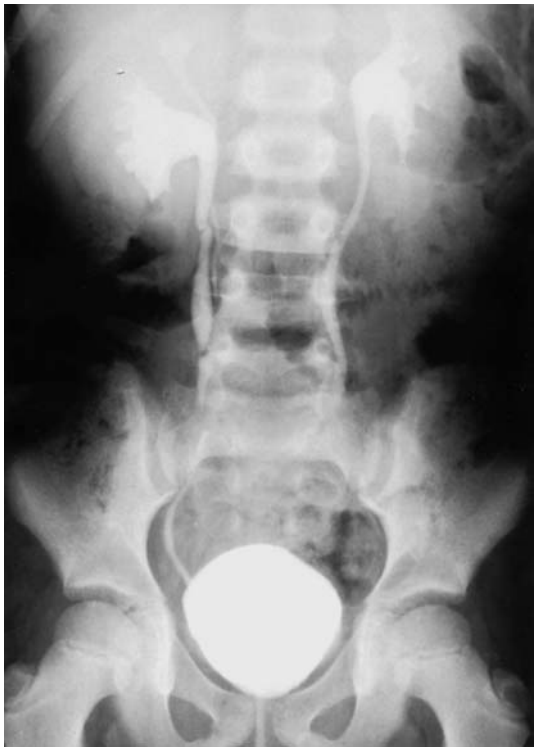


Fig. 5.35. Bifid collecting system. On this IVU the ureters fuse at their lower lumbar segment. There is a sub-obstruction on the ureter draining the lower pole

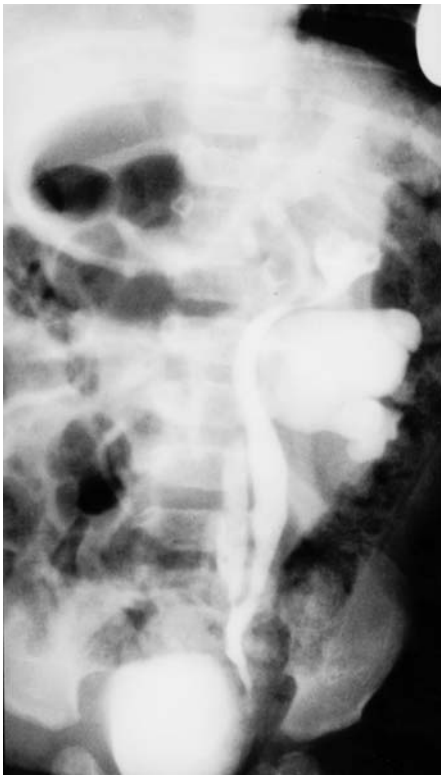


Fig. 5.36. Left bifid collecting system with VUR on VCU

5.4 Duplex Collecting Systems

5.4.1 Etiology and Epidemiology

Complete duplication is thought to result from two separate ureteral buds presenting on the mesonephric duct (Glassberg et al. 1984). The orifice of the ureter draining the lower segment of the kidney migrates more cephalad and lateral than the ureter draining the upper part of the kidney (Weigert-Meyers law). When both orifices open close to each other at a normal location, no complications occur. On the contrary, when they open apart from each other and away from the normal location, complications occur: the lower pole is usually associated with VUR and the upper pole with ureteral ectopia or ucele with secondary obstruction. Dysplasia of the upper pole is also very common and seems to be related to an abnormal position of the ureteral bud on the renal blastema (Mckie and Stephens 1975). Complete ureteral duplication occurs in 1 out of 500 patients, most often with no complications (Fig. 5.37).

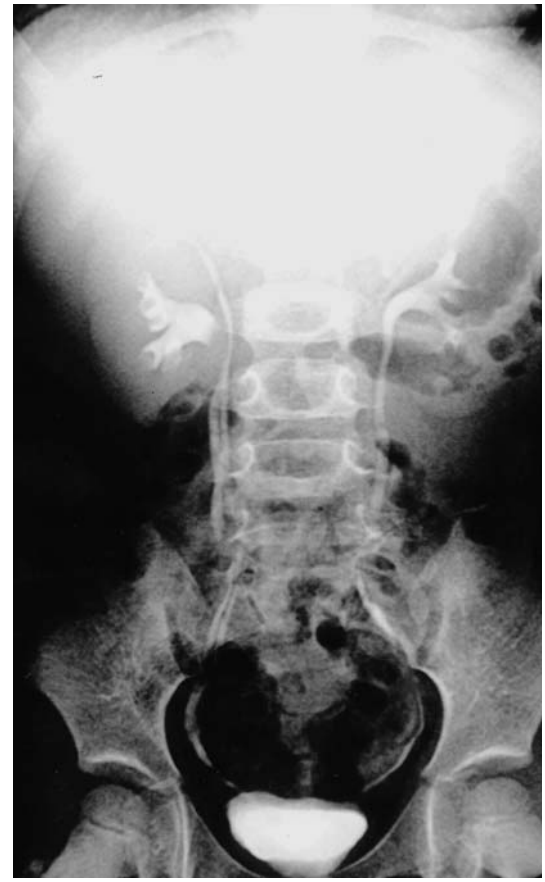


Fig. 5.37. IVU of complete bilateral non-complicated duplication

5.4.2 Presentation and Circumstances of Diagnosis

Uncomplicated duplex kidney is usually detected during a US examination that demonstrates two distinct renal hila separated by a bridge of normal parenchyma (Fig. 5.38). Unless there is a clinical indication, no further examination is necessary.

Many complications may occur and involve any of the poles of the duplex kidney, sometimes both, such as dilatation of the upper or lower pole, pyonephrosis, VUR, ectopic ureter, or ucele.

Abnormal duplex kidneys used to be and are still detected during the work-up of urinary tract infection or urinary dribbling in girls. They are more and more often demonstrated during fetal life. In utero, it is possible to differentiate between the two collecting systems particularly if one is dilated. It is even possible to differentiate between ectopic ureter and ucele in utero (Joseph et al. 1989; Avni et al. 1991; Abuhamad et al. 1996; Vergani et al. 1999; Caione et al. 1989; Jee et al. 1993). Other forms of presentation include interlabial mass in girls or bladder outlet obstruction. Both conditions are related to urethral prolapse of the ucele (Nussbaum 1983).

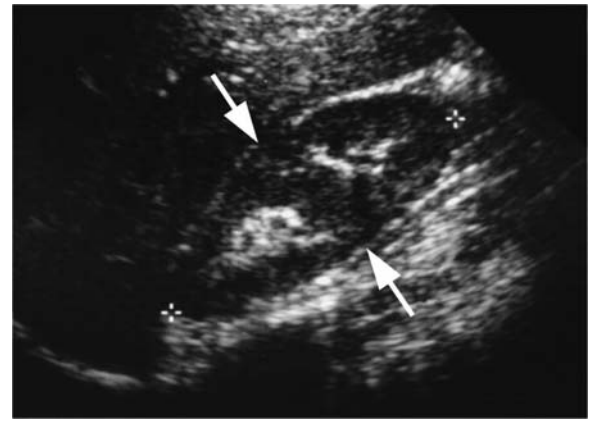


Fig. 5.38. US of renal duplication: sagittal scan of the right kidney. The two hyperechoic sinusal entities are separated by a parenchymal bridge (*arrows*)

5.4.3 The Work Up of Duplex Kidneys: General Considerations

The findings of obstetrical US have to be confirmed after birth by US first. US usually demonstrates the two renal poles and the ureterohydronephrosis involving one or both moieties. It displays easily intravesical uceles; however, the technique cannot always demonstrate ectopic ureters. VCU is performed thereafter in order to detect VUR, including ectopic ureter reflux, and to evaluate the ucele. MR imaging is performed whenever anatomical information is needed on the morphology of the duplex system. The technique is able to provide all the anatomical details as well as some functional information after gadolinium enhancement. Isotope studies are mandatory to determine renal function that remains in the dilated and dysplastic renal moiety. This complete work up is mandatory in order to orient the best therapeutic approach (Avni et al. 2001, 2000).

5.4.4 Duplication and VUR

VUR is much more likely to occur into the lower than in the upper pole of a duplex kidney. Lower-pole VUR is the most common abnormality that is associated with a duplex kidney (Fig. 5.39). The degree of VUR varies from mild to severe and can be graded like VUR into single systems. Massive VUR into a markedly dilated system may be misinterpreted as VUR in a single system. The VUR in the lower pole may be an isolated finding or may coexist with other types of pathologies and especially obstruction of the upper pole (Claudon et al. 1999).

The so-called reflux nephropathy (RN) of the lower pole is commonly associated with VUR. It may be present already at birth with no pre-existing urinary tract infection (fetal RN). VUR may occur simultaneously in both moieties; this implies that the ureteral openings within the bladder are very close or even common. VUR that flows into the upper pole usually only corresponds to an ectopic ureteral opening into the urethra close to the bladder neck (Bissett and Strife 1987).

VUR into the lower pole may also occur after endoscopic unroofing of an ucele (Blyth et al. 1993). The natural history of VUR into the lower pole is similar to VUR into a single system; it may resolve spontaneously (Ben Ami et al. 1989; Peppas et al. 1991).

5.4.5 Ureteral ectopia

Typically, the ureter draining the upper pole develops caudal to the normal location and is often ectopic,

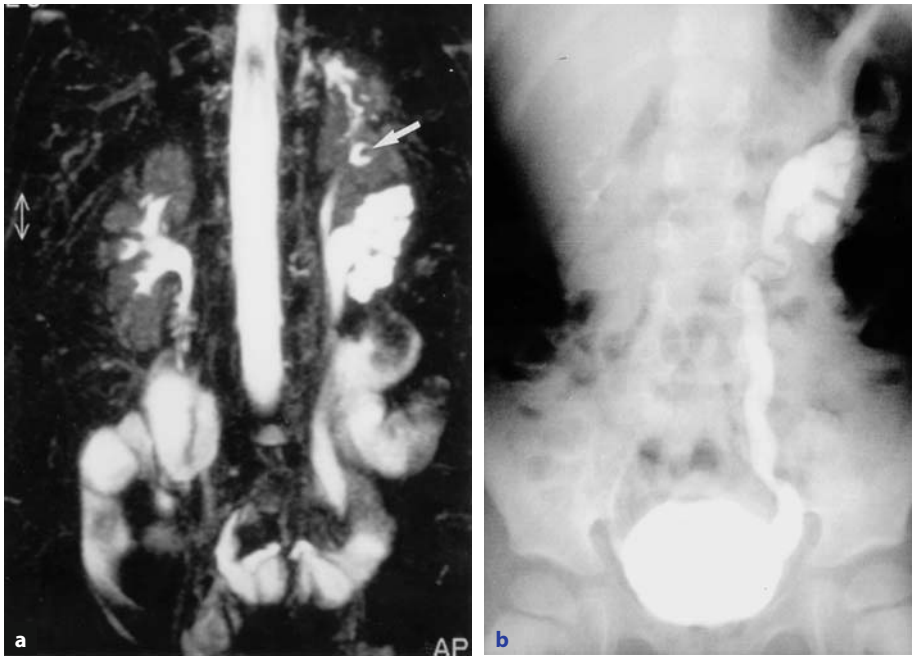


Fig. 5.39a,b. VUR into the lower pole of a duplex system. **a** Left grade III–IV VUR into the lower pole (right grade II VUR). **b** MR urography displaying the monocalyceal upper (*arrow*) and dilated lower collecting systems (T2-weighted coronal sequence)

somewhere along the pathway of the mesonephritic system. In boys, ectopic ureteral orifices open most usually into the posterior urethra, but also into the ejaculatory ducts or the epididymis (the condition should therefore be suspected in orchiepididymitis). In girls, the ectopic ureter drains into the bladder neck, the vagina, or the uterus. Ectopic ureter is usually associated with obstruction, rarely with VUR, or both (Fig. 5.40).

As mentioned above, more and more cases are diagnosed during obstetrical US and evaluated at birth. In these children, the anomaly will be confirmed by US after birth and further work up will include VCU and MR urography (Fig. 5.40). In older children, ectopic ureters may be detected during the work up of urinary tract infection. Typical clinical presentations include orchiepididymitis in boys and urinary dribbling in girls. Yet, many cases may evolve unrecognized up to late childhood since many ectopic draining upper poles function poorly (Share and Lebowitz 1990). Usually the duplex system is detected on US examination with the dilatation of the lower or the upper pole. The technique can suggest an ectopic insertion, but usually cannot demonstrate it (Nussbaum et al. 1986). On IVU, a duplex collecting system can be suspected when the renal parenchyma related to the upper pole is still functioning. Like US, the technique is unable to demonstrate the ectopic insertion. The ectopic ureter may occasionally opacify during a VCU (Fig. 5.41). Contrast-enhanced CT and better MR urography are both able to demonstrate the ectopic extravesical insertion even though the upper pole parenchyma is small or functions poorly (Figs. 5.40, 5.41) (Avni et al. 1997; Share and Lebowitz 1990; Braveman and Lebowitz 1991).

Upper pole heminephrectomy is required in order to stop the urinary dribbling or recurrent urinary tract infection when the dysplastic upper pole is still functioning. The inferior part of the ureter is usually left in place and may display reflux. MR imaging (with Gd injection) is able to determine the remaining function of the dysplastic parenchyma (Avni et al. 1997).

5.4.6 Ureterocele

Ureterocele is the other anomaly that can be associated with the upper pole of a duplex kidney. Uceles represent a dilatation of the intravesical portion of the ureter. They may be associated with a wide spectrum of anomalies at the upper pole, in the bladder, and in the urethra. Large uceles may be in relation with tiny upper poles, whereas small uceles may be highly obstructive (Fig. 5.42). Uceles have been classified into stenotic, sphincteric, sphincterostenotic, cecoureterocele, blind ucele, and nonobstructed ucele according to their location and degree of obstruction (Lebowitz and Avni 1980; Share and Lebowitz 1989). The cecoureteroceles are located down into the posterior urethra (Fig. 5.43), and their surgical correction is more difficult. Again, as for ectopic ureter, many uceles are detected during fetal US allowing rapid evaluation and treatment at birth. They are also detected during the work up of urinary tract infection and more rarely as an interlabial mass in the baby girl.

Uceles are best visualized on US examination as a cystic structure within the bladder (Figs. 5.42–5.44) (Cremin 1986; Daniels and Allen 1994; Nussbaum et al. 1986). Small low-positioned uceles may remain unrecognized with this technique. Their differential diagnosis on US includes the Gartner duct cyst and the Wolffian duct cyst, which are extravesical and may be associated with genital or renal anomalies (Fig. 5.45) (Higashi et al. 1990; Kapoor et al. 1989; Trigaux et al. 1991). Uceles are also well visualized on IVU (Fig. 5.43), MR urography (Figs. 5.46, 5.47) and VCU. On IVU or VCU, the differential diagnosis should include air bubble, blood clot, lithiasis, tumor, or balloon catheter (Lebowitz and Avni 1980). US is usually sufficient for this differential. On VCU the uceles may display varying appearances. During the filling phase, the ucele may disappear, evert, or prolapse within the urethra and induce bladder outlet obstruction (Figs. 5.43, 5.48) (Lebowitz and Avni 1980; Bellah et al. 1995). The fear of this type of obstruction has led several teams to propose early endoscopic unroofing of the ucele (Blyth et al. 1993; Shekarriz et al. 1999; Jayanthi and Koff 1999; Husmann et al. 1999). The advantage of the method is that it helps to drain the obstructed urinary tract, providing hope of improving function and rendering heminephrectomy unnecessary. The disadvantage is that secondary VUR into the upper pole may supervene, making reimplantation necessary. After incision, the ucele collapses and appears as a pseudomass within the bladder (Rypens et al. 1992).

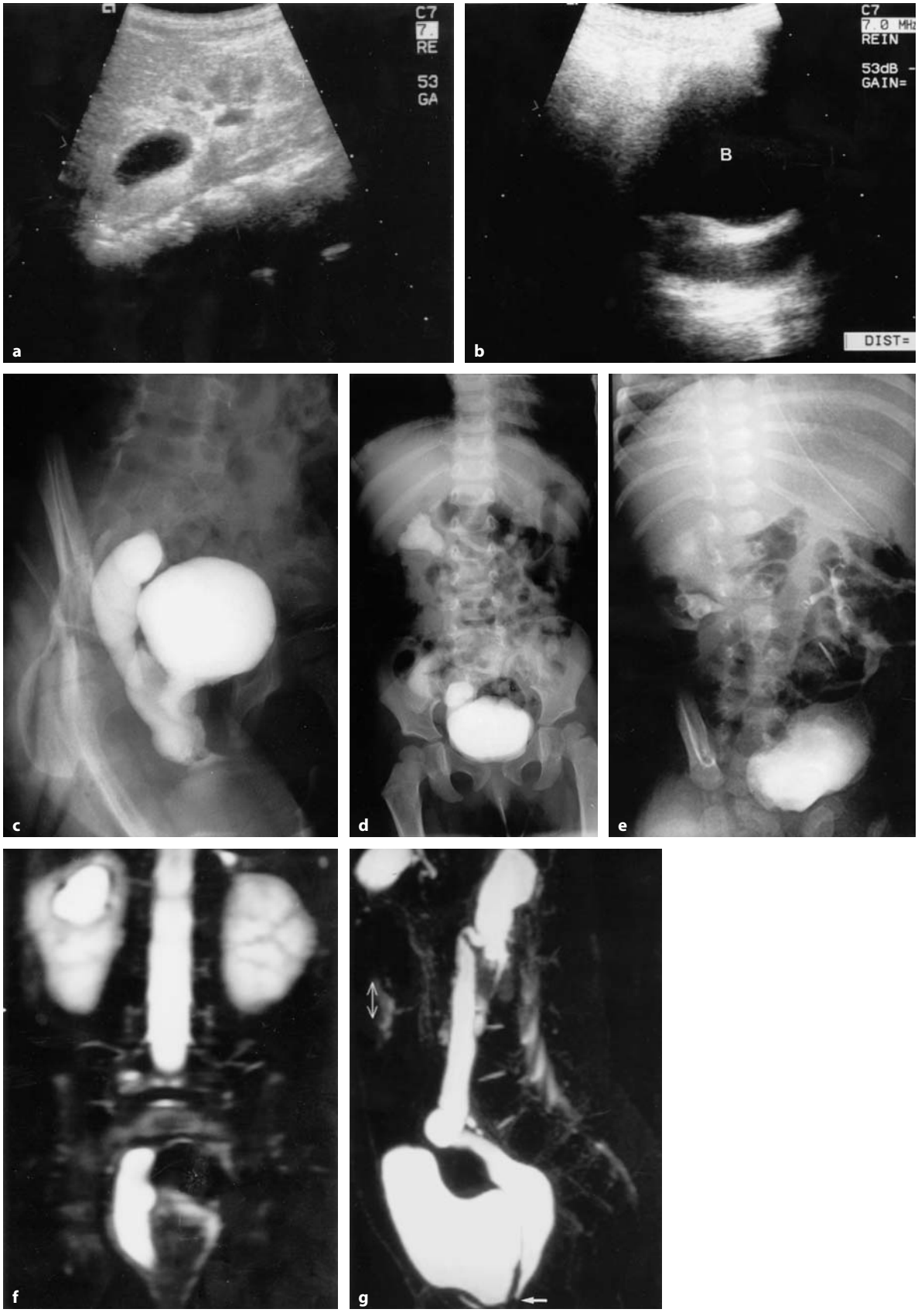
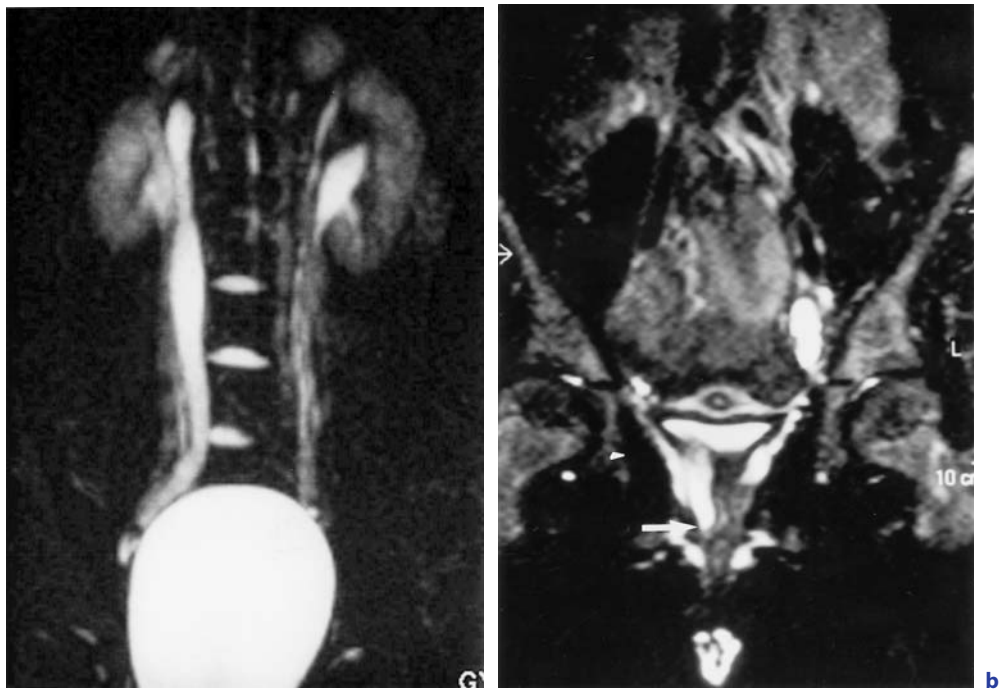
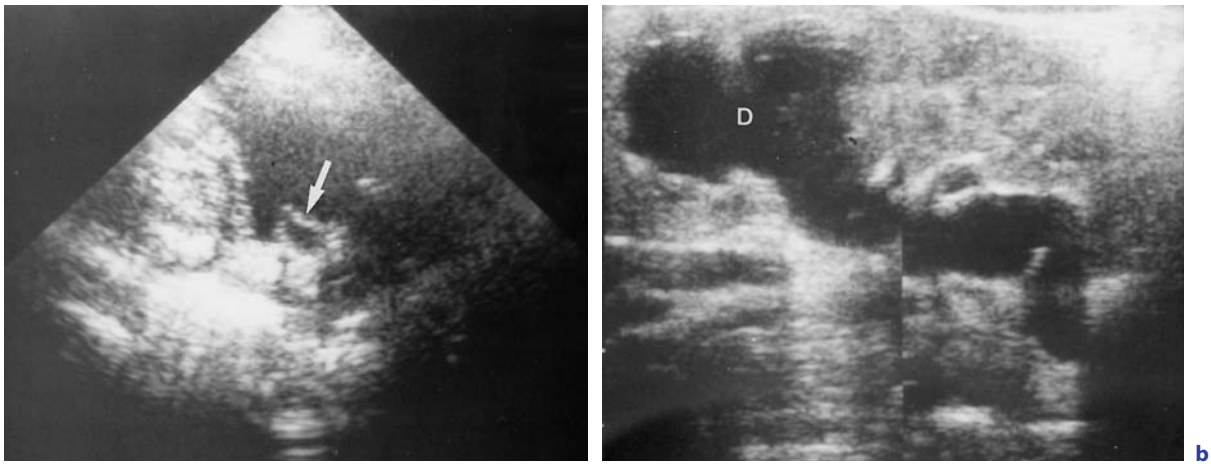


Fig. 5.40a–g. Right duplex collecting system with ectopic uretral insertion of the upper pole in a 6-month-old baby girl. **a** US of the kidney (between *crosses*): dilatation of the upper pole. **b** Right sagittal scan of the bladder (*B*). The ureter is dilated (between *crosses*), but its insertion cannot be visualized. **c** VCU: during voiding, the ureter opacifies and the insertion seems located in the urethra (there is also a vaginal VUR). **d** VUR reaches the pyelocalyceal system of the upper pole. **e** IVU: the opacification of the right upper pole is poor. **f** MR urography: coronal SPIR T2 sequence showing the right duplication and the inferior insertion. **g** MR urography: sagittal inversion-recovery T2 sequence with MIP reconstruction shows the low extravesical insertion of the upper pole ureter (*arrow*)



a b

Fig. 5.41a,b. Ectopic vaginal insertion of an upper pole ureter (7-year-old girl with urinary dribbling). **a** MR urography T2-weighted sequence shows bilateral duplication with dilated right upper pole ureter. **b** MR urography on the bladder: vaginal ectopia of the ureter corresponding to the upper pole (*arrow*)



a b

Fig. 5.42a,b. Small obstructive ureterocele. **a** Small intravesical ureterocele (*arrow*). **b** Important dilatation (*D*) of the corresponding upper pole

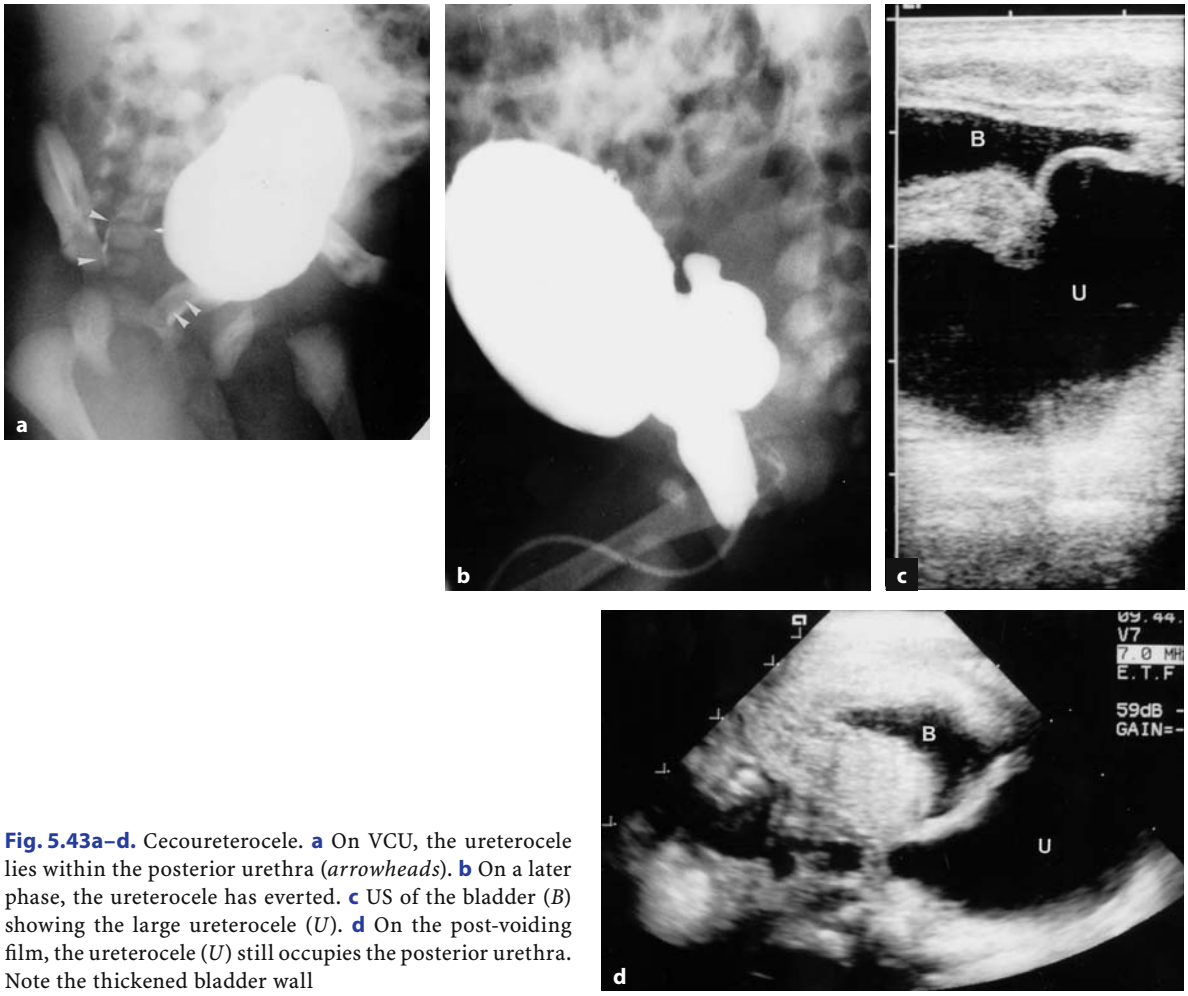


Fig. 5.43a–d. Cecoureterocele. **a** On VCU, the ureterocele lies within the posterior urethra (*arrowheads*). **b** On a later phase, the ureterocele has everted. **c** US of the bladder (*B*) showing the large ureterocele (*U*). **d** On the post-voiding film, the ureterocele (*U*) still occupies the posterior urethra. Note the thickened bladder wall

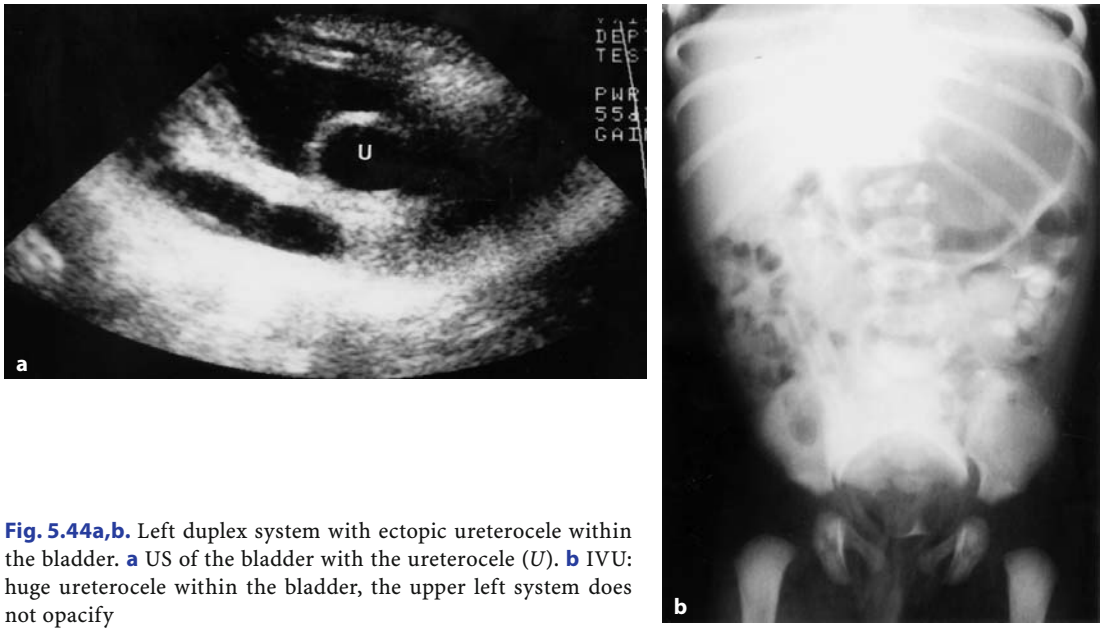
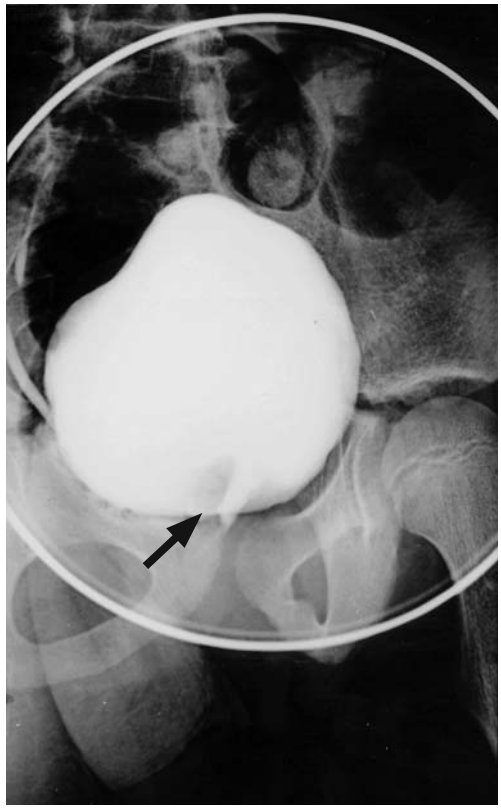


Fig. 5.44a,b. Left duplex system with ectopic ureterocele within the bladder. **a** US of the bladder with the ureterocele (*U*). **b** IVU: huge ureterocele within the bladder, the upper left system does not opacify



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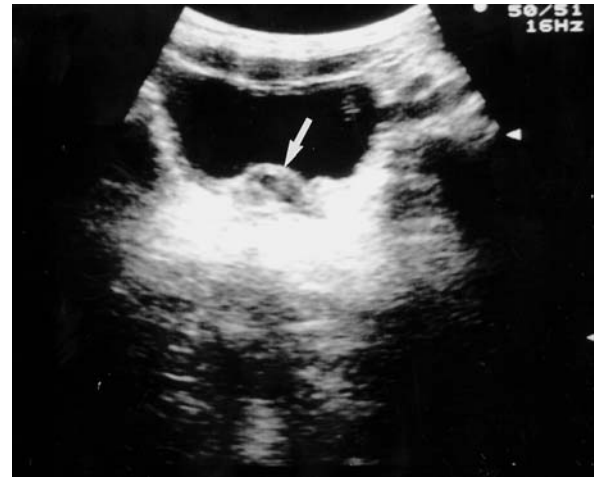
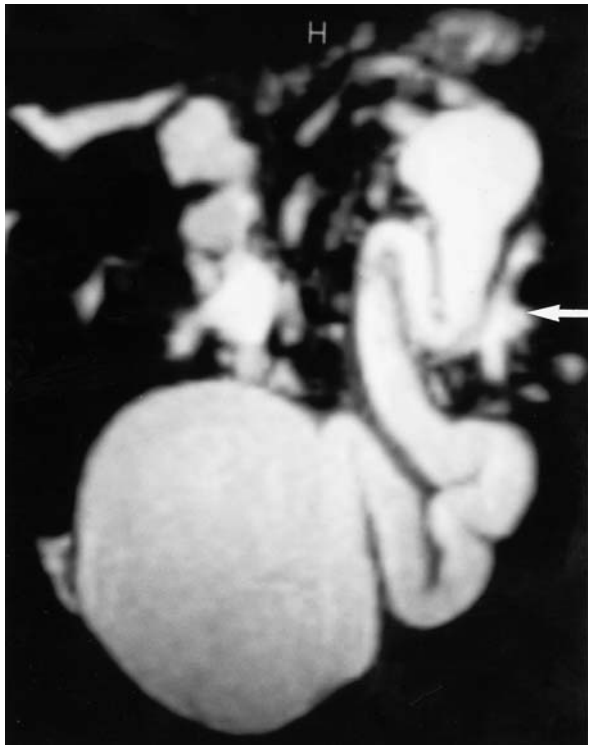


b

Fig. 5.45a, b. Cystic Mullerian remnant in a girl with left renal agenesis. **a** VCU shows a pseudoureterocele (*arrow*) and a right side VUR. **b** US displays a cystic structure posterior to the bladder neck (*arrow*)



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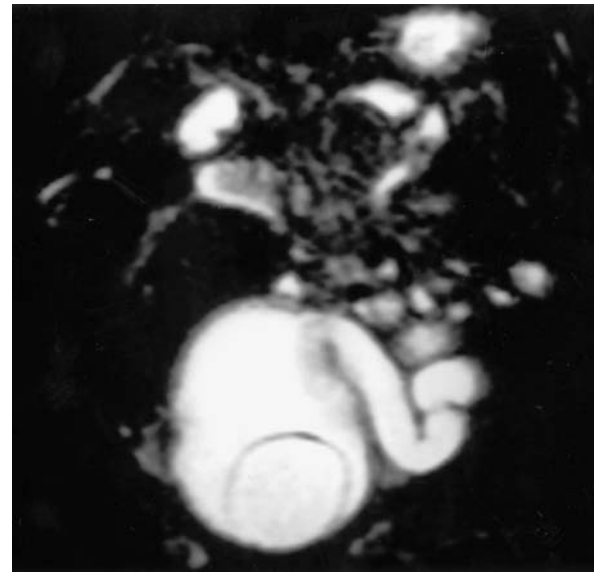


b

Fig. 5.46a,b. MR urography of a left duplex system. **a** Inversion recovery coronal view showing the dilated upper and lower nondilated moiety (*arrow*). **b** Source images allow the visualization of the ureterocele

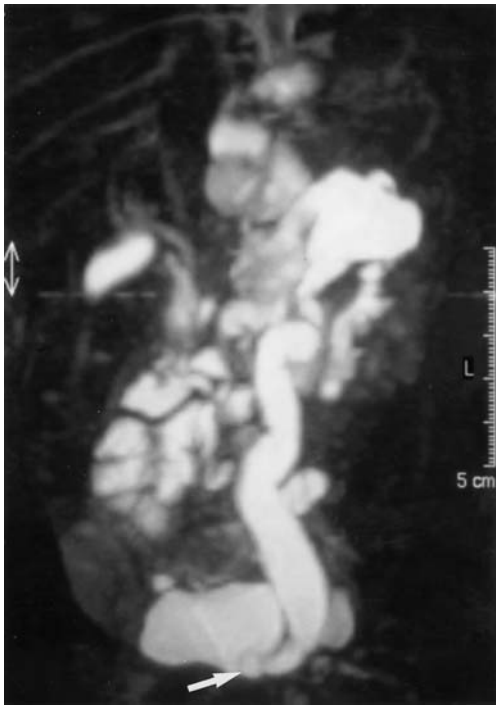


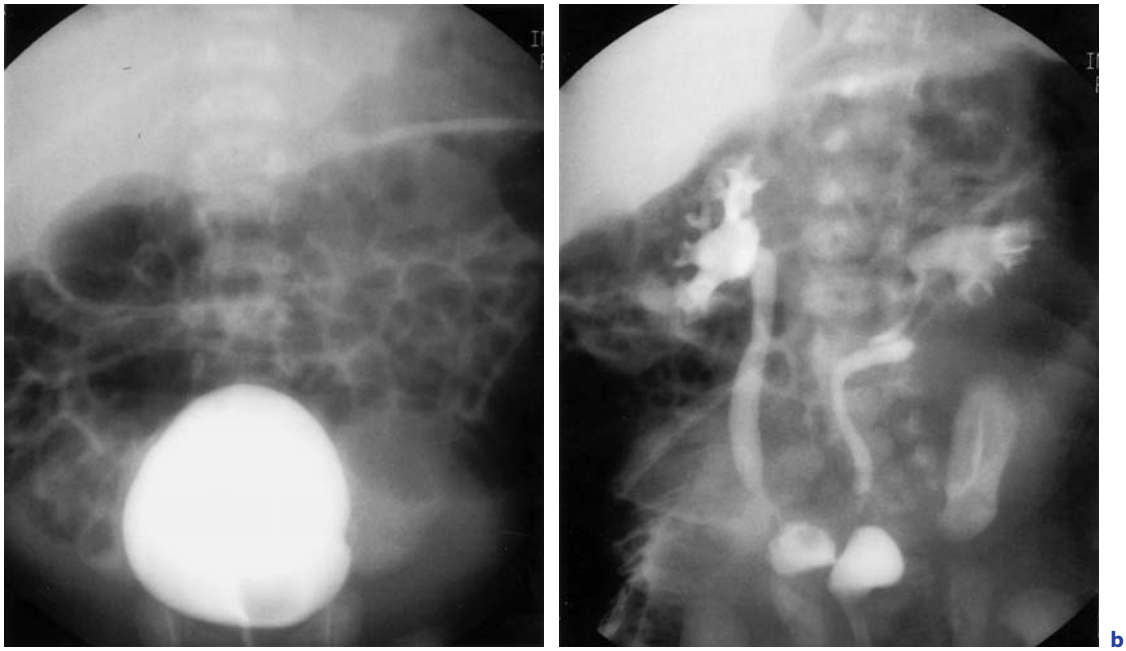
Fig. 5.47. MR urography of duplex system with ectopic ureterocele, T2 inversion-recovery sequence. The small ureterocele (*arrow*) was not visualized by US

5.4.7 (Cystic) Dysplasia of the Upper Pole

The appearance and function of the parenchyma at the upper pole of a duplex kidney vary widely. It may appear normal with a preserved function; this usually occurs in duplex kidneys with normally or near-normally positioned ureteral openings. On the contrary, the parenchyma may be very thin and poorly functioning in relation with ectopic ucele or ectopic ureters (Gartell et al. 1983; Corrales and Elder 1996). The condition is usually detected by US, sometimes in utero. The condition may be recognized later in childhood due to infection or dribbling. IVU is usually insufficient to demonstrate the poorly functioning upper pole; CT or MR urography and isotopes are complementary in demonstrating the morphology and the function of the dysplastic renal moiety (Fig. 5.49) (Share and Lebowitz 1990; Avni et al. 1997). The dysplastic upper pole may involute progressively, in a way similar to multicystic dysplastic kidney.

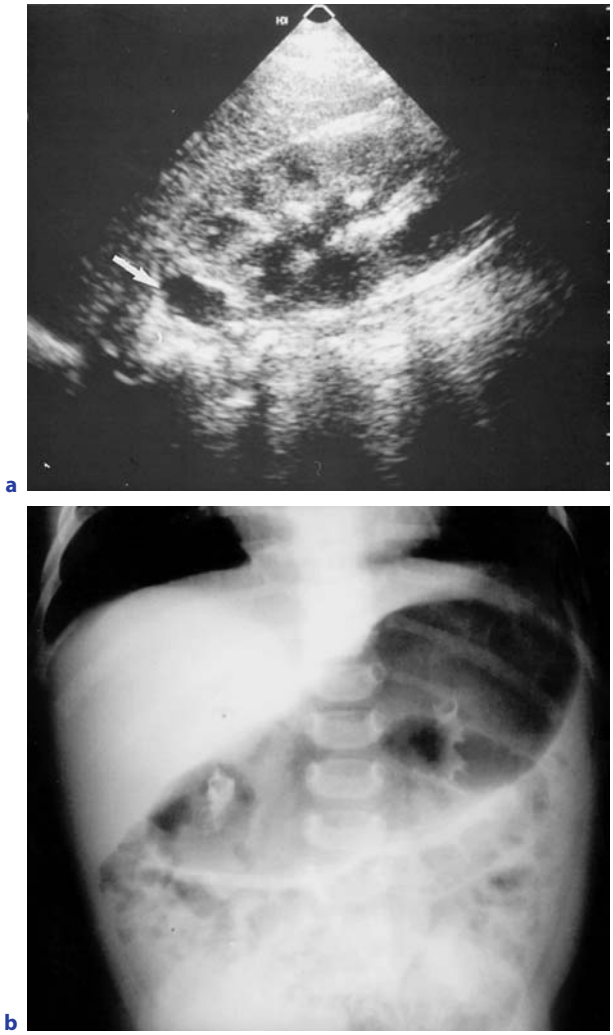
5.4.8 Other Types of Obstruction in Duplex Kidney

Obstruction may occur at many levels including the UPJ of the upper and lower pole (the latter is the



a **b**

Fig. 5.48a,b. Eversion of an ureterocele. **a** Filling phase of the VCU: the ureterocele is seen within the bladder. **b** After voiding, the ureterocele has now everted; bilateral VUR is also present (right grade II; lower left pole grade II)



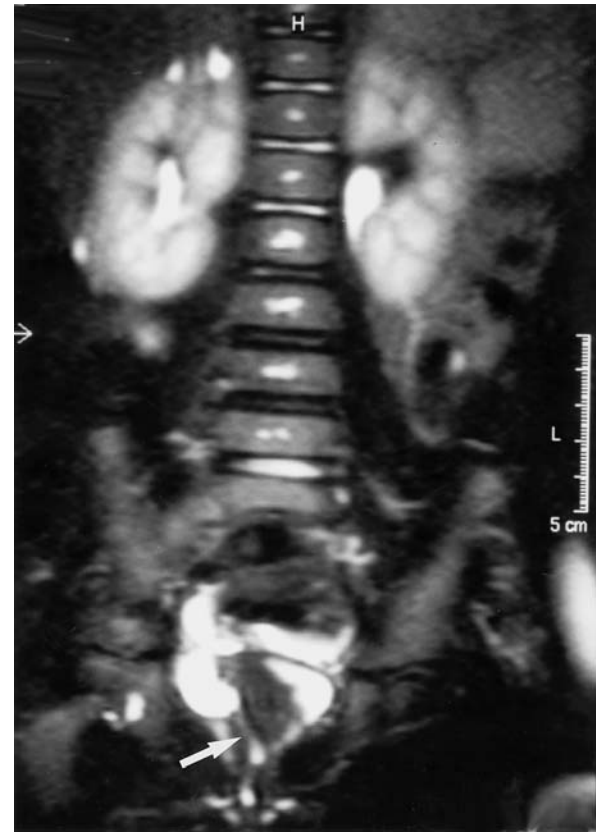


Fig. 5.49a–c. Cystic dysplasia of the upper pole of a right duplex kidney. **a** On US, a single cyst (*arrow*) is visualized on the sagittal scan of the right kidney. **b** On IVU, the upper pole does not opacify. **c** MR urography displays the cystic upper pole and the extravesical insertion of the corresponding ureter (*arrow*) (SPIR T2 sequence)

most common) (Fig. 5.50). Obstruction may also occur at the UVJ of one or both ureters (Fig. 5.51) (Ulchaker et al. 1996; Ho et al. 1995).

5.5 Triplication and Quadruplication of the Ureter

Triplication and quadruplication of the ureter are very unusual conditions that can only be diagnosed on IVU (Fig. 5.52) (Hassan 1990; Sourtzis et al. 1994).

5.6 Conclusion

Many anomalies occur at the level of the collecting system. The morphology of the anomalies is best evaluated by IVU if the kidney function is preserved and by MR urography if no or poor function persists.

Conclusion

A wide variety of anomalies occur in duplex kidneys. Imaging is mandatory in order to characterize the precise anatomy and to orient surgery.

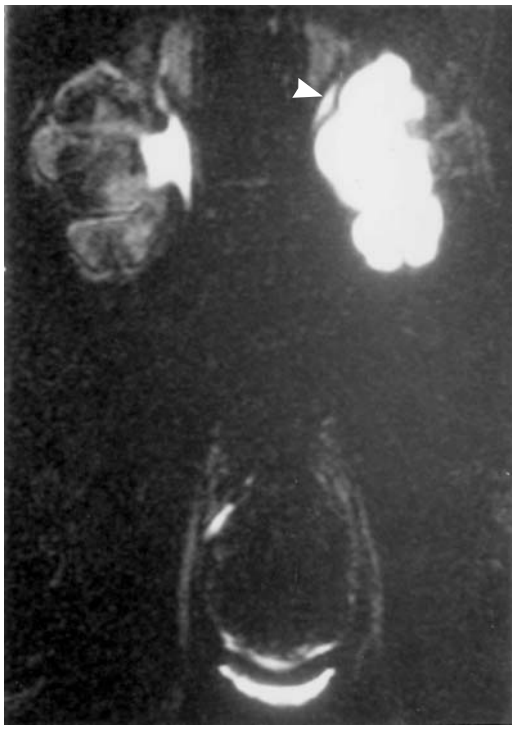


Fig. 5.50. UPJ obstruction on the lower pole displayed by MR urography (T2-weighted sequence). The *arrowhead* points to the upper pole system

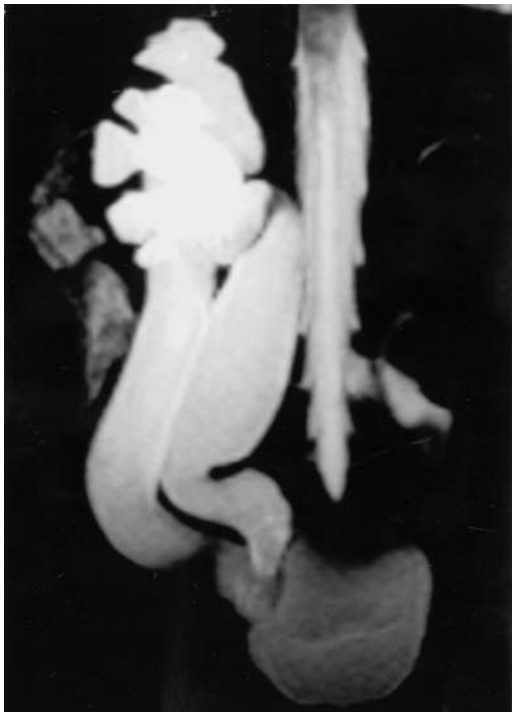


Fig. 5.51. UVJ obstruction on the upper and lower moieties displayed by MR urography (inversion-recovery sequence with MIP reconstruction)

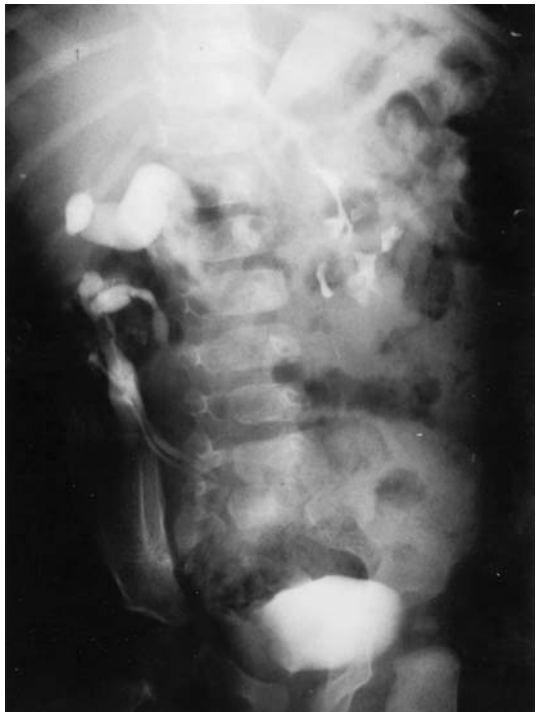


Fig. 5.52. IVU demonstration of ureteral quadruplication (courtesy of L. Sourtzis, MD)

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Abnormalities of the Lower Urinary Tract and Urachus

6

Jean-Nicolas Dacher

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J. N. Dacher, MD, PhD
Professor, Department of Radiology, University Hospital Charles Nicolle, 1, Rue de Germont, 76031 Rouen, France

6.1 Prenatal Diagnosis

Nowadays, maternal fetal sonography is able to diagnose most congenital abnormalities of the lower urinary tract (Eurin et al. 1999). A normal bladder is visible in the fetal abdomen as early as the 13th week of gestation. Its identification can be facilitated by color Doppler encoding of blood flow in the umbilical arteries alongside. Later during pregnancy, the bladder should be examined on several occasions during maternal fetal sonography to ensure that the bladder fills and empties. Cycles last 30–45 min (Patten et al. 1990). Normal ureters are not visible. The normal bladder appears as a thin-walled fluid-filled cavity. Any bladder abnormality (size, wall thickening) should lead to a joint analysis of the kidneys (cavities and parenchyma), fetal gender, abundance of amniotic fluid and fetal lungs.

6.1.1 Absence of Normal Bladder

Absence of any visible bladder can reveal either cloacal or bladder exstrophy. In both malformations, which may present with omphalocele (Grignon and Dubois 1999), there is an open defect of the abdominal or perineal wall. Widening of the distance between pubic bone echoes can be shown by prenatal sonography. This finding (Fig. 6.1) can also be shown in epispadias, the third and less severe malformation in this spectrum.

Cloacal malformation (Lebowitz 1997) exclusively occurs in the female phenotype and should not be confused with cloacal exstrophy. Cloacal malformation represents the most severe degree of imperforate anus (Hendren 1998). Prenatal diagnosis is difficult because a septated fluid-filled cavity can be mistaken for a normal bladder. However, echogenic

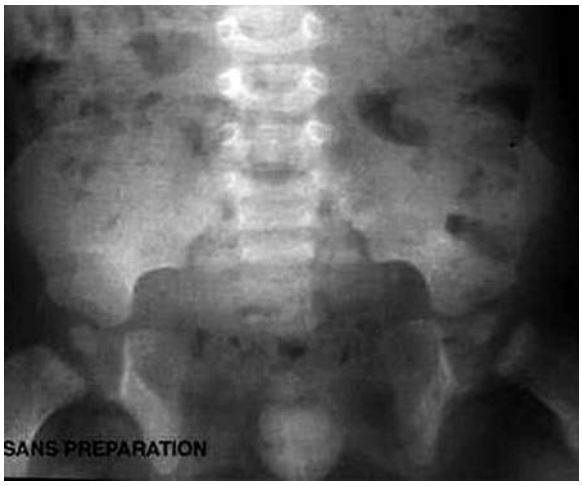


Fig. 6.1. AP radiograph of the pelvic cavity showing widening of the pubic symphysis in a girl with vesical exstrophy

debris can substantiate the diagnosis because it has been shown to result from a mixture of urine and meconium (Bear and Gilsanz 1981). At birth, there is only one perineal opening, and communication between the urethra, the vagina and the rectum is shown by imaging. Widening of the pubic bones may be associated to the cloacal malformation as well as many other malformations (involving the axial skeleton, spinal cord, heart or kidneys and urinary tract). The prognosis of this severe malformation improved dramatically with the contribution of Hardy Hendren (Miller 1993).

6.1.2 Megacystis

Megacystis can be physiological in two conditions. Firstly, transient megacystis has been described during the first trimester of pregnancy (Sebire et al. 1996). Secondly, megacystis can be observed in normal female fetuses by the end of pregnancy (Eurin et al. 1999). Establishing the latter diagnosis requires normal kidneys, nondilated upper tracts and normal fetal micturition. In female fetuses, megacystis should not be confused with a distended vagina due to an imperforate hymen or a duplicated uterus.

Transient megacystis may be a sign of obstruction and/or vesicoureteric reflux. In boys, it could be the consequence of transient bladder outlet obstruction and the starting point of a series of abnormalities. Notably, it could explain the male predominance in neonatal vesicoureteric reflux. This hypothesis was raised after the observation of children presenting with reflux, a dilated posterior urethra and no posterior urethral valves (Avni et al. 1992; Avni and Schulman 1996). Another hypothesis has come from experimental surgery. Premature urachal closure could induce hydroureteronephrosis in male fetuses (Gobet et al. 1998). Such a transient obstruction has also been suspected as being responsible for the prune-belly syndrome, which associates megacystis, ureterohydronephrosis, undescended testis and hypoplasia of muscles of the abdominal wall (Pagon et al. 1979).

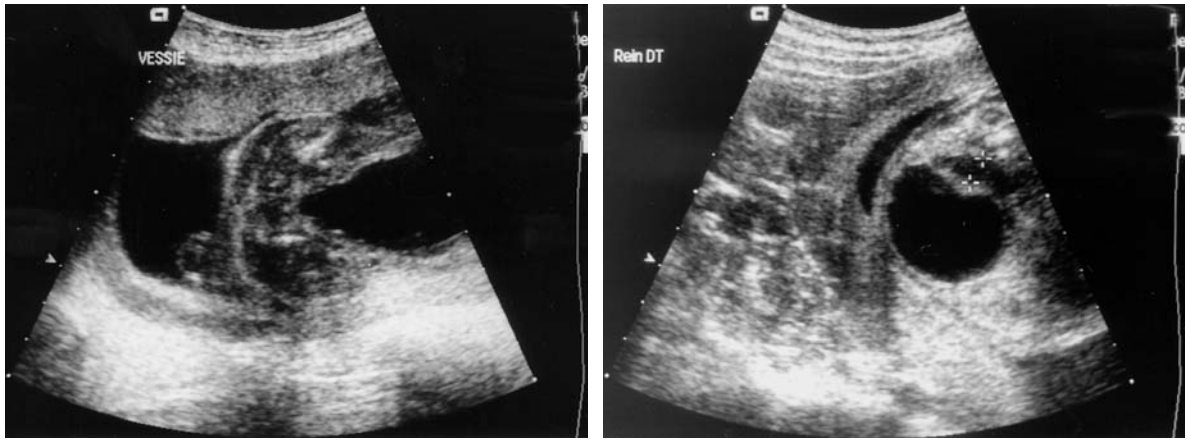
Posterior urethral valves in male fetuses are the most common cause for persistent megacystis associated with bilateral hydronephrosis (Fig. 6.2). Other prenatal sonographic findings include distended posterior urethra, increased bladder wall thickness, patent urachus, different degrees of renal dysplasia (cysts, cortical hyperechogenicity), bilaterally dilated and tortuous ureters, hydronephrosis, urinoma and ascites. Prenatal presentation is variable, and the absence of renal dilatation cannot preclude the diagnosis. The differential diagnosis (Table 6.1) includes other pathological conditions (Abbott et al. 1998), and postnatal radiological investigations are still useful to assess the anatomy of the lower urinary tract.

Many factors have to be taken into account in prenatal management of severe bilateral obstruction. Poor outcome factors include precocious diagnosis, oligohydramnios, lung hypoplasia, sonographic signs of dysplasia, presence of any other fetal malformation, urinary excretion of sodium above 75 mEq/l and urinary beta$_2$-microglobulin higher than 12 mg/l.

Termination of pregnancy can be proposed to parents, depending on local law, when several factors of poor prognosis are present. Some authors believe that prenatal urinary diversion could be beneficial to the neonate in spite of variable results and many potential complications (Lewis et al. 1998). Prenatal vesicoamniotic shunting could benefit patients with a second-trimester diagnosis of valves, moderate oligohydramnios, no evidence of renal dysplasia and equivocal biological findings (Eurin et al. 1999).

Conclusion

Bladder examination is part of any maternal-fetal sonography. Abnormality can reveal either transient or constituted obstruction of the lower urinary tract.



a b

Fig. 6.2a,b. Prenatal sonography in a 22-week gestational age male fetus. **a** Megacystis with dilated posterior urethra. Moderately dilated left kidney (not shown). **b** Huge dilatation of the right kidney with perirenal urinoma (courtesy of D. Eurin)

Table 6.1. Prenatal diagnosis of megacystis

Pathology	Physiology (see text)
Posterior urethral valves	Transient megacystis (10–14 weeks)
Megacystis-megaureter association (high-grade reflux)	Isolated megacystis by the end of pregnancy in girls
Reflux	
Megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS)	
Prolapsed ectopic ureterocele	
Urethral atresia (fatal)	
Prunebelly syndrome	
Caudal regression syndrome	
Cowper's gland cysts	

6.2 Posterior Urethral Valves

Posterior urethral valves consist of abnormal mucosal folds between the urethral wall and the distal end of the verumontanum. The classification established by Young at the beginning of the twentieth century appears questionable from an endoscopic perspective (Dewan et al. 1992). Young had identified three types of valves. Type I was described as a bicuspid valve radiating distally from the posterior edge of the verumontanum to the anterior aspect of the proximal membranous urethra. Type I valves are by far the most frequent, representing 95% of all cases. Type III posterior urethral valves are more circumferential (diaphragm like) and have been thought to be a remnant of the urogenital membrane.

Young type II valves were first described as "mucosal folds extending cranially from the verumontanum to the bladder neck" (Dewan et al. 1992); they could be a different disease and the consequence of dysfunctional voiding with bladder-sphincter dyscoordination.

Membranous obstruction is more likely than the valvular mechanism that gave its name to the malformation (Dewan and Goh 1995). This concept is referred to as congenital obstructive posterior urethral membrane (COPUM). As a matter of fact, most children seem to present with the same membranous abnormality more or less modified by the passage of indwelling catheters or a Whitaker diathermy hook (Whitaker and Sherwood 1986).

On endoscopy, valves are described as a membranous obstruction with a posterior pin-hole orifice adjacent to the verumontanum. Disposition of valves is oblique, the distal attachment being anterior. Valves usually balloon distally so that they can traverse the external sphincter.

There is great variability in clinical presentation. The most obstructive forms are usually detected by prenatal sonography, and the child's management starts at birth. Less severe forms can be detected during early infancy or even during childhood. Of course, renal consequences are extremely variable (from no alteration in forms revealed in older children to severe renal impairment and bladder dysfunction in neonatal cases).

6.2.1 Posterior Urethral Valves in Neonates: Imaging and Follow-Up

Management of fetuses and neonates with prenatal diagnosis of posterior urethral valves should be performed in a fetal medicine and pediatric surgery reference center. In each new case, the great variability of presentation makes different specialists' participation necessary in the difficult decision-making process. Both the surgeon and the radiologist should be involved in the discussion and in patient care before birth. The quality of management is frequently improved when the surgeon can explain the principles of postnatal treatment to the parents during pregnancy. In order to plan postnatal management, prenatal findings including sonographic measurements, images and biological findings should be communicated to the pediatric radiologist.

After birth, radiological evaluation is routinely performed during the first hours of life. Prenatal sonographic findings are confirmed, and precise assessment is facilitated by usage of a high-frequency transducer. The huge bladder and the dilated posterior urethra are shown and measured. Bilateral ureterohydronephrosis is frequent. Analysis of the renal parenchyma (echogenicity, cysts, thickness) is important even if it cannot quantify renal function. Renal dysplasia seems to depend on the timing in gestation and the presence of individual factors such as vesicoureteric reflux or urinoma (Blane 1994; Peters et al. 1992).

Perirenal urinoma (Fig. 6.2) (ascites or even hydrothorax) may be present. Such fluid collections are the consequence of the rupture of calyceal fornices due to increased pressure. This has been described as the "pop-off" mechanism (Rittenberg 1988). However, the presence or absence of urinoma does not clearly correlate with renal function impairment.

The same day, VCU is performed commonly after suprapubic puncture (Fig. 6.3). Aspiration of stagnant urine is performed via a vesical catheter that can be left in place thereafter. All precautions must be taken to ensure sterility given the increased risk of post-procedural infection. Infection could be life threatening for the baby and devastating for renal function. Retrograde opacification would be technically possible since valves produce only one-way obstruction. However, it can be difficult to pass through the bladder neck due to the dilated posterior urethra, which can retain the tip of the tube. Moreover, retrograde catheterization yields a higher risk of infection, and it could probably modify the endoscopic appraisal of the anatomy. For these various reasons, we have chosen the suprapubic technique in this situation.

While the bladder is opacified percutaneously, leakage into the prevesical space can occur. This should not interrupt the examination since it resolves spontaneously. The bladder appears thick-walled with marked sacculations and trabeculations. Diverticula may be present.

Reflux (usually unilateral) is frequent (Fig. 6.4). It has to be graded, and oblique films can be taken to analyze the lower segment of the refluxing ureter. Delayed films should be taken to analyze reflux clearance. Voiding time is often long, and patience may be required. This is, however, an essential diagnostic step since it shows the discrepancy between the anterior and posterior segments of the urethra with a posteriorly located orifice. In classical descriptions, VCU showed the "sail in the wind" sign in Young

Fig. 6.3. Suprapubic voiding cystourethrography in a neonate with posterior urethral valves. A high-capacity heavily trabeculated bladder was opacified. Distended posterior urethra. Valves are ballooned by contrast medium ("sail in the wind" sign)

type I posterior urethral valves (Fig. 6.3). It showed the "wind in sock" sign in Young type III posterior urethral valves. Again, these different patterns are more likely to be the consequence of endo-urethral procedures rather than different diseases.

The main differential diagnosis is the megacystis-megaureter association (Willi and Lebowitz 1979; Reuter and Lebowitz 1985), which is due to massive reflux and the phenomenon of aberrant micturition (Fig. 6.5). Prenatal diagnosis is relatively straightforward in female fetuses, but more subtle in males (absence of a dilated posterior urethra).

After voiding cystourethrography (VCU), iodinated contrast medium is aspirated, and the bladder is slowly drained by the catheter. Electrocoagulation of the valves is performed during the following hours. Because the bladder catheter cannot be left inside the bladder for an extended period, and because there is severe alteration of the bladder contractility, renal diversion is frequently required during the first few months of life (bilateral nephrostomy or ureterostomy). Imaging follow-up of children is based on the association of nuclear medicine studies, MR urography and direct opacifications.

Continence is often a problem in children and adolescents with a history of obstructive posterior urethral valves. Urodynamic studies are sometimes helpful to evaluate vesical and sphincter functions. Growth of the prostate gland during puberty often yields transient or definite improvement (Pfister et al. 1996).

In spite of extensive and precocious surgical treatment following prenatal diagnosis, many patients with a perinatal history of posterior urethral valves have subsequent deterioration of their renal function. Usually, if renal function quickly improves immediately after obstruction relief, then deterioration slowly develops in the following years (Drozdz et al. 1998). End-stage renal disease occurs in most patients with a history of severe obstruction during the first 20 years of life.

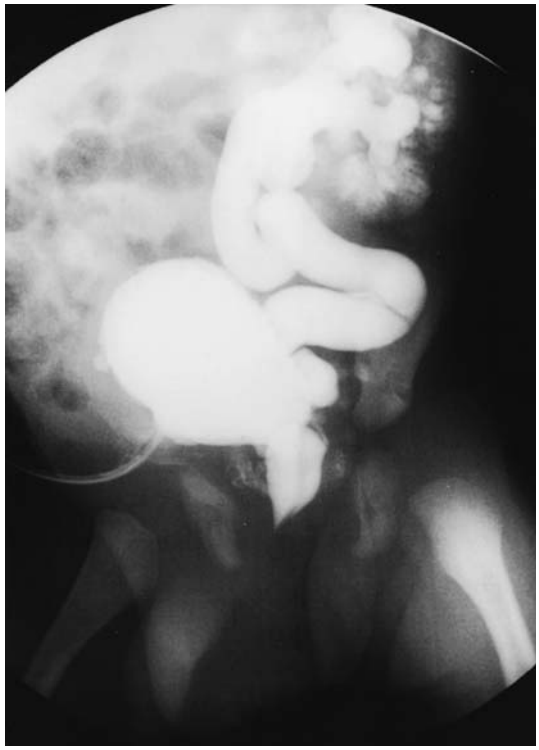


Fig. 6.4. Suprapubic voiding cystourethrography in a neonate with posterior urethral valves. Reflux into the seminal vesicles. High-grade left vesicoureteric reflux into a very dilated upper urinary tract. Note intrarenal reflux

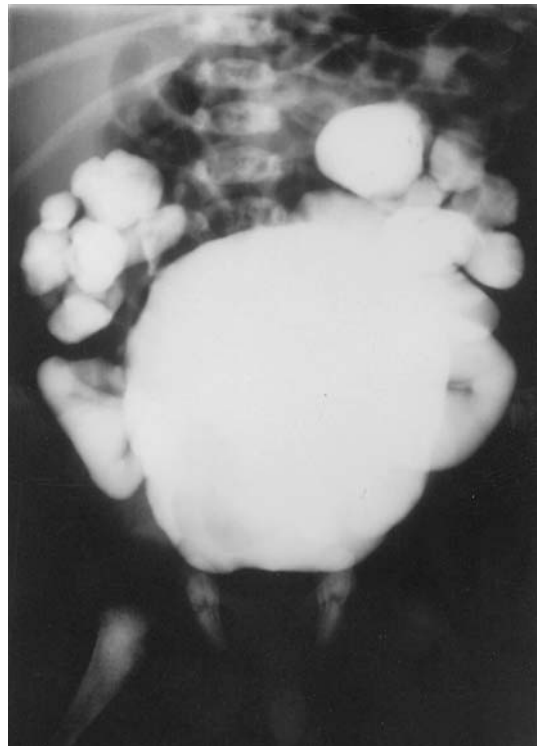


Fig. 6.5. VCU in a neonate with prenatal diagnosis of megacystis and bilateral ureterohydronephrosis. Absence of posterior urethral valves. Megacystis megaureter association by aberrant micturition phenomenon

6.2.2 Diagnosis in Older Boys

The clinical presentation is completely different in older children. The main complaint is usually dysuria or infection (Fig. 6.6). Megacystis and thickening of the bladder wall are less frequent. Kidneys are usually normal, as is renal function. The differential diagnosis should include the other causes of bladder outlet obstruction (see below) and functional disorders such as dysfunctional voiding with severe bladder-sphincter dyscoordination. Both VCU and urodynamic studies can be diagnostic (Fig. 6.7). In case of valves, there is reduced urinary flow with no reinforcement of the perineal electric activity.

There is a broad spectrum in posterior urethral valves. It should be remembered that some boys may have marked folds with no obstruction at all (Dewan and Goh 1995). This frequent radiological or endoscopic finding should be correlated with clinical complaints in order to ensure proper management of patients.

Conclusion

Optimal neonatal management of boys with a prenatal diagnosis of posterior urethral valves necessitates excellent cooperation among obstetricians, pediatricians, surgeons and radiologists. Unfortunately, end-stage renal disease is still a frequent outcome.

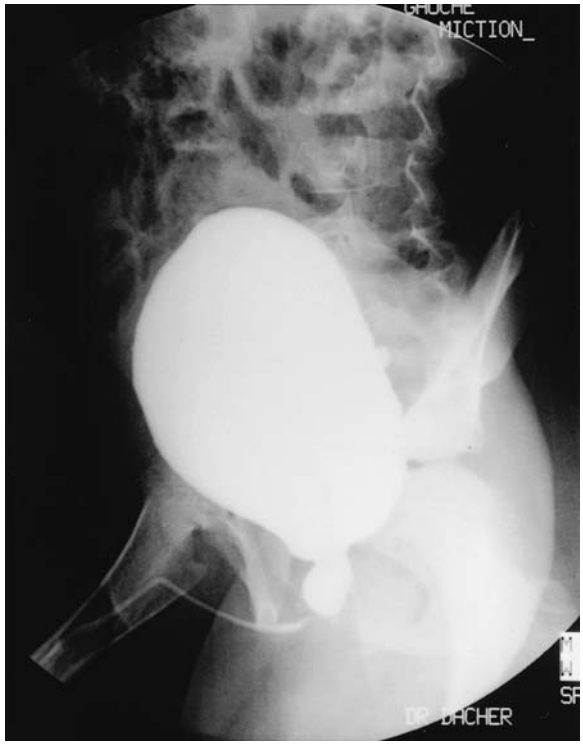


Fig. 6.6. VCU in a 7-year-old boy with dysuria. No prenatal diagnosis. No history of infection. Valves are shown during micturition. No reflux. Diagnosis was confirmed by endoscopy

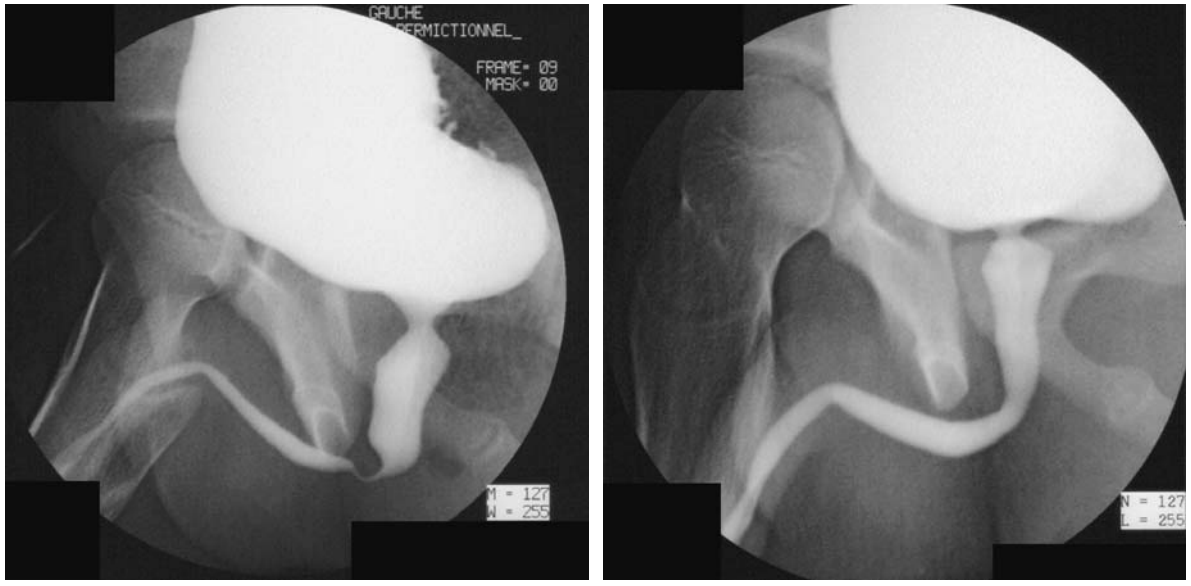
6.3 Other Causes of Bladder Outlet Obstruction

6.3.1 Urethral Polyp

Extremely rare in childhood, the urethral polyp is usually solitary and consists of a pedunculated structure, originating from the posterior urethra, developing in the bladder neck, which can prolapse in the urethra during micturition (Foster and Garrett 1986). Hematuria, nonneurogenic bladder-sphincter dysfunction and infection may reveal the abnormality. On ultrasound, it appears echogenic. The main differential diagnosis of urethral polyp is an ectopic ureterocele that has ruptured either spontaneously (Fig. 6.8) or after endoscopic incision. VCU is helpful, showing a mobile filling defect in the projection of the base of the bladder. Bladder trabeculations and diverticula can be associated. Surgical removal is the treatment of choice. Such an anomaly has occasionally been described in association with hepatoblastoma in the Beckwith-Wiedemann syndrome (Bockrath et al. 1982).

6.3.2 Ureterocele Prolapse

Ectopic ureterocele develops at the lower end of the upper pole ureter of a duplicated kidney. It is a cyst-like thin-walled structure that is known to be mobile and variable in shape. During fetal life, the ureterocele can prolapse into the posterior urethra and create obstruction (Fig. 6.9). Bilateral hydronephrosis and megacystis can subsequently develop. Clinical diagnosis can be made at birth in girls with a perineal soft tissue mass, megacystis and bilateral urinary tract obstruction. Sonographic diagnosis can be difficult when the ectopic ureterocele has



a b

Fig. 6.7. a VCU in a 7-year-old boy with dysuria, showing extrinsic compression of the urethra due to abnormal sphincter contraction during micturition. This functional anomaly should not be mistaken for posterior urethral valves. Urodynamic studies favor dysfunctional voiding with bladder-sphincter dyscoordination during voiding. Biofeedback physiotherapy was carried out. Clinical outcome was favorable. **b** Follow-up VCU shows normalization of urethral anatomy during micturition

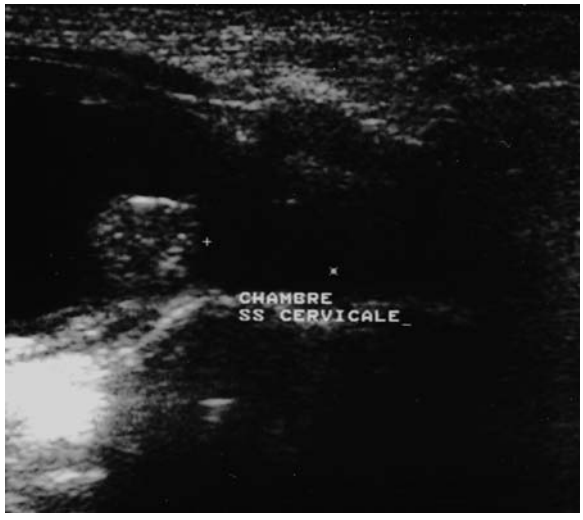


Fig. 6.8. Sagittal US view of the bladder neck in a male neonate with left duplicated ureter. The echogenic mass visible in the bladder neck is a spontaneously ruptured ectopic ureterocele, draining the dysplastic upper pole of the duplicated left kidney. Urethral polyp is the main differential diagnosis

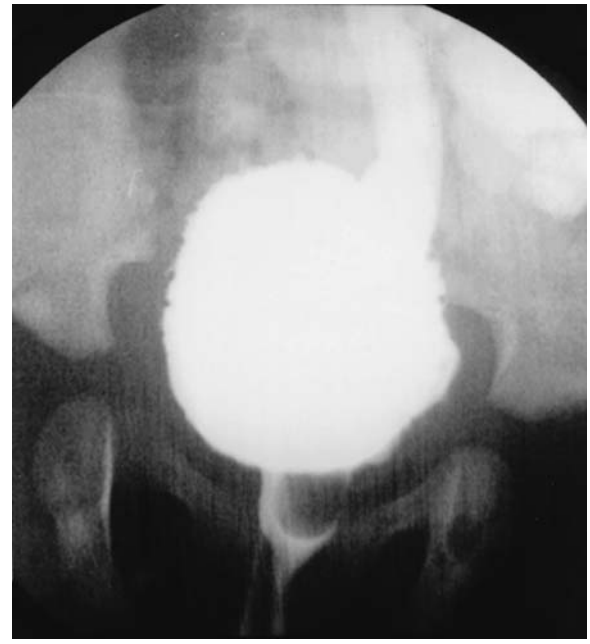


Fig. 6.9. VCU in a female neonate with prenatal diagnosis of megacystis and hydronephrosis. Vesicoureteric reflux into the lower pole of a left duplicated kidney. Left upper pole ureter is obstructed by an ectopic ureterocele that is prolapsed in the urethra during micturition

spontaneously ruptured (Fig. 6.8). In this case, the differential diagnosis with a urethral polyp can be difficult (see above). The phenomenon has also been described in boys with a single ureterocele (Diard et al. 1981).

6.3.3 Cobb's Collar, Urethral Diverticula and Cowper's Gland Cysts

Cobb's collar (Cobb et al. 1968) is a congenital narrowing of the bulbar urethra with no connection to the verumontanum (Dewan et al. 1994). It was shown that Cobb's collar is frequently associated with tubular or cystic dilatation of Cowper's glands ducts (also called syringocele) (Dewan 1996), both structures arising embryologically from the urogenital membrane area.

In most cases, narrowing of the bulbar urethra with or without retrograde opacification of Cowper's glands ducts has no pathological significance (Beluffi et al. 2006) (Fig. 6.10). However, retention cysts may occur and induce urinary flow obstruction. Fetal infravesical obstruction may complicate Cowper's gland cysts as well (Dhillon 1993).

Urethral diverticulum can be either acquired or congenital (Fig. 6.11). Congenital diverticula can be found anywhere in the urethra, but largely predominate on the ventral surface of the penile urethra (Rimon et al. 1992). It was recently hypothesized from a retrospective study that anterior urethral valves and diverticula could be the consequence of a ruptured Cowper's gland cyst (McLellan 2004).

Secondary diverticula seem to be more frequent. They can be related to previous trauma or a catheter (in patients with neurogenic bladder), to previous surgery or to periurethral suppuration (bacterial or parasitic). A stone may develop in any kind of urethral diverticulum.

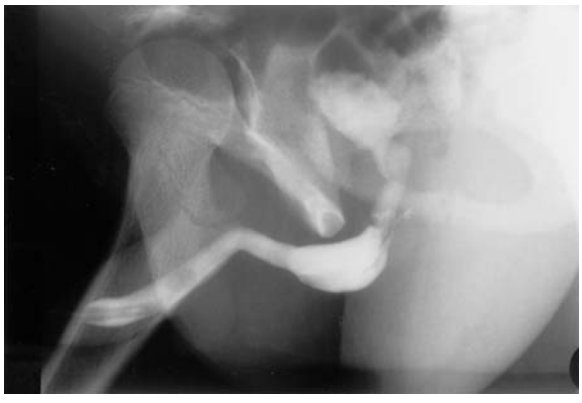


Fig. 6.10. Urethrography in an adolescent boy. Normal visualization of Cowper's glands

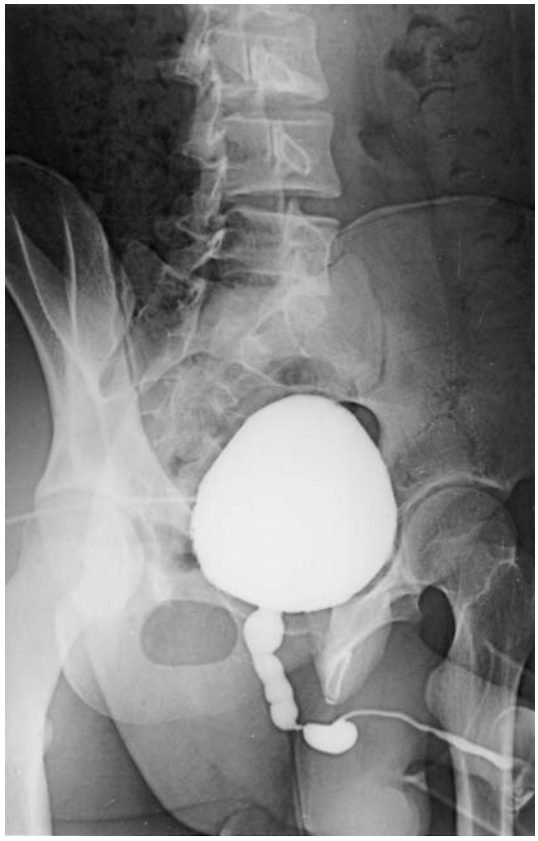


Fig. 6.11. VCU in a 7-year-old boy with history of dysuria; no history of trauma. During micturition, a distended posterior urethra was identified as well as a diverticulum associated with stenosis

6.3.4 Tumor

Rhabdomyosarcoma is the most frequent malignant tumor of the lower urinary tract (Bisset et al. 1991). Peak incidence is during the first 3 years of life, and cases have been reported in neonates. The bladder, the prostate gland and the vagina are the most commonly involved sites. Urinary frequency, hematuria, palpable abdominal mass, fever and constipation may reveal the disease. Passage of the tumor is most common in vaginal lesions. The site of origin is often difficult to detect, and conclusions should not be based on ultrasound findings.

Imaging helps determine the extent of the lesion. Ultrasound usually shows an irregular polypoid mass (grape-like) infiltrating the base of the bladder. Thickening of the bladder wall can be associated, as well as dilatation of one or both ureters. On VCU, an irregular filling defect of the base of the bladder is shown, and the floor of the bladder appears elevated. There may be irregular thinning of the posterior urethra in boys. Residual urine is frequent. Nowadays, the reference imaging modality is multiplanar MRI with fat-suppression sequences and gadolinium enhancement. Helical CT with 2D reformatting can also be helpful.

Conclusion

The association of ultrasound, VCU and cystoscopy helps establish a proper differential diagnosis among the causes of congenital or acquired bladder outlet obstruction.

6.4 Other Urethral Congenital Abnormalities

A great variety of urethral abnormalities may be found, most of them in boys. Evaluation is based on VCU or urethrography. Endoscopy is often useful. Normal variants should be kept in mind in order to avoid misinterpretation. For example, compression of the pendulous urethra by a nonopaque urinal and proximal dilatation is a frequent cause of error (Rink and Mitchell 1990).

Hypospadia is a frequent anomaly of the urinary meatus that can be associated with significant stenosis and dilatation of the male urethra. Though possible in most cases, catheterization of the urethra can be difficult and painful.

Epispadia is part of the heterogeneous exstrophy-epispadia complex. It may occur in males and females. Widening of the pubic symphysis is usually associated. Continence is variable in those patients, so imaging and urodynamic studies in these patients should be directed towards this handicap and the detection of associated anomalies. Duplication of the bulbous urethra is extremely rare. It may be complete or blind-ended, ventral or dorsal (Barbagli et al. 1996). Finally, megalourethra (Stephens and Fortune 1993) is an enlargement of the pendulous urethra with no evidence of distal obstruction. It could be the consequence of late canalization of the epithelial core in the glans. It may be a part of the prune-belly syndrome.

Conclusion

Diagnosis of urethral congenital abnormalities is based on clinical examination, the voiding phase of VCU and endoscopy.

6.5 Bladder Diverticula

Bladder diverticulum consists of herniation of the vesical mucosa through a defect in the muscular wall of the bladder (Fig. 1.1.6). This entity was first described in paraplegic patients with neurogenic bladder. In rare cases, hydronephrosis has been described in association with bladder diverticula (Lebowitz 1997). More commonly, diverticulum is associated with ipsilateral reflux. Its presence could predict the absence of spontaneous resolution of reflux (Blane et al. 1994). Sonography is often negative, and VCU usually yields the accurate diagnosis, pending the performance of left and right oblique views of the full bladder. Diverticula may be hidden behind the opacified bladder on AP views. Bladder diverticulum may also be an incidental finding, and it does not require any treatment when no association with either reflux or obstruction is present. The main differential diagnosis consists of ectopic ureterocele eversion (Bellah et al. 1995) (Fig. 1.1.8).

Conclusion

Oblique films on VCU can show bladder diverticula that can cause obstruction, reflux or be a normal variant.

6.6 Congenital Cystic Disease of the Seminal Vesicle

This uncommon disorder (King et al. 1991) can be acquired or congenital. When congenital, the cyst is usually associated with anomalies of the ipsilat-

eral mesonephric duct. A cyst can be discovered on bladder ultrasound. In the axial plane, it can be confused with a dilated ureter. An orthogonal scan helps to make the differential diagnosis (the structure remains rounded in case of a congenital cyst). Associated renal and/or ureteral anomalies (multicystic dysplastic kidney, renal agenesis, duplication of collecting system and ectopic ureter), urethral or bladder anomalies (valves, reflux into the cyst and/or the ipsilateral ureter) can be detected on ultrasound, cystography, MR and/or CT (Hernanz-Schulman et al. 1989). Cystoscopy is a useful complementary examination to look for trigonal abnormalities and an ectopic ureteral orifice.

Conclusion

Congenital cystic disease of the seminal vesicle is often associated with anomalies of the ipsilateral kidney and ureter.

6.7 Bladder Stones

Endemic bladder stones are mostly observed in boys in Africa and the Indian subcontinent. Those primary calculi are likely related to nutritional deficiencies. In contrast, the bladder stone has become very uncommon in children in western countries. The recognized lithogenic factors are infection (*Proteus mirabilis*), stasis, hypercalciuria (which can be associated with nephrocalcinosis), bladder scars, intestine in the bladder mucosa (in exstrophy or after surgical augmentation of the bladder), ileal dysfunction (inflammatory bowel disease, intestine inserted into the urinary tract) and long-standing intravesical foreign bodies (catheter). Adolescent children and adults with neurogenic bladder on clean intermittent self-catheterization can develop stones on their pubic hair (Lebowitz and Vargas 1987). Diagnosis is obvious on ultrasound and plain film when the stone is located in the bladder. It should be remembered that a stone can be located in the posterior urethra; a calcified stone can be hidden behind a lead shielding of the gonads (Fig. 6.12).

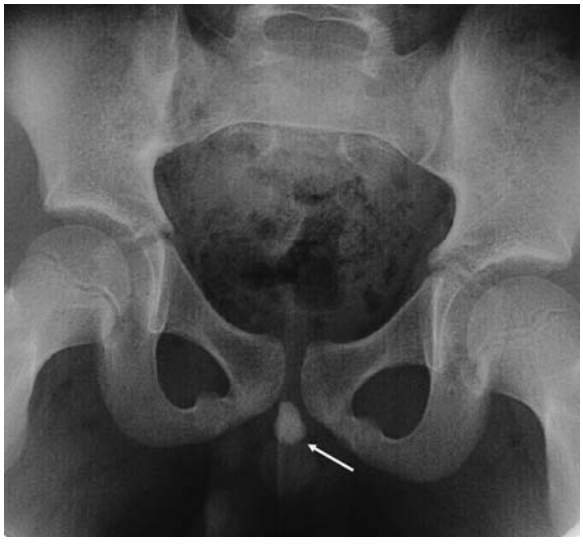


Fig. 6.12. Plain film showing a calcified stone in the posterior urethra (*arrow*) in a boy complaining of dysuria

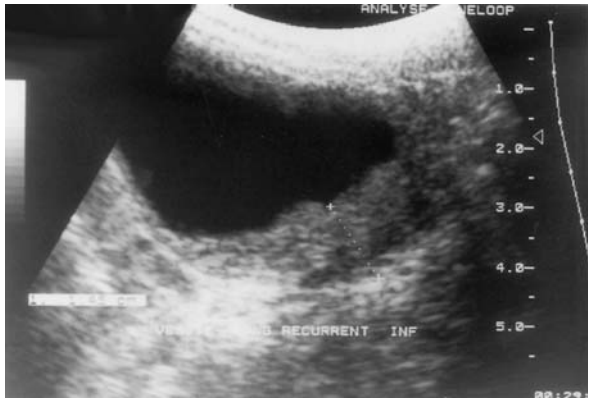
Conclusion

If diagnosis of a bladder stone is obvious, in most cases on plain film and US, finding its explanation can be more challenging.

6.8 Infection

The spectrum of urinary tract infection includes cystitis in children. Imaging is not relevant in common cystitis in an adolescent girl. However, in some patients, children with cystitis may present with dysuria, gross hematuria and moderate fever. If ultrasound is performed, irregular thickening of the bladder wall can be shown. Such thickening can be tricky to interpret when the bladder is not filled, which is common in these children with frequent voiding.

In some patients, inflammatory changes can be so intense that infravesical obstruction with bilateral hydronephrosis is created. Differentiating pseudotumoral cystitis (Hoeffel et al. 1993) and a tumor can be difficult and occasionally may require more sophisticated imaging modalities (MRI, cystoscopy and biopsy) (Fig. 6.13). This applies to another rare inflammatory condition of the urinary bladder of unknown origin, eosinophilic cystitis. This inflammatory process is characterized by eosinophilic infiltration of the bladder wall. MR findings of this



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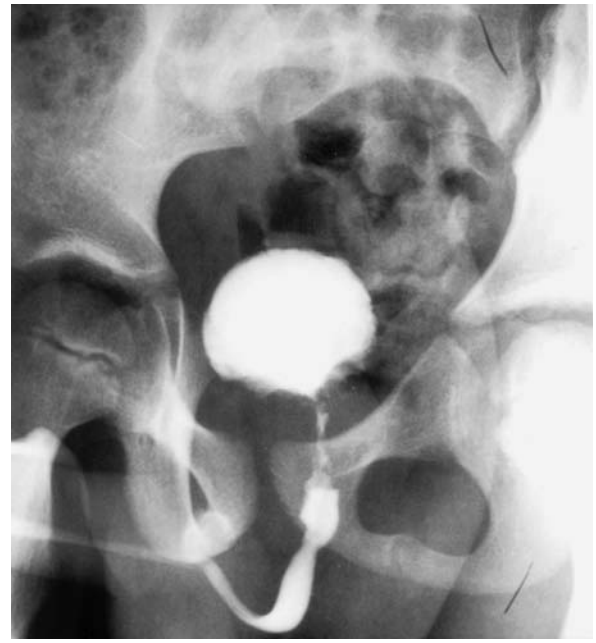

b

Fig. 6.13a,b. US and VCU in a 7-year-old boy with gross hematuria and painful dysuria. **a** Irregular thickening of the base of the bladder on US. **b** Elevation of the bladder, irregular stenosis of the bladder neck, and proximal posterior urethra. Prostatic rhabdomyosarcoma was suspected. Cystoscopy and biopsies were negative. Urinary culture was positive. Final diagnosis was *E. coli* pseudotumoral cystitis

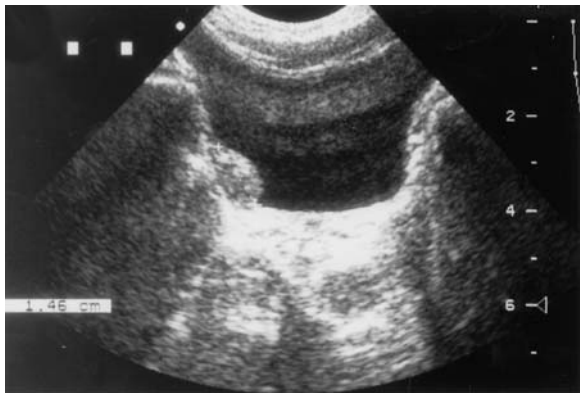

Fig. 6.14. Bladder US in an 8-year-old girl returning from western Africa. Nodular echogenic lesion is protruding into the bladder lumen. Diagnosis was urinary schistosomiasis

condition are specific; there is a smooth and nearly circumferential thickening of the bladder wall showing prominent low intensity on T2-weighted images, which may histologically represent high cellularity due to massive eosinophilic infiltration (Tamai et al. 2007).

In children living in Africa, parasitic infection should be included in the differential diagnosis of cystitis. In schistosomiasis, nodular infiltrates of the bladder wall are commonly shown with ultrasound (Fig. 6.14).

Conclusion

Bacterial, viral or fungal infection of the bladder can be associated with a pseudotumor.

6.9 Urachus

The urachus is the remnant of an embryonic connection coursing from the dome of the fetal bladder to the umbilicus. After birth in normal children, it is limited to a thin cord-like structure. Rarely, a patent urachus is present at birth. More commonly, urachal diverticulum is present at the dome of the bladder (Fig. 6.15). Diagnosis can be made on VCU on lateral views. An urachal cyst is another pathogenic remnant of an urachus. It may be isolated or multiple. Infection can occur (Newman et al. 1986). Diagnosis is based on the association of clinical findings and ultrasound, which shows a superficial midline abscess-like structure. Urachal carcinoma does not occur in childhood (Thomas et al. 1986), but this possible complication in adulthood justifies surgical excision of urachal cysts in children.

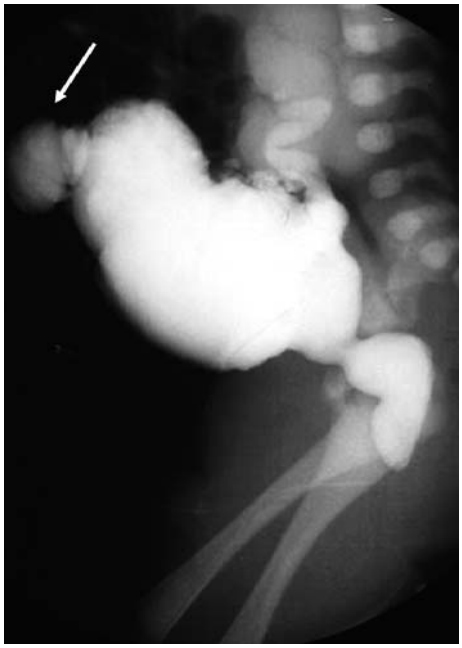

Fig. 6.15. VCU in a neonate with posterior urethral valves. Huge diverticulum of the urachus is visible on this lateral view (*arrow*)

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Lower Urinary Tract Anomalies of Urogenital Sinus and Female Genital Anomalies

7

Theresa E. Geley and Ingmar Gassner

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7.1 Introduction

Congenital anomalies of the female genital tract result from müllerian duct anomalies and/or abnormalities of the urogenital sinus or cloaca. Failure of fusion of the müllerian ducts results in a wide variety of fusion abnormalities of the uterus, cervix, and vagina (Gruenwald 1941). Müllerian duct abnormalities may occur alone or in association with urogenital sinus or cloacal malformations. Persistence of the cloaca is believed to be caused by an abnormal development of the dorsal part of the cloaca and the urorectal septum (Stephens 1983b; Nievelstein et al. 1998). Urogenital sinus malformations occur after the cloaca has been organized into the urogenital sinus and the anus (Williams and Bloomberg 1976). Early and complete assessment of the patients, including radiological and biochemical examinations, is mandatory to provide an optimal basis for treatment that will have a great influence on the quality of the patient's later life. Due to the close embryologic relationship between the urinary and the genital tract, malformations involving both organ systems are very common. Understanding the development of the urogenital system is necessary to comprehend the full spectrum of congenital anomalies of the female genitalia.

Ovarian cysts are frequently seen during prenatal and postnatal pelvic ultrasound and have, therefore, been included in this chapter, although they are not closely related etiologically to the above-mentioned malformations and organ systems.

T. E. Geley, MD
Section of Pediatric Radiology, University of Innsbruck, Medical School, Anichstrasse 35, 6020 Innsbruck, Austria

I. Gassner, MD
Section of Pediatric Radiology, University of Innsbruck, Medical School, Anichstrasse 35, 6020 Innsbruck, Austria

7.2 Embryology of the Female Genitalia

Sex determination at the chromosome level is related to the presence or absence of a Y chromosome. Those individuals with a Y chromosome (including XXY, XXXY, etc.) will develop into males, and those without one will become females. Some individuals, however, will undergo what is referred to as 46, XX testicular disorder of sex development (DSD) or 46, XY complete gonadal dysgenesis, also called primary sex reversal, whereby the X and Y chromosomes cross over and exchange the sex determination SRY gene (Hughes et al. 2006; Koopman 1995; Marrakchi et al. 2005). This relatively rare occurrence (approximately 1 in 20,000 births) can lead to males with two X chromosomes and females with a Y chromosome. While gonad development is a result of the presence or absence of the sex determination gene, sex differentiation is determined by the hormonal products of the gonads including the müllerian-inhibiting substance (MIS) produced by sertoli cells.

The two factors produced by the testes, androgen, and MIS, are essential for the formation of the external and internal male genitalia as well as for the suppression of further development of the müllerian duct into female genital structures. In the absence of a Y chromosome, zygotes with two or more X chromosomes will develop ovaries and female internal and external genitalia. Whereas the X chromosome is essential for development, zygotes lacking a Y chromosome (45X) are viable, but are unable to develop differentiated gonads (streak gonads) (Aaronson 1992; Wilson and Goldstein 1975).

Both the internal and the external genital organs develop in coordination with the urinary and anorectal system at an early stage of gestation (Fig. 7.1). The internal genital organs as well as the lower urinary system originate from two paired urogenital structures that develop in both sexes: the mesonephric ducts (wolffian ducts) and the paramesonephric ducts (müllerian ducts) (Moore 1993). At 5 weeks of gestation the ureteral bud arises from the distal segment of the wolffian duct to grow dorsally and soon becomes connected with the primordium of the permanent kidney or metanephric blastema. The ureteral bud forms the ureter, the renal pelvis, calyces, and the intrarenal collecting ducts and acts as an inducer of differentiation of the renal blastema into the adult kidney. Between the 6th and the

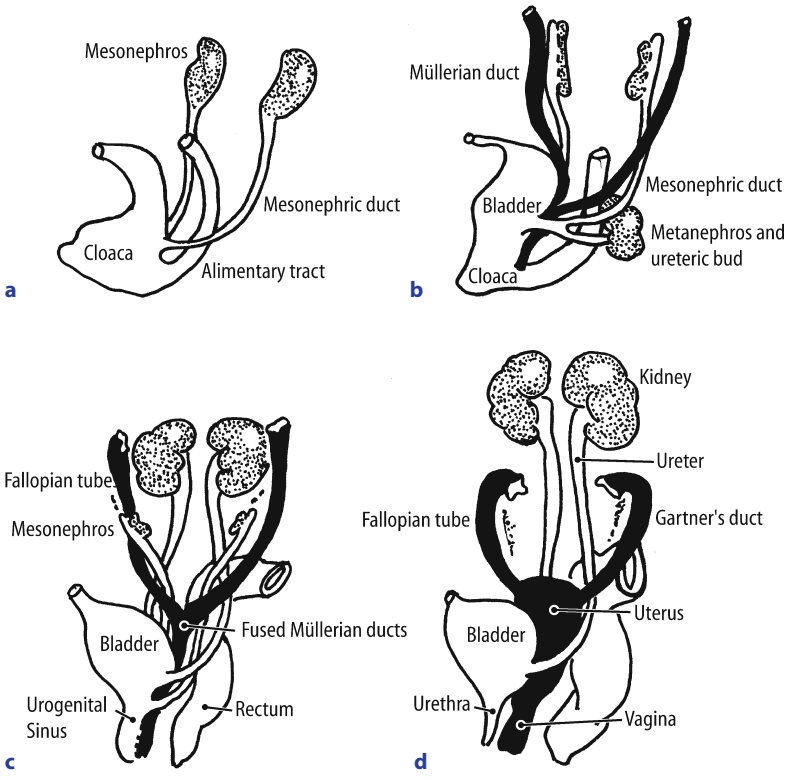


Fig. 7.1a–d. Schematic presentation of the embryology of the female genitourinary tract. **a** The mesonephric ducts (wolffian ducts) connect the mesonephros to the cloaca. **b** At approximately 5 weeks of gestation the ureteric bud originates from the wolffian duct, reaches the metanephros and induces its differentiation into the kidney while the mesonephros degenerates. The müllerian ducts fuse at about 7–9 weeks in the midline to form the uterovaginal canal. **c** At 8 weeks the uterovaginal canal reaches the urogenital sinus at the müllerian tubercle. The urogenital sinus results from the separation of the cloaca into urogenital sinus and rectum. **d** The vagina becomes patent at approximately 22 weeks. The wolffian ducts are resorbed and remnants are referred to as Gartner's duct

8th week the segment of the wolffian duct distal to the origin of the ureteral bud dilates and is incorporated into the wall of the vesicourethral canal. The ureter undergoes a craniolateral shift relative to the wolffian duct to open into the bladder. With further growth of the surrounding structures, the ureteral opening migrates to the lateral corners of the bladder trigone, while the wolffian ducts descend with the urogenital sinus. In the female, the wolffian duct epithelium forms the posterior wall of the entire urethra (Stephens 1983a).

During the 6th week of gestation the müllerian ducts develop alongside the wolffian ducts (Gruenwald 1941). The müllerian ducts are divided into two segments demarcated by the insertion of the ligamentum inguinale, which eventually becomes the round ligament. The distal segments of the müllerian ducts move towards the midline and soon fuse into a single tube, the uterovaginal canal. The septum that divides the uterovaginal canal disappears at 11 weeks. The uterovaginal canal elongates to join the urogenital sinus at the müllerian tubercle between the two openings of the wolffian ducts. Further differentiation and canalization result in the formation of the uterus and the cervix. At 12 weeks the vagina forms. Induced by the fusion of the uterovaginal canal with the urogenital sinus, bilateral endodermal evaginations, the sinovaginal bulbs, form in the area of the müllerian tubercle (Moore 1993). The sinovaginal bulbs proliferate into the primitive vaginal plate. Canalization of this plate starts at the urogenital sinus forming the vaginal epithelium and the entire wall of the distal third of the vagina. The nonepithelial components of the proximal two-thirds of the vagina, however, are of uterovaginal canal origin.

The proximal segments of the müllerian ducts remain un-united to form the fallopian tubes. In females the wolffian duct is finally resorbed, leaving only scattered remnants forming an interrupted channel alongside the fallopian tubes, the proximal uterus, within the cervix and the anterolateral wall of the vagina, ending at or just above the level of the hymen. These remnants are then referred to as Gartner's duct.

Development of the external genital organs, the urethra, and the anus involve transformation processes of the internal and external cloaca, which are separated by the cloacal membrane in a transverse plane (Stephens 1983a; Nievelstein et al. 1998). At 4 weeks the internal cloaca is a single chamber, into which issue the large intestine, the hindgut, the allantois, and the wolffian ducts.

Between the 4th and 6th weeks, the complex process of partitioning the internal and the external cloaca into separate urinary and anorectal systems takes place. The theories formulated by Rathke (1882), Retterer (1890), and Tourneux (1888) dominated the understanding of the development of the cloaca for decades. More recently, however, a new model of cloacal development has been put forward by Van der Putte (1986), Hartwig (1992), and Kluth et al. (1995). According to their theory, the distance between the caudal tip of the urorectal septum and the cloacal membrane decreases due to the unfolding process of the embryo and does not involve an active proliferation process of the urogenital septum as suggested earlier. According to this model, the urorectal septum is formed by fusion of the surrounding extraembryonic mesoderm of the yolk sac and allantois. The tip of this septum marks the cranial border of the cloaca and subdivides the internal cloaca into the urogenital sinus and the anorectal canal. However, fusion between the cloacal membrane and the urorectal septum, as suggested by the previous theories, never occurs (Nievelstein et al. 1998). The cloacal membrane eventually ruptures to allow communication between the internal and the external cloaca.

The process of partitioning then spreads caudally into the external cloaca. The perineal mound (i.e., the tip of the urorectal septum) separates the urogenital sinus from the anus. The inner genital folds proliferate to form the perineum and the labia minora, whereas the outer genital folds develop into the labia majora.

7.3 Müllerian Duct Anomalies

Based on the embryological development of the female genital system, uterovaginal malformations are classified as müllerian agenesis in cases of a developmental defect of the caudal portion of the müllerian ducts (Mayer-Rokitansky-Küster-Hauser syndrome), disorders of lateral fusion resulting from failure of the two müllerian ducts to fuse, and disorders of vertical fusion that are caused by faults in the union between the müllerian tubercle and derivatives of the urogenital sinus (transverse vaginal septum, cervical agenesis, disorders of the hymen). Disorders of lateral fusion are very heterogeneous,

but are best classified according to Buttram and Gibbons who proposed a classification of müllerian anomalies in 1979, which is now the guideline of the American Fertility Society. According to this classification, müllerian duct anomalies are classified into six groups. A particular patient, however, may not necessarily fit neatly into a single category. Class I–class V are shown in Figures 7.2–7.4; class VI (not shown) refers to a uterus with luminal changes secondary to in utero exposure to diethylstilbestrol (DES), used to prevent miscarriage between the late 1940s and the 1970s.

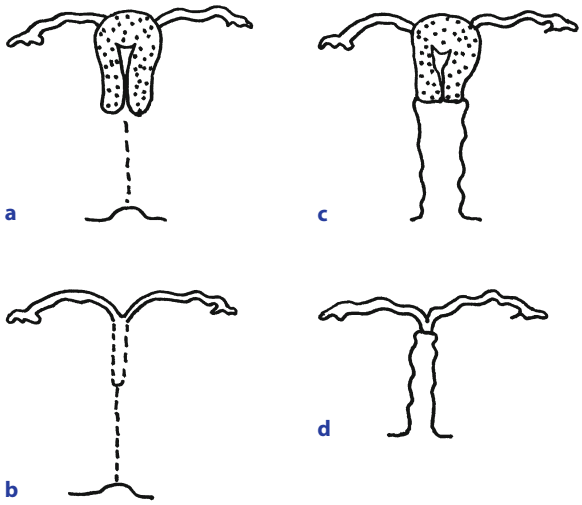


Fig. 7.2a–d. Schematic presentation of class I: Müllerian agenesis or hypoplasia. **a** Vaginal. **b** Combined vaginal and fundal. **c** Cervical. **d** Fundal

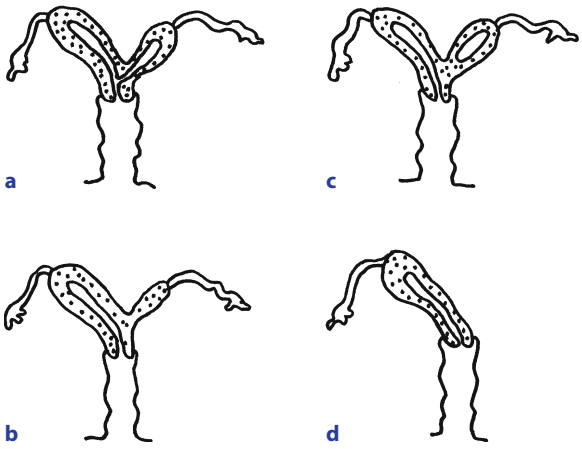


Fig. 7.3a–d. Schematic presentation of class II: unicornuate uterus. **a** With a rudimentary, communicating horn. **b** The rudimentary horn has no cavity, no endometrium. **c** The rudimentary horn is noncommunicating with active endometrium. **d** No rudimentary horn

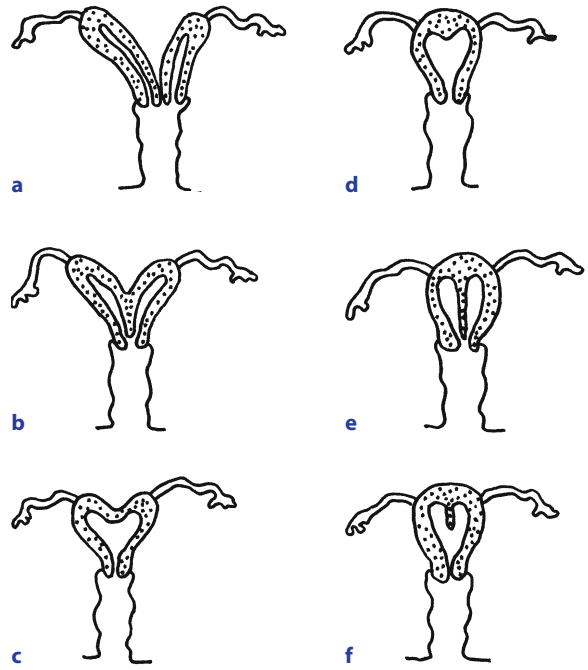


Fig. 7.4a–f. Schematic presentation of classes III, IV, and V. **a** Uterus didelphys (class III); **b–d** bicornuate uterus (class IV): **b** complete, **c** partial, **d** arcuate; **e**,**f** septate uterus (class V): **e** complete, **f** partial

Due to the frequent association of vertical and lateral fusion disorders, vaginal anomalies are best considered according to the presence or absence of an obstruction.

Syndromes reported to be associated with genital anomalies in the female encompass Mayer-Rokitansky-Küster-Hauser syndrome (müllerian agenesis), MURCS association (*mü*llerian duct aplasia, *r*enal agenesis/ectopia, *c*ervical somite dysplasia), hand-foot-genital syndrome (bifid uterus, double uterus, septate vagina), VATER, VACTEL, VACTERL, VACTER association (*v*ertebral, *v*ascular, and *a*nal *a*nomalies, *a*uricular defects, *c*ardiovascular anomalies, *t*racheoesophageal fistula, *e*sophageal atresia, *r*enal anomalies, *r*adial defects, *r*ib and *l*imb anomalies), Beckwith-Wiedemann syndrome (bicornuate uterus), EEC syndrome (transverse vaginal septum), Fraser syndrome (bicornuate uterus, vaginal atresia, rudimentary uterus), Roberts syndrome (septate vagina), renal-genital-ear anomalies (vaginal atresia), Schinzel-Giedion syndrome (hymenal atresia), Jarcho-Levin syndrome (uterus didelphys) (Taybi and Lachman 1996), and finally Pallister-Hall syndrome (vaginal atresia) (Unsinn et al. 1995).

7.3.1 Müllerian Agenesis

Mayer-Rokitansky-Küster-Hauser syndrome is characterized by the absence of the entire vagina or, more commonly, the proximal two-thirds of the vagina; absence or abnormalities of the uterus; and malformations of the upper urinary tract (Fig. 7.5). It affects 1 in 4,000–5,000 otherwise normal (46 XX) girls. Mayer-Rokitansky-Küster-Hauser syndrome type A (typical form) shows normal-appearing external genitalia, absence of the vagina and uterus, normal fallopian tubes, normal ovaries, and no renal anomalies. In type B (atypical form), the uterus may be normal except for the lack of a conduit to the introitus or may be rudimentary, commonly show-

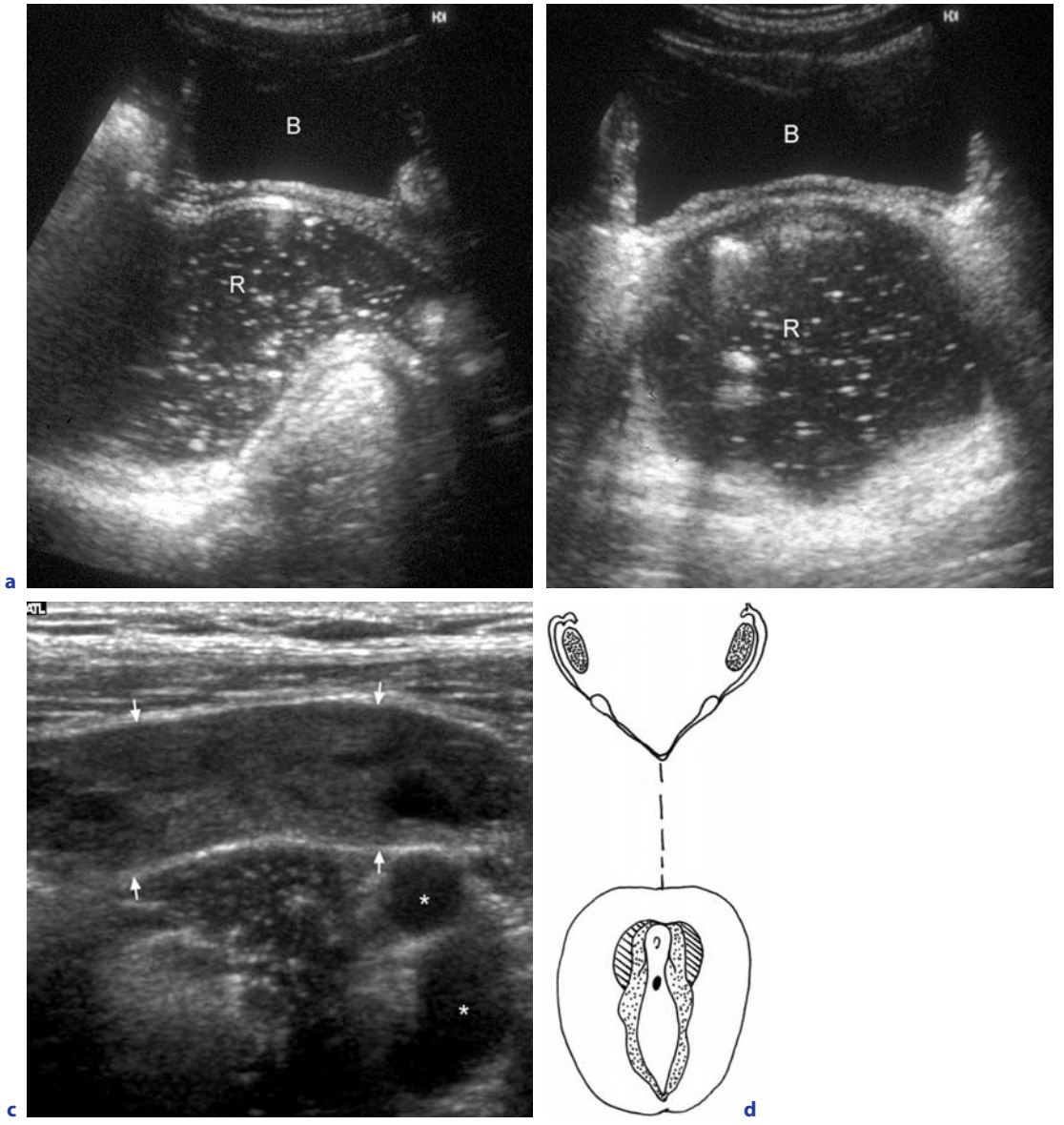


Fig. 7.5a–d. Mayer-Rokitansky-Küster-Hauser-syndrome in a 10-year-old girl with normal external genitalia and normal female karyotype. **a** Longitudinal, **b** transverse pelvic sonograms: between the fluid-filled rectum (*R*) and the bladder (*B*), neither vagina nor uterus is visualized. **c** Transverse scan through the right iliac fossa: Normal ovary (*arrows*) with follicles. Iliac vessels (*asterisks*). **d** Schematic representation of genital anomalies encountered in Mayer-Rokitansky-Küster-Hauser syndrome. The rudimentary uterine horn consists of muscle bundles and some endometrial tissue. The tubes and ovaries are normally displayed. The perineal anatomy shows a female phenotype, but no vaginal opening

ing disorders of the lateral fusion with aplasia of one or both uterine horns, or asymmetry of the horns if both are present. However, any of the lateral or vertical fusion abnormalities with or without obstruction may be seen. The fallopian tubes are abnormally developed (hypoplasia and aplasia of one or both tubes) and ovarian anomalies such as inguinal hernia containing an ovary, no descent of the ovary, absence of the ovary, or streak ovaries have been reported (Taybi and Lachman 1996; Bazi et al. 2006).

Malformations of the upper urinary tract occur in up to 50% (Rosenberg et al. 1986) of all affected females and include renal hydronephrosis, agenesis, fusion, dysplasia, and unilateral ectopia. Associated anomalies of the ureters such as ectopia and vesicoureteral reflux have also been reported. Skeletal anomalies are seen in approximately 10% (Taybi and Lachman 1996) of patients who have malformations of the spine, such as wedge vertebrae, fusions, rudimentary vertebral bodies, and supernumerary vertebrae. Absence or underdevelopment of one lower sacral segment and coccyx as well as tethered spinal cord have been reported. Other skeletal anomalies include syndactyly, absence of a digit, long proximal phalanx of digits 3 and 4, long metacarpals of digits 1–4, carpal abnormalities, hypoplasia of the thenar eminence, and bilateral femoral hypoplasia.

The typical patient seeks medical advice at the expected time of onset of puberty because of primary amenorrhea. Upon physical examination the external genitalia are those of a normal female, although the introitus may end in a shallow blind pouch. Depending on whether there is a functional endometrium, cyclic or intermittent abdominal pain may be present due to hematocolpos or hematometrocolpos. Mayer-Rokitansky-Küster-Hauser syndrome is the second most frequent cause of primary amenorrhea after the classic Turner syndrome.

The classic Turner syndrome (55% of 45 X0 patients) shows ovarian dysgenesis, primary amenorrhea, and infantile uterus, vagina, and breasts. Less commonly, a mosaicism (X/XX, X/XY, X/XX/XY), isochromosome X, ring X, or partial deletion of the X chromosome is found. In chromosomal mosaic patients the whole spectrum from absent to infantile to normal-sized ovaries, uterus, and vagina can be seen, explaining why 5% of all Turner syndrome patients have spontaneous menstruation. Patients carrying a Y chromosome in their karyotype have a higher risk for developing gonadoblastoma (Siegel 1995).

7.3.2 Disorders of Vertical Fusion

The disorders of the vertical fusion of the müllerian ducts consists of transverse vaginal septa, imperforate cervix, and cervical agenesis and results from faults in the junction between the descending müllerian ducts and the ascending urogenital sinus. In transverse septa the interruption may be complete or incomplete and occur at any level of the vagina, sometimes at multiple levels. The vagina is obliterated by fibrous connective tissue with vascular and muscular elements lined by squamous epithelium. The septum may be a thin membrane, but more commonly involves a whole segment of the vagina (segmental vaginal atresia). An increased incidence of associated proximal müllerian duct anomalies is found, such as lateral fusion abnormalities of the uterus, stenosis, hypoplasia, or absence of the uterus and the fallopian tubes (Silverman and Kuhn 1993).

Although of different embryological origin, the imperforate hymen is commonly listed together with defects of the vertical fusion of the müllerian ducts. The hymen membrane separates the vaginal lumen from the urogenital sinus and is entirely of urogenital sinus origin. The hymen membrane usually ruptures in the perinatal period and remains as a thin fold around the vaginal orifice. As with all vaginal obstructions found in association with a normal uterus, imperforate hymen may either be symptomatic in the newborn period or after onset of puberty due to the development of hydrocolpos/hydrometrocolpos or hematocolpos/hematometrocolpos, respectively. A protruding interlabial mass in association with a midline pelvic mass is found upon physical examination. Imperforate hymen is the simplest and most easily correctable of all vaginal obliterations. It is not associated with an increased incidence of müllerian duct or renal anomalies (Silverman and Kuhn 1993).

7.3.3 Disorders of Lateral Fusion

Incomplete fusion of the distal segments of the two müllerian ducts results in various degrees of bifidity of the uterus and/or vagina (Jarcho 1946) (Fig. 7.6). Disorders of the lateral fusion are rare in the general population and, in the absence of obstruction, are asymptomatic during childhood or at puberty. However, these anomalies are more frequently encoun-

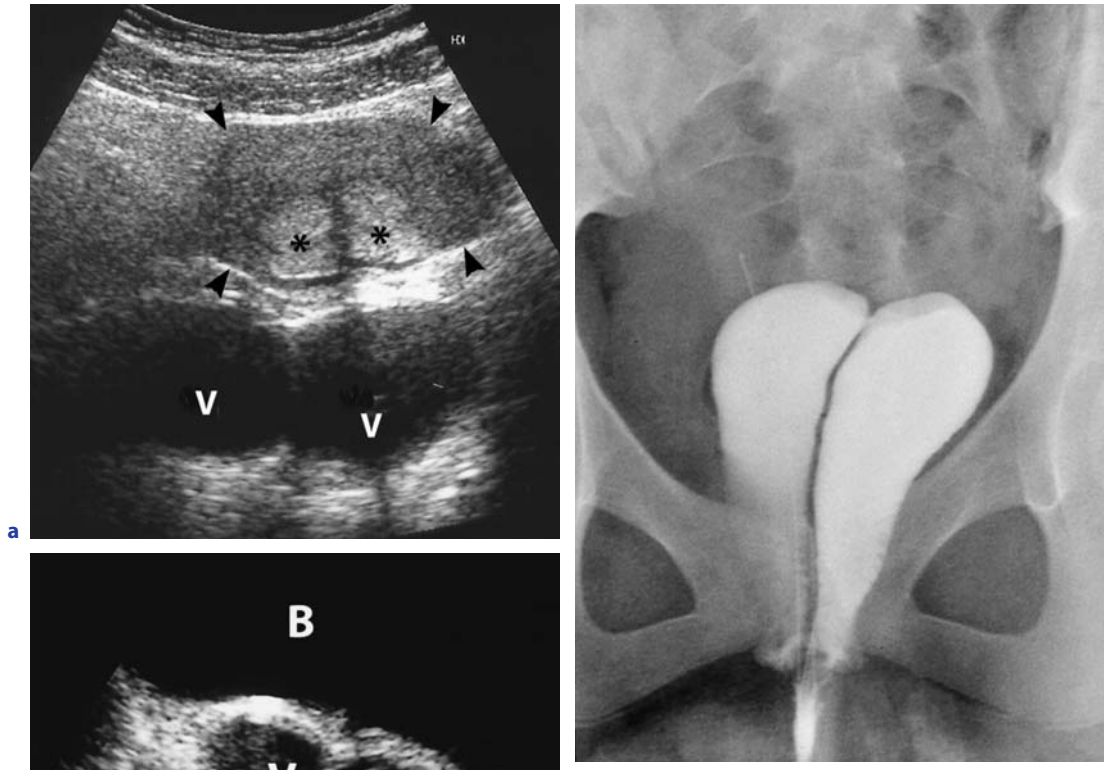


Fig. 7.6a–c. Uterus didelphys with double vagina in a 16-year-old girl. **a** Filling of the vagina with plain sodium solution. Transverse sonogram shows two uteri (*closed arrowheads*) with thickened, echogenic endometrium (*asterisks*) and two fluid-filled vaginas (*V*) behind the empty bladder. **b** With a slightly oblique transducer position no sonographic dropout occurs and allows clear demonstration of the two separate vaginas (*V*). *B*, Bladder. **c** Contrast filling of the vagina. Anterior posterior view of the double vagina after retrograde filling. The septum is clearly visible

tered in infertile women. This group of uterine malformations includes septate, bicornuate, didelphic, and unicornuate uterus (Figs. 7.2–7.4) (Buttram and Gibbons 1979). A minor and relatively common form of fusion defects of the müllerian ducts is simple septate vagina, in which the vagina is divided in two lateral compartments by a midline sagittal septum without uterine anomalies.

7.3.4 Vaginal Anomalies With or Without Obstruction

Because of the frequent association of vertical with lateral fusion anomalies, it is useful to consider vaginal anomalies according to the presence or the absence of obstruction (Fig. 7.7). Nonobstructive vaginal anomalies encompass bifid vagina, longitudinal vaginal septum, and incomplete transverse septum. Among the obstructive vaginal anomalies are imperforate hymen, complete transverse vaginal septum, and atresia of the uterine cervix and vagina, as mentioned above, as well as unilateral obstructive vaginal septum and obstruction of a unilateral rudimentary horn.

Unilateral obstructive vaginal septum. In some cases of duplicated uterus with a midline vaginal septum the caudal end of one hemivagina, more often the left, is obstructed (uterus didelphys with septate

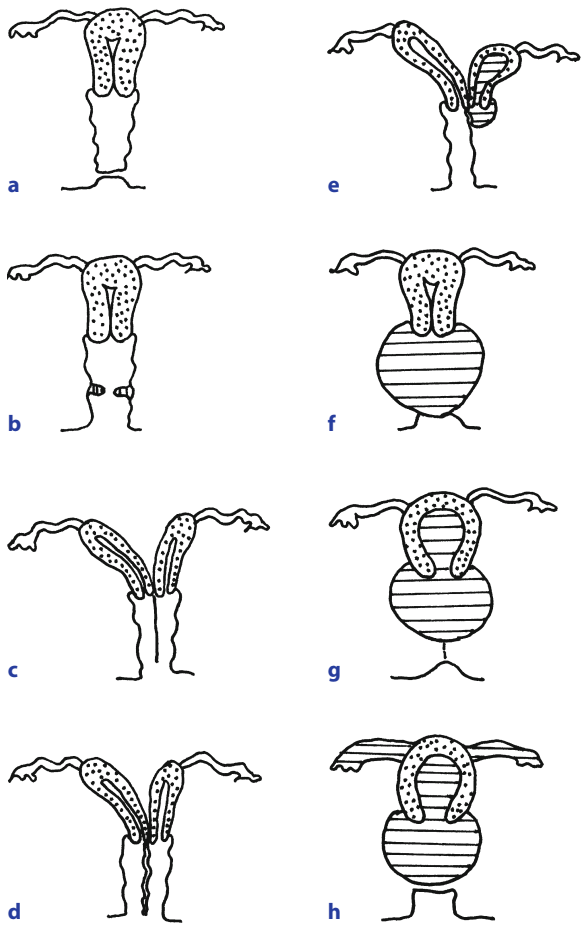


Fig. 7.7a–h. Schematic presentation of vaginal anomalies with and without obstruction. **a** Imperforate hymen. **b** Incomplete transverse vaginal septum. **c** Longitudinal vaginal septum, uterus didelphys. **d** Bifid vagina, uterus didelphys. **e** Obstruction of a hemivagina, hematometrocolpos, uterus didelphys. **f** Imperforate hymen, hematocolpos; a protruding vestibular mass is found. **g** Partial vaginal agenesis, hematometrocolpos. **h** Transverse vaginal septum, hematometrocolpos, spilling of menstrual blood via the fallopian tubes

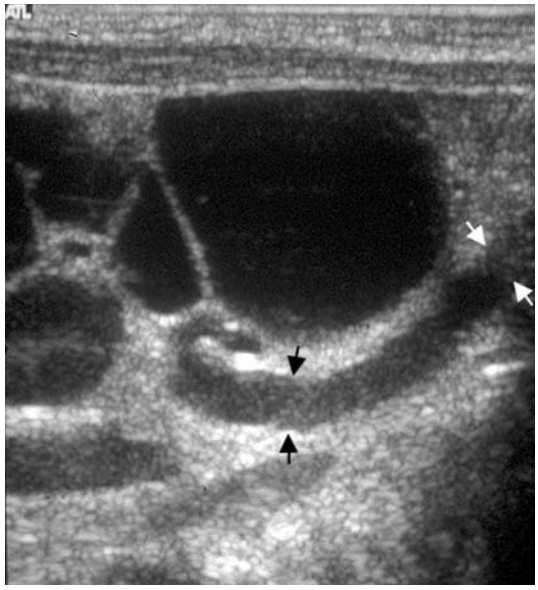
vagina and uterovaginal obstruction) (Fig. 7.8). No hymen tissue is found on the obstructed side. The disorder may present at birth with a pelvic mass due to accumulated genital secretion. The ipsilateral fallopian tube may also be enlarged. More commonly, however, the patient presents at puberty with a pelvic mass and cyclic abdominal pain despite a normal menstrual blood flow. The obstructed vaginal compartment may protrude as a cystic mass from the introitus. An obstructed hemivagina and double uterus are almost always associated with severe ipsilateral renal anomalies (renal agenesis, renal dysplasia, ectopia, ipsilateral ectopic ureter, and hydronephrosis) due to the close developmental association between the genital system (originating from the müllerian ducts) and the urinary system (originating from the wolffian ducts) (Silverman and Kuhn 1993).

Obstruction of a unilateral rudimentary horn. This condition is found at the extreme end of the spectrum of müllerian duct anomalies (Fig. 7.3). One of the two müllerian ducts fails to develop or is partially or completely (unicornuate uterus) resorbed. The ipsilateral fallopian tube is, therefore, absent or rudimentary, whereas both ovaries are present and functional. If a rudimentary hemiuterus contains functioning endometrium, the patient may develop an accumulation of mucus within this structure, during the neonatal period, or blood, at the time of puberty. Renal agenesis or severe renal dysplasia on the side of the missing or malformed hemiuterus is the rule (Gilsanz et al. 1982; Woolf and Allen 1953).

Conclusion

Due to the close developmental relationship of the urinary and the genital tract, malformations frequently occur in both of these systems. Major renal anomalies are common in patients presenting with unilateral obstruction or agenesis of duplicated structures derived from the müllerian duct.

Fig. 7.8a–g. Uterus didelphys with left multicystic dysplastic kidney (*MCDK*) and ipsilateral vaginal obstruction. **a** Longitudinal scan (*coronal plane*) of the left flank. *MCDK*: multiple anechoic cysts of variable size and shape that do not communicate with each other. The dilated ureter (*arrows*) could be traced from the MCDK to the obstructed ipsilateral left vagina. **b** Transverse pelvic sonogram shows two uterine fundi: right fundus (*closed arrowheads*), left fundus (*open arrowheads*). **c** Transverse scan at lower level than **b** shows a left-sided cyst representing obstructed left vagina (*LV*). **d**,**e** Longitudinal sonograms obtained after instilling saline solution in vagina demonstrated fluid-filled patent right vagina (*RV*) with right uterus (*arrowheads*); **e** atretic left vagina (*LV*) with left uterus (*arrowheads*). Obstructing membrane (*arrow*). **f** Transverse scan shows the atretic left ureter (*closed arrowheads*) bulging into the atretic left vagina (*asterisk*). Functional right vagina (*open arrowheads*). **g** Schematic representation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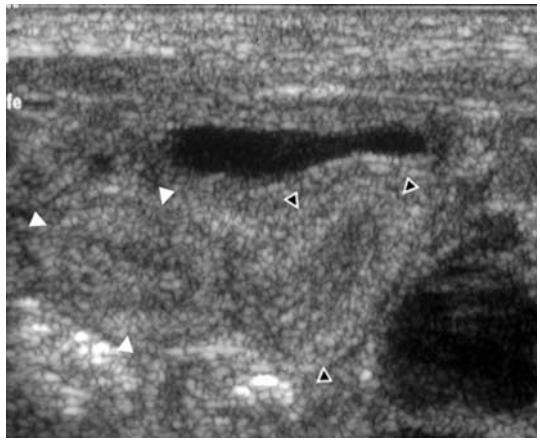
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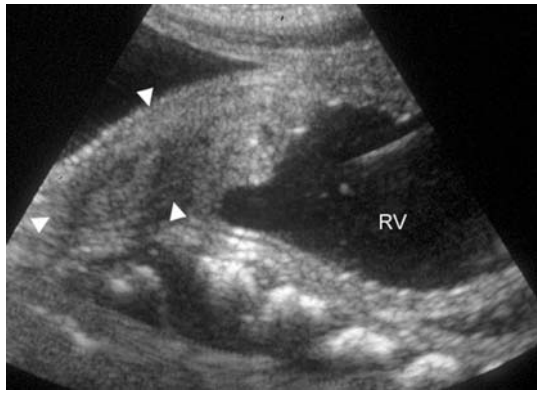

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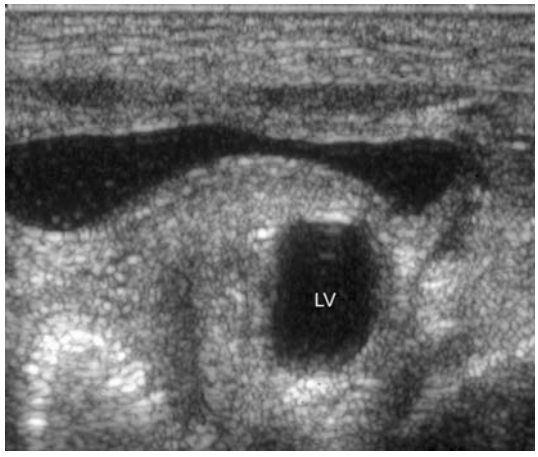

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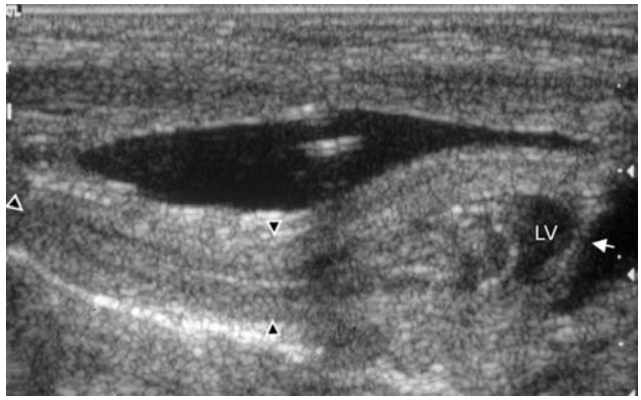

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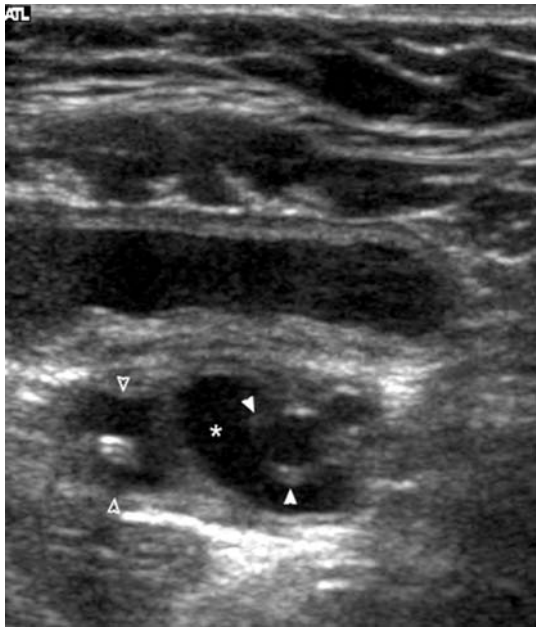
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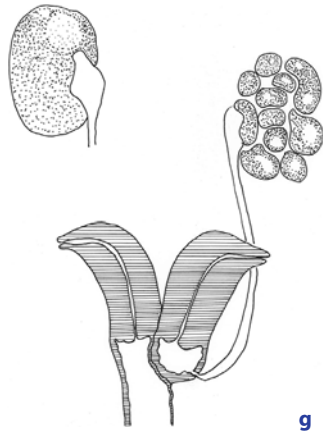
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7.3.5 Diagnostic Imaging of Müllerian Duct Anomalies

Pediatric radiologists will commonly come across müllerian duct anomalies at two different stages of a girl's life. In neonates diagnostic requests encompass evaluation of a palpable abdominal mass and delineation of associated genital malformation in urogenital sinus anomalies. In adolescent girls delay in puberty or primary amenorrhea as well as pelvic abdominal pain after the onset of puberty are the most common reasons for consultation.

Ultrasound is the most common first-step imaging technique in the evaluation of patients of both age groups. Subsequent tests such as MR imaging and fluoroscopic studies provide additional information (Fielding 1996; Wagner and Woodward 1994). In particular, patients with müllerian agenesis may need MR imaging to clearly document their ovaries and the rudimentary uterus (Rosenberg et al. 1986; Rosenblatt et al. 1991; Lang et al. 1999).

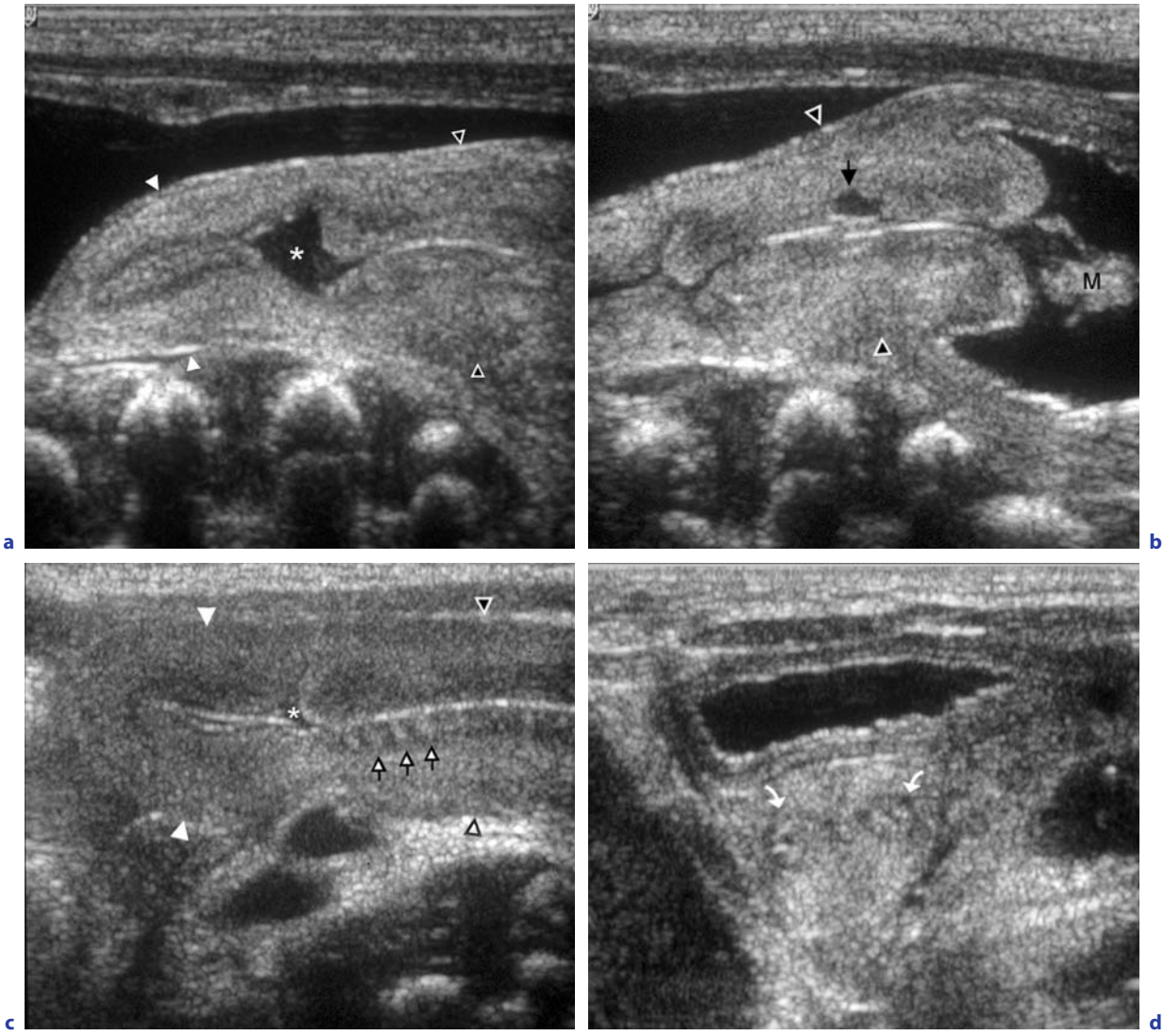

Fig. 7.9a–d. Normal neonatal uterus. **a–c** Longitudinal sonograms: the cervix and fundus are clearly discernible. The cervix (*open arrowheads*) has a greater diameter and length than fundus (*closed arrowheads*). There is a small amount of fluid within the endometrial canal at the junction of fundus and cervix (*asterisk*). Single nabothian cyst in the cervix (*closed arrow*). The inner layer of myometrium is hypoechoic (subendometrial halo). Echogenic endometrial glands (*open arrows*). In the fluid-distended vagina cervical mucus adherent to the vaginal part of cervix is visible (*M*). **d** Transverse scan at the level of the fundus shows the uterine horns (area where the tubes enter the uterus; *curved arrows*)

Due to the high association of müllerian duct anomalies with anomalies of the urinary tract, every patient diagnosed with genital malformations, whether newborn or adolescent, needs a careful investigation of the urinary tract. Renal ultrasound and voiding cystourethrography should be performed on all patients diagnosed with a duplicated uterine system. Pelvic sonography, on the other hand, is mandatory in patients with unilateral renal agenesis, ectopia, multicystic dysplastic, or horseshoe kidney (Gilsanz et al. 1982; Woolf 1953; Gilsanz and Cleveland 1982). In cases of müllerian agenesis spinal ultrasound in newborns and MR imaging in older girls as well as plain X-rays are required to rule out spinal cord anomalies and skeletal anomalies, respectively.

Sonographic features of the uterus in neonate, prepubertal, and pubertal girls. Under the influence of maternal and placental hormones the neonatal uterus is more prominent and measures 3.5 cm in length and 1.4 cm in thickness, with a definable endometrial stripe (Fig. 7.9).

An uterus didelphys or bicornuate uterus can, therefore, readily be demonstrated. The prepubertal uterus is smaller, has a tube shape, and a non-apparent endometrium, making it almost impossible to evaluate uterine anomalies (Fig. 7.10).

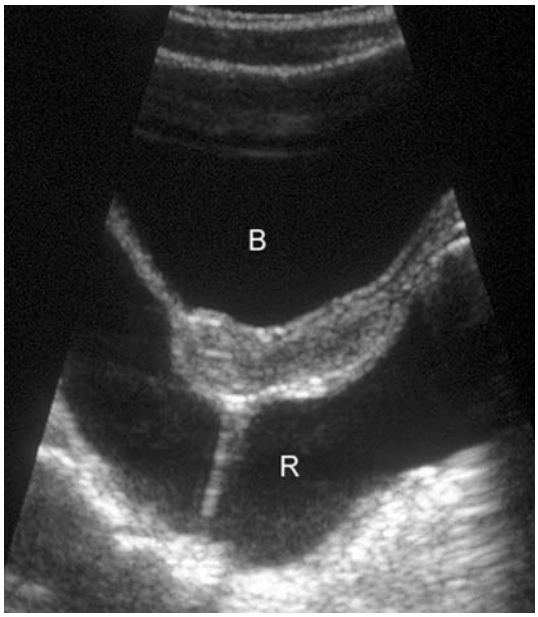

Fig. 7.10. Normal prepubertal uterus of a 4-year-old girl. The uterus is small with a fundus to cervix ratio of 1:1. *B* bladder, *R* rectum

Estrogen stimulation at the onset of puberty results in fundal swelling and endometrial echo (Fig. 7.11). The postpubertal uterus has the adult pear-shaped appearance and measures 5–8×1.5×3 cm (Teele and Share 1992; Ziereisen et al. 2005) (Fig. 7.11).

Sonographic features of hydro/hematocolpos and hydrometro-/hematometrocolpos. Sonographic evaluation of a newborn or adolescent girl with a palpable abdominal mass may reveal a midline cystic mass reflecting congenital hydrocolpos or hydrometrocolpos in the former and hematocolpos or hematometrocolpos in the latter (Figs. 7.12, 7.13).
In some cases the cystic dilatation of the vagina may be very impressive with the less easily distensible uterus attached to it as a small cap-like structure. The fluid-filled vagina and/or uterus may be seen as a cystic structure homogeneously and completely filled appearing as a solid mass, or cystic with scattered internal echoes, or completely anechoic. A fluid-debris level might be found and is a crucial finding in congenital hydrocolpos/hydrometrocolpos that differentiates the vagina from the bladder (Blask et al. 1991a,b). Association of hydro/hematocolpos and hydrometro/hematometrocolpos with an obliterate introitus or a shallow blindly ending vaginal pouch is strongly suggestive of müllerian agenesis or transverse vaginal septum, but has to be distinguished from pelvic masses caused by an imperforate hymen or unilateral occlusion of a duplicated vagina (Blask et al. 1991b).

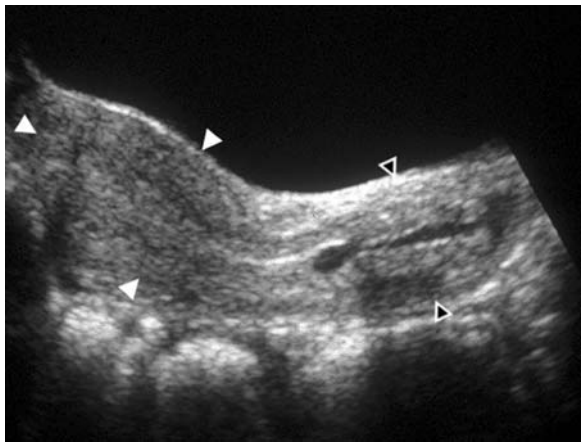

Fig. 7.11. Normal postmenarchal uterus of a 12-year-old girl. Longitudinal sonogram: pear-shaped uterus. Diameter and length of the fundus (*closed arrowheads*) are greater than those of the cervix (*open arrowheads*)

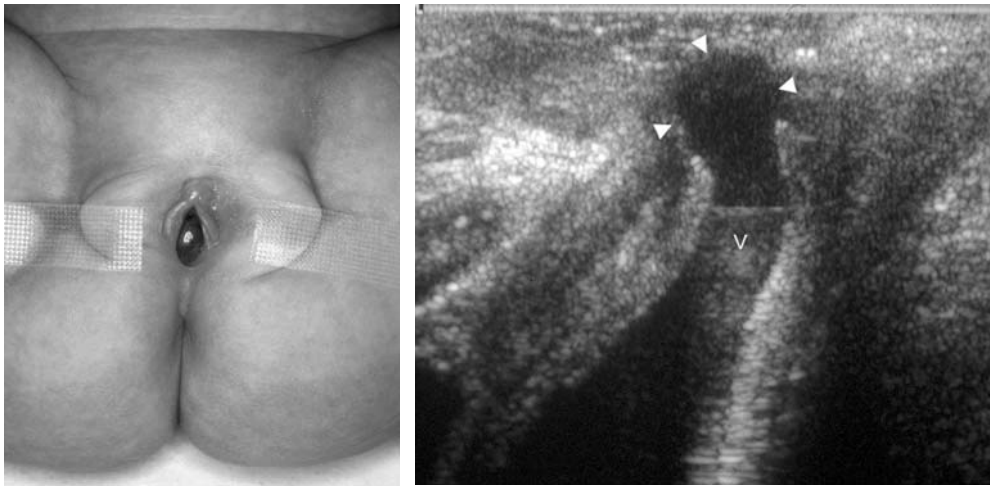

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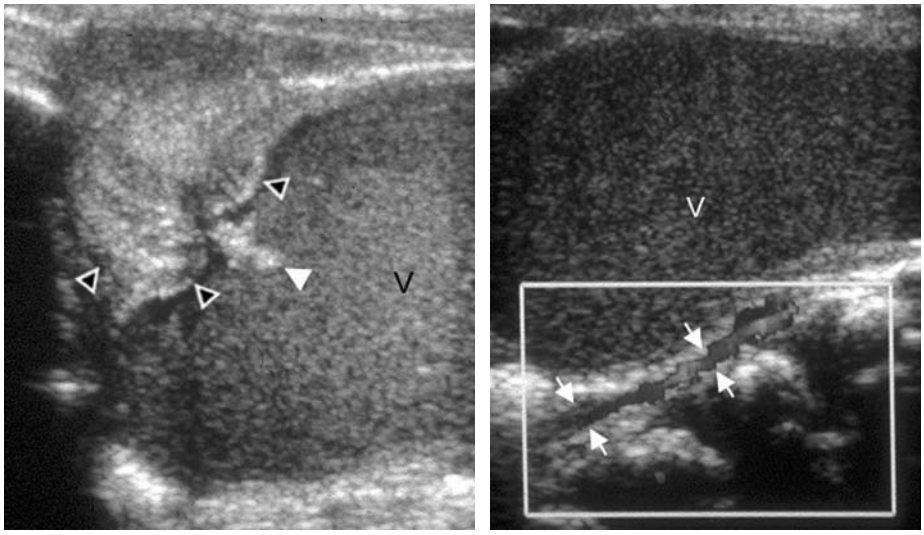
Fig. 7.12a,b. Imperforate hymen with moderate hydrocolpos. **a** The imperforate hymen protrudes between the labia. **b** Translabial sagittal scan: the vagina (*V*) is moderately dilated and the fluid protrudes the hymen (*arrowheads*) spherically



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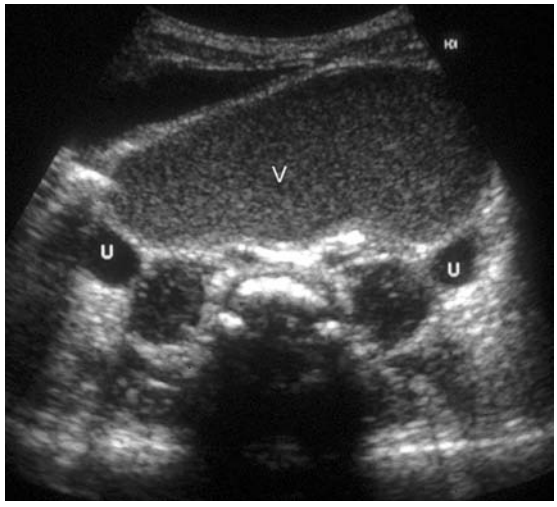

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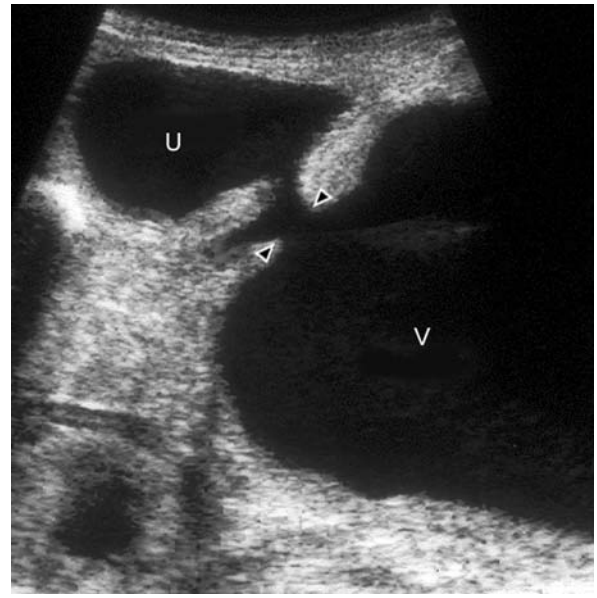
Fig. 7.13a–c. Imperforate hymen with excessive hydrocolpos. **a**,**b** Longitudinal scans: the low-level echoes within the markedly dilated vagina (*V*) represent mucous secretions. **a** The uterus with cervix (*open arrowheads*) projects into the dilated vagina (*V*). Mucus plug (*closed arrowhead*) adherent to the cervical ostium. **b** The hydrocolpos (*V*) compresses the inferior vena cava (*arrows*). **c** Transverse pelvic scan: the ureters (*U*) are dilated due to distal ureteral compression. *V*; hydrocolpos

In addition, fluid may be found in the peritoneal cavity due to spillage of genital secretion/menstrual blood via the fallopian tubes. Repeated backflow of menstrual blood results in endometriosis and chronic epithelial tubal changes that jeopardize fertility (Fig. 7.14).

Diagnostic imaging of vaginal anomalies. Vaginal anomalies without obstruction are usually asymptomatic unless they represent a mechanical obstacle during intercourse or delivery. Either fluid filling of the vagina under sonographic guidance or traditional vaginography with contrast material is effective in delineating these malformations (Pellerito et al. 1992; Rosenberg et al. 1986). In our experience traditional vaginography is restricted in value by only demonstrating the inner contour of the vagina (Gassner 2004). Frequently the uterus does not opacify, and the proximal impression of the cervix/cervices or the lateral impression caused by an obstructed hemivagina may at times be difficult and confusing. Filling the vagina with either ultrasound contrast agents or plain salt solution combined with ultrasound, however, overcomes these problems. In our experience, fluid instillation into either the bladder or the rectum or both significantly increases the



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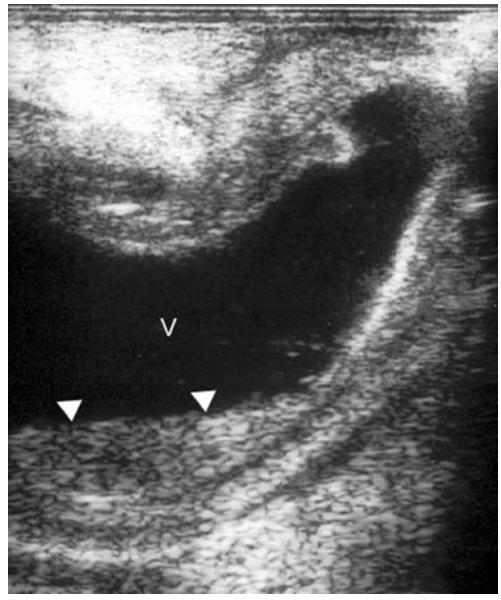

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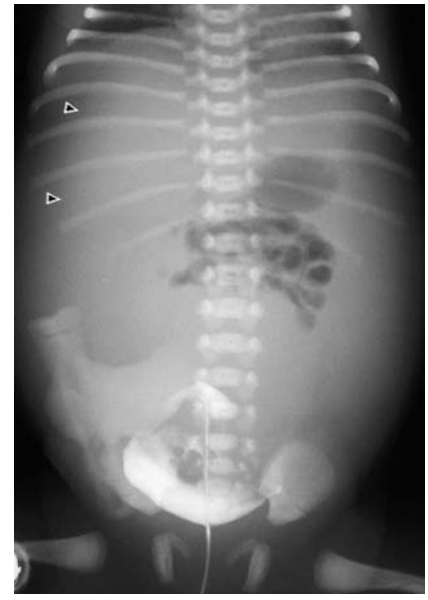

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Fig. 7.14a–c. Imperforate hymen with hydrometrocolpos and ascites due to spillage of genital secretions via the fallopian tubes into the peritoneal cavity. **a**,**b** Sagittal scans: the vagina (*V*) as well as the uterus (*U*) are dilated with broad communication through the cervical ostium (*open arrowheads*). The vagina shows a fluid-debris level (*closed arrowheads*). **c** Distended, fluid-filled abdomen. The air-filled loops of bowel cluster in the center of the abdomen. The lateral edge of the liver (*arrowheads*) is visible

performance of ultrasound by generating "sonographic windows" surrounding the uterus and vagina (Kiechl-Kohlendorfer et al. 2001).

Filling the vagina in a newborn is performed via an 8-F feeding tube. A catheter of adjusted size is used in older girls. Simultaneously performed transabdominal or perineal ultrasound delineates the internal anatomy and patency of the vagina, the presence of one or two cervices, and allows the differentiation of a cystic mass being related to an obstructed vagina, an ureterocele, renal cysts (multicystic dysplastic kidney) (Fig. 7.8), or a dilated Gartner's duct or a Gartner's duct cyst. Gartner's duct cysts are usually asymptomatic, do not exceed 2 cm in size, and typically exhibit a hypoechoic, sharply delineated cystic structure in close proximity to the anterolateral wall of the cervix (Rosenfeld and Lis 1993). In the rare cases of the ureteral bud failing to separate from the wolffian ducts, a single ectopic ureter may terminate directly or via Gartner's duct or a Gartner's duct cyst into the bladder neck, the urethra, the vaginal vestibule, or the vagina itself (Currarino 1982). A single ectopic ureter is always accompanied by ipsilateral renal hypoplasia, dysplasia, or agenesis (Gharagozloo and Lebowitz 1994).

Conclusion

In the evaluation of müllerian duct anomalies in neonates and adolescent girls, sonography is the most useful first-step examination technique. In all patients with congenital malformations of the inner genitalia, the urinary tract needs to be evaluated.

7.4 Ovarian Cysts

Congenital ovarian cysts in the fetus and newborn used to be considered uncommon. With the introduction of ultrasound as a screening procedure during pregnancy, the detection of both small and large cysts has increased. The presence of small follicular cysts is a common and normal finding in neonatal ovaries and can already be seen after the 26th week of gestation in prenatal ultrasound. They are usually less than 1 cm in diameter (Fig. 7.15), contain clear fluid, and resolve spontaneously within a few months after birth. Ovarian cysts are thought to be caused by maternal hormonal stimulation and have been found associated with hypersecretion of placental hCG or increased placental permeability to hCG (Müller-Leisse et al. 1992).

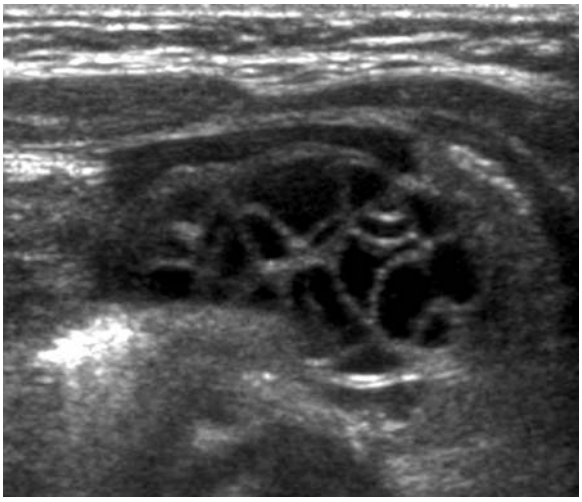


Fig. 7.15. Normal ovarian appearance in the neonate. Transverse scan: the ovary contains multiple follicular cysts

Furthermore, an increased frequency of ovarian cysts is found in infants of diabetic mothers or mothers who had toxemia or a large placenta complicating Rh sensitization as well as in infants suffering from adrenogenital syndrome (Silverman and Kuhn 1993; Topaloglu et al. 1997).

Great variations in the size of ovarian cysts are well documented, and they may occupy nearly the whole of the abdomen. According to their sonographic morphology, two forms of ovarian cysts are described: simple and complex cysts. Although simple cysts are purely cystic without internal echoes, complex cysts, which result from salpingotorsion and subsequent ovarian infarction or hemorrhage into a simple cyst, may show a fluid-debris level, a retracting clot, or thick septa. Due to autoamputation complex, cysts may be found anywhere in the abdomen. Up to 30% of large simple cysts undergo torsion, which most often happens prior to birth. Torsion of an ovarian cyst occurring in postnatal life may be asymptomatic or may cause fever, irritability, vomiting, leukocytosis, and abdominal tenderness. Hemorrhage within an ovarian cyst may also occur without signs of torsion. Lower abdominal pain and tenderness are common features in these cases (Silverman and Kuhn 1993). Controversy still exists as to whether conservative

(close observation), intermediate (percutaneous needle aspiration of large simple cyst under sonographic guidance, percutaneous drainage of complex cysts), or aggressive (surgical removal) therapy is more appropriate. Müller-Leisse et al. (1992) demonstrated considerable regression of the ovarian cysts in almost all of their conservatively treated patients, regardless of the sonographic appearance of the cyst and, therefore, recommend conservative treatment in asymptomatic patients and percutaneous puncture of space-occupying cysts.

Ovarian cysts, however, that compromise bowel function, have ruptured and cause ascites or hemoperitoneum, or require biopsy for histological examination due to their unspecific appearance, have to be surgically evaluated (Aslam et al. 1995). If surgical exploration is performed every attempt to salvage the gonad should be made. Viable ovarian tissue may still be present even if macroscopically invisible (Brandt et al. 1991; Brandt and Helmrath 2005).

Bilateral ovarian cysts in older girls are often found in association with cystic fibrosis, untreated hypothyroidism (Lindsay et al. 1983), Cushing syndrome, and other endocrinopathies with increased circulating androgen levels. Bilateral ovarian enlargement with discrete cysts has been seen in children with McCune-Albright syndrome (fibrous dysplasia, patchy cutaneous pigmentation, sexual precocity) (Rieth et al. 1981) and in patients suffering from polycystic ovarian disease.

In polycystic ovarian disease, both of the generally enlarged ovaries contain many small follicular cysts (2–6 mm), but larger cysts may also be present. Polycystic ovarian syndrome (Stein-Leventhal syndrome) is characterized by the association of polycystic ovaries with irregular menses, prolonged uterine bleeding, amenorrhea, anovulation, and often hirsutism and obesity. The clinical manifestation of this syndrome begins at or shortly after puberty.

Unilateral or bilateral ovarian follicular cysts of various sizes are frequently observed in girls with precocious puberty (onset of secondary sexual characteristics before 8 years of age). These cysts may either be secondary to ovarian stimulation by an increased level of circulating pituitary gonadotropins (central precocious puberty) or functional cysts similar to those seen in normal girls (partial precocious development). However, in some cases a large ovarian cyst may assume an autonomous function and be responsible for precocious puberty due to excessive estrogen production.

Conclusion

The presence of small ovarian follicular cysts is a normal ultrasound finding whatever the age. In neonates cysts may be found to be rather prominent due to maternal hormonal stimulation.

7.4.1 Diagnostic Imaging of Ovarian Cysts

Ultrasound has proven reliable in differentiating simple cysts (unilocular-transonic) from complex cysts (fluid–debris level, retracting clot, thick septa) (Figs. 7.16, 7.17). Simple cysts should be monitored for spontaneous resolution and may be aspirated under sonographic guidance if the threat of secondary torsion is considerably high.

Complex cysts may present anywhere in the abdomen and frequently bleed during or immediately after birth so that a fluid–sludge level or an evolving clot can be seen (Figs. 7.16, 7.17). In some cases, percutaneous puncture of the cyst can be diagnostic in showing evidence of increased estradiol in the withdrawn fluid.

Complex ovarian masses need to be differentiated from cystadenoma, pelvic inflammatory disease, neoplasm, enteric duplication cysts, and benign teratomas. Sonography permits the correct diagnosis with a high confidence level in simple cysts, and occasionally a specific diagnosis of ovarian teratoma can be made when highly echogenic foci with shadowing are demonstrated within a complex adnexal mass. However, ultrasound was not found to be reliable to distinguish between hemorrhagic cysts and benign teratoma in cases where no calcification or fat was present (Wu and Siegel 1987). The sonographic appearance of benign ovarian teratomas is a predominantly cystic structure containing focal areas of soft-tissue echogenicity and septation. In addition, complicated ovarian cysts often have thick echogenic walls resulting from dystrophic calcification associated with infarction. These sonographic appearances may be indistinguishable from the typical "thick-walled sign or double-wall sign" described for enteric cysts (Godfrey et al. 1998). Further investigations such as CT or MR imaging are sometimes inevitable to provide a specific diagnosis in these cases.

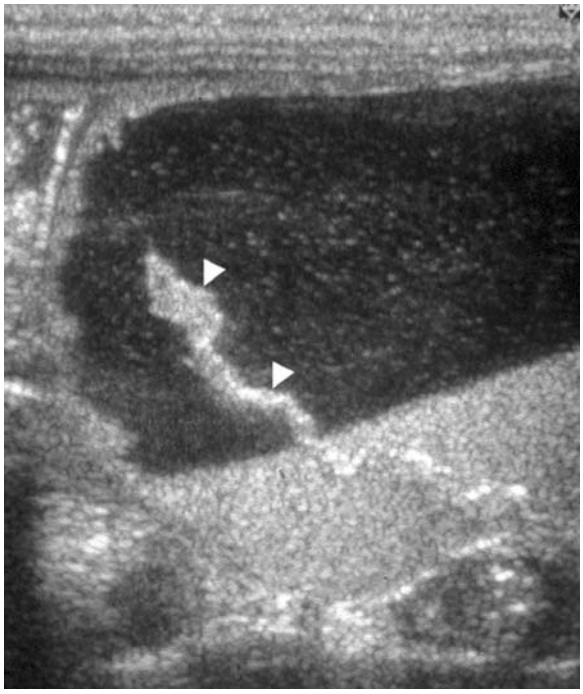


Fig. 7.16. Congenital ovarian cyst in a newborn of diabetic mother complicated by torsion. Longitudinal sonogram of the right hemiabdomen shows a large cyst with low-level echoes, a fluid-debris (blood) level, and an undulating thick membrane (fibrin; *arrowheads*). The cyst decreased in size and resolved completely

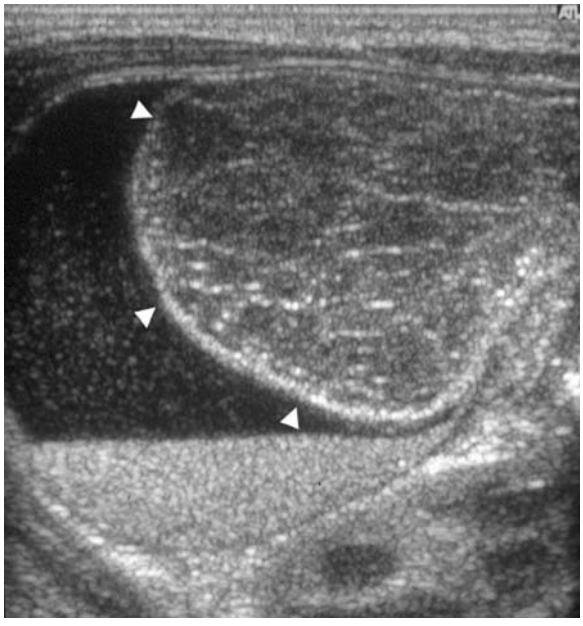


Fig. 7.17. Congenital ovarian cyst complicated by torsion. Transverse scan shows the large cyst with low-level echoes, a fluid-debris level, as well as a huge retracting clot (*arrowheads*). The cyst and clot resolved completely

Conclusion

Sonography is a reliable imaging technique to differentiate between simple and complex ovarian cysts. Unrelated to their sonographic appearance, ovarian cysts show a high potential for self-resolution. Conservative treatment with sonographic monitoring seems appropriate for most cases.

7.5 Lower Urinary Tract Anomalies of Urogenital Sinus

The most common urogenital sinus malformations a radiologist will come across are patients suffering from female hypospadias (simple urogenital sinus), intersexual conditions, and cloacal malformation (urogenital sinus associated with anorectal malformation) (Fig. 7.18).

Urogenital sinus is suspected during physical examination of a newborn with a normally placed anus in association with either ambiguous genitalia or a normal external genitalia, but only a single perineal opening within the vestibulum. It is either

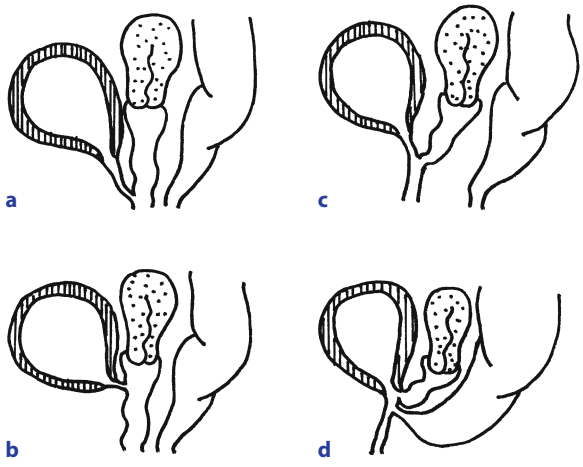


Fig. 7.18a–d. Schematic presentation of lower urinary tract anomalies of the urogenital sinus. **a** Distal female hypospadia: the urethral meatus lies in the roof of the vagina. **b** Proximal female hypospadia. **c** Urogenital sinus. **d** Persistent cloaca. The most common anatomy of persistent cloaca is shown. There is a urogenital sinus; the vagina enters just below the bladder neck, the rectum enters just below the vagina. The confluence level can be high, intermediate, or low

isolated or found in association with chromosomal and hormonal abnormalities or as a cloacal variant. Neonates with urogenital sinus frequently have ambiguous genitalia, since a main cause of this malformation stems from virilization of a female fetus or an intersex anomaly. However, urogenital sinus may also result from incomplete development of the lower vagina and the external genitalia may appear completely normal (Marshall et al. 1979).

In patients with ambiguous genitalia, determination of the sex has to be performed using biochemical, genetic, and radiological studies in order to exclude the life-threatening salt-losing form of adrenogenital syndrome and to provide adequate information to the parents.

7.5.1 Female Hypospadias

In female hypospadias the urethral meatus is positioned in the anterior wall of the vagina (Figs. 7.18, 7.19). Merguerian and McLorie (1992) regard female hypospadias as a mild form of urogenital sinus. Currarino (1986) and Knight et al. (1995) describe female hypospadias as an abnormality of the urethra itself caused by a defect in the differentiation of either the wolffian ducts, which form the dorsal part of the urethra, or the urogenital sinus, which develops into the distal third of the vagina. Differentiation defects of the wolffian duct lead to the development of the more severe proximal hypospadias, whereas developmental anomalies of the urogenital sinus result in the less severe distal hypospadias.

Distal hypospadias is more likely to have a urethra of normal diameter with no meatal stenosis and may, therefore, be asymptomatic or cause symptoms such as postmicturition incontinence and imperfect control, recurrent urinary tract infections, and urethral syndrome (referring to isolated urethritis with symptoms of increased frequency, pain during micturition, urgency, and dyspareunia) once sexual intercourse has commenced (Van Bogaert 1992).

The more severe cases of proximal hypospadias often show a narrowing of the urethra with signs of urinary outflow obstruction and are commonly associated with cloacal anomalies and female pseudohermaphroditism (Knight et al.1995).

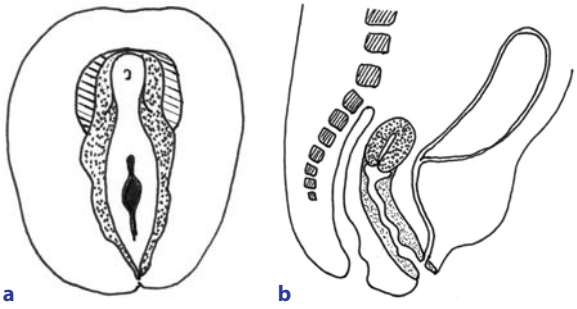


Fig. 7.19a,b. Schematic representation of female hypospadia. **a** The perineal anatomy shows a female phenotype but no urethral opening. **b** The urethral meatus is in the roof of the vagina

7.5.1.1 Diagnostic Imaging of Female Hypospadias

In mild forms of female hypospadias the urethral meatus is on the roof of the vagina just inside the introitus and might be entirely overlooked unless attempts to catheterize the urethra, usually for radiologic evaluation of the urinary tract, are frustrated by the inability to locate the meatus (Balk et al. 1982). In these patients the urethra must be catheterized blindly using a catheter with a curved tip (Coudé catheter). To rule out associated malformations both kidneys, the uterus and the vagina of these patients should be examined. The more severe cases of female hypospadias are usually part of a complex urogenital malformation and diagnostic evaluation will, therefore, be discussed below.

Conclusion

Inability to locate the urethral meatus in a little girl may be due to the presence of female hypospadias. In these patients the urethral meatus is positioned in the anterior wall of the vagina and catheterization has to be attempted blindly.

7.5.2 Urogenital Sinus in Disorders of Sex Development

Disorders of the external genitalia are especially troubling for parents because of the unconscious emotional significance of these reproductive structures, and it is the role of the radiologist to assist in assigning the correct gender of the neonate and to anticipate and diagnose any life-threatening conditions related to intersexual states. According to the Consensus statement on management of intersex

2006, the three major types of disorders of sex development (DSD) with ambiguous genitalia are referred to as 46, XX DSD, 46, XY DSD and ovotesticular DSD (Hughes et al. 2006).

7.5.2.1 46, XX Disorders of Sex Development

In most instances 46, XX disorders with ambiguous genitalia (former female pseudohermaphroditism) result from either exposure of a female fetus to excessive androgens or sex chromosome disorders.

The most common causes of androgen excess are congenital adrenal hyperplasia, followed by placental aromatase deficiency, masculinizing maternal hormones, and administration of androgenic drugs to women during pregnancy. The increased level of androgens within the fetal blood stream causes virilization of the external genitalia, which may vary from minimal phallic enlargement of the clitoris to almost complete masculinization (Fig. 7.20). The degree of masculinization of the fetus is thought to be related to the time and amount of androgen exposure. If the androgen stimulus is received after 12 weeks of gestation, only clitoral hypertrophy will occur (Merguerian and McLorie 1992). Earlier androgen exposure results in urogenital sinus and a higher degree of ambiguity of the external genitalia. At birth these patients present with marked clitoral enlargement, variable degree of labioscrotal fold fusion and rugation. The opening of the urogenital sinus at the clitoral base may mimic penile hypospadias.

Congenital adrenal hyperplasia. This is caused by a family of autosomal recessive disorders of adrenal steroidogenesis leading to a deficiency of cortisol. Lack of glucocorticoid hormone causes an increase in corticotropin, hyperstimulation of the fetal adrenal gland, and excessive androgen synthesis. One out of three adrenal enzymes involved in the pathway on which glucocorticoids are synthesized is affected. The condition 21-hydroxylase deficiency counts for 90–95%, and a defect of 11β-hydroxylase is found in 5–8% of cases (New 2003). The remaining patients show defects of other enzymes involved in steroidogenesis. Due to impaired aldosterone biosynthesis, salt-losing symptoms are common in 21- and 3β-hydroxysteroid dehydrogenase deficiencies and usually present soon after birth. Owing to allelic variants, severe and mild forms are described for each defect (Chan-Cua et al. 1989).

Placental aromatase deficiency. This results from a very low aromatizing activity of the placenta and thus fails to convert androgens derived from fetal dehydroepiandrosterone into estrogens (Shozu et al. 1991; MacGillivary et al. 1998).

Virilizing maternal tumors. These include adrenal adenoma, androblastoma, luteomas, and Krukenberg tumors and are reported to cause fetal virilization. In cases of unclear hermaphroditism, evaluation of the mother should always include measurement of her plasma androgen levels.

Administration of androgenic drugs to pregnant women. Over the past couple of years this mainly iatrogenic problem has been significantly reduced by replacing virilizing progestational compounds with nonvirilizing analogs in the treatment of threatening abortion. The frequent cause of ambiguous genitalia in sex chromosome DSD is mixed gonadal dysgenesis.

Mixed gonadal dysgenesis is a condition of abnormal and asymmetrical gonadal development, and/or sex chromosomal mosaicism, as well as retained mullerian ducts. A number of abnormalities have been reported in the karyotype, most commonly a mosaicism 45,X/46, XY. The phenotypical expression may be ambiguous, or male, or female depending on the extent of the mosaicism. The gonads may not be symmetrical, thus the development of the müllerian duct and wolffian duct may be asymmetrical, too (Donahoe et al. 1979). In the presence of dysgenetic gonadal tissue and Y chromosome material, there is a high risk of the development of tumors such as gonadoblastomas and seminoma-dysgerminomas with the risk exceeding 50% as the 3rd decade is approached. Removal of the gonads is usually indicated.

7.5.2.2 46, XY Disorder of Sex Development

46, XY disorder of sex development with ambiguous genitalia (former male pseudohermaphroditism) is most frequently caused by an abnormal plasma testosterone level or an abnormal testosterone response. The most common causes are disorders in androgen synthesis or action.

5-alpha reductase deficiency is an androgen biosynthesis defect that blocks the transformation of testos-

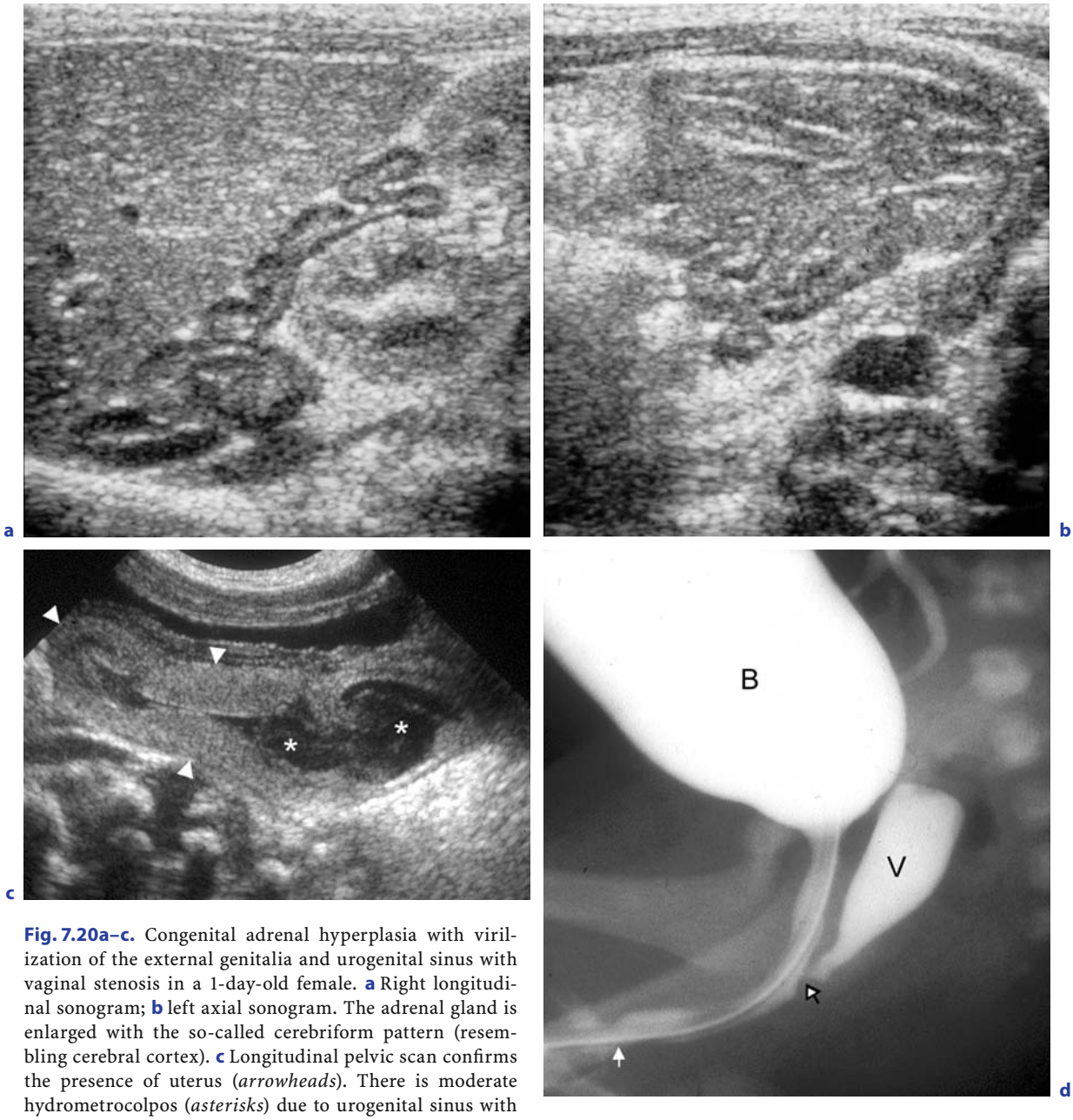


Fig. 7.20a–c. Congenital adrenal hyperplasia with virilization of the external genitalia and urogenital sinus with vaginal stenosis in a 1-day-old female. **a** Right longitudinal sonogram; **b** left axial sonogram. The adrenal gland is enlarged with the so-called cerebriform pattern (resembling cerebral cortex). **c** Longitudinal pelvic scan confirms the presence of uterus (*arrowheads*). There is moderate hydrometrocolpos (*asterisks*) due to urogenital sinus with vaginal stenosis. **d** The bladder is catheterized. Contrast material fills the bladder (*B*) and during micturition the vagina (*V*). Stenotic vaginal communication (*open arrow*). Urogenital sinus opening (*closed arrow*)

terone into the more potent 5-alpha dihydrotestosterone (DHT). The affected 46XY individuals have high normal to elevated plasma testosterone levels with decreased DHT levels and elevated testosterone/DHT ratios. DHT is necessary to exert androgenic effects farther from the site of testosterone production. A 5-alpha reductase deficiency results in a disorder characterized by female phenotype or severely undervirilized male phenotype with development of the epididymis, vas deferens, seminal vesicle, and ejaculatory duct, but also a pseudovagina (Imperato-McGinley and Zhu 2002).

Androgen insensitivity syndrome (AIS) is also called testicular feminization and results from a complete or partial absence of cytoplasmic receptors for testosterone in target tissues (Holterhus et al. 2005). It is an X-linked (band Xq11-q12) disorder with an inci-

dence of 1 in 62,000 male births. The feminization is a consequence of increased testicular secretion of oestradiol, peripheral conversion of androgens to oestradiol and a lack of testosterone function during fetal development. Serum LH and FSH are elevated as testosterone is ineffective at the hypothalamus. The syndrome is characterized by a 46, XY karyotype and negative sex chromatin. It is divided into two main categories: complete (CAIS) and partial (PAIS). CAIS results in bilateral testes, absent or hypoplastic wolffian ducts, and female-appearing external genitalia with diminished axillary and pubic hair development (Collins et al. 1993).

In PAIS the degree of sexual ambiguity varies widely from individual to individual. PAIS can include other disorders, such as Reifenstein's syndrome (also known as Gilbert-Dreyfus syndrome or Lubs syndrome), which is associated with hypospadias, gynecomastia, and cryptorchism.

CAIS is rarely discovered during childhood, unless a mass is felt in the abdomen or groin that turns out to be a testicle. Most with this condition are not diagnosed until they fail to menstruate or they try to become pregnant. PAIS, however, is often discovered during childhood because the affected child has both male and female physical characteristics and/or ambiguous genitalia such as partial fusion of the outer vaginal lips, an enlarged clitoris, or a short, blind-ending vagina.

7.5.2.3 Ovotesticular Disorder of Sex Development

Ovotesticular disorder of sex development (former true hermaphroditism) is a very rare form of intersex disorder characterized by the presence of both ovarian and testicular tissue in the same individual. There may be an ovary on one side and a testis on the other, but more commonly one or both gonads is an ovotestis containing both types of tissue. External genitalia are often ambiguous, the degree depending mainly on the amount of testosterone produced by the testicular tissue between 8 and 16 weeks of gestation. It is rare for both types of gonadal tissue to function.

Conclusion

Phenotypic sex differentiation is determined by hormonal products of the gonads. Anomalous hormone production during fetal development frequently results in ambiguous genitalia.

7.5.2.4 Diagnostic Imaging of Urogenital Sinus Anomalies

In *congenital adrenal hyperplasia* (Willi 1991; Chertin et al. 2000) the primary task of the radiologist is to demonstrate the level of communication between the vagina and the urethra, the anatomy of the internal genitalia and to rule out kidney anomalies and adrenal gland hyperplasia. Sonographic evaluation of the patient is usually the first-step imaging technique to provide detailed information on the urogenital system. Sonography is then to be followed by conventional radiology using contrast material to visualize the exact anatomy of the malformation. Transabdominal ultrasound demonstrates the internal genitalia, delineates müllerian duct anomalies, and rules out any obstructions such as hydrocolpos and hydrometrocolpos (Blask et al. 1991a), and allows investigation of the kidneys and adrenal glands at the same time. Urinary tract anomalies are common and include renal agenesis, ectopia, and cystic dysplasia as well as uni- and bilateral hydronephrosis, vesicoureteral reflux, and signs of urinary outflow obstruction (Woolf and Allen 1953). Enlargement of the adrenal cortex occurs in many, but not all babies with congenital adrenal hyperplasia. Demonstration of enlarged adrenal glands with a wavy configuration of their limbs, however, is highly suspicious of congenital adrenal hyperplasia even before biochemical or genetic data can be obtained (Fig. 7.20) (Teele and Share 1991; Hernanz-Schulman et al. 2002; Barwick et al. 2005).

After the patient has been evaluated by ultrasound, fluoroscopic studies with water-soluble contrast material are required to examine the exact anatomy of the malformation (Fig. 7.20). Barium paste or another opaque material is useful for marking the external orifice on the perineum and the urethra and/or the urogenital sinus is catheterized. If the catheter enters the bladder, voiding cystourethrography should be performed in the lateral position to demonstrate the urethra as well as the vagina during micturition and to rule out vesicoureteral reflux. If only the vagina is filled, however, the catheter should be left in place and a second catheter passed anteriorly into the urogenital sinus in an attempt to catheterize the urethra. The relative position of the vaginal orifice both to the urethra and to the vestibulum can then be demonstrated.

Using ultrasound and contrast studies, a definitive diagnosis of anatomical features and associated

genitourinary tract malformations can be made. More invasive imaging techniques such as endoscopy and MR imaging can thus frequently be postponed until shortly prior to surgical repair.

In *androgen insensitivity syndrome* ultrasound will demonstrate an absent uterus, no or a blind ending vagina, and testes located in the inguinal canal, labia, or intra-abdominal. Coexistence with urologic abnormalities has to be is expected such as unilateral renal agenesis (Tokgoz et al. 2006). The patient is at increased risk of undergoing malignant transformation of the undescended gonad. The gonads should not be removed until puberty and growth are complete, but closely monitored sonographically during childhood.

Conclusion

Narrowing differential diagnosis of the possible cause of urogenital sinus as well as demonstration of its anatomical features can be achieved at a high confidence level using contrast studies and ultrasound to assess pelvic structures and the adrenal glands.

7.5.3 Cloacal Malformation

The cloacal malformation is the most complex type of imperforate anus with confluence of the rectum, vagina, and bladder in a urogenital sinus. Cloaca is exclusively seen in phenotypic females and occurs in one of every 40,000–50,000 newborns. Cloaca should not be confused with cloacal exstrophy, a malformation due to a failed closure of the lower abdominal wall seen in boys and girls. The diagnosis of cloacal malformation includes a wide spectrum of pelvic and perineal anomalies (Jaramillo et al. 1990; Hendren 1998). At the mild end of the spectrum is a persistent urogenital sinus opening with an anteriorly placed anus adjacent to it (incomplete cloaca), while in more severe malformations all three tracts converge inside the pelvis. Variants of the cloacal malformations include the presence of an accessory filiform channel or sinus that connects the bladder or urethra to the perineum, anomalies of the vagina, and the so-called posterior cloaca, where the urogenital sinus is posteriorly placed and found to open either into the orthotopic rectum or perineally close to the normal anus (Pena and Kessler 1998) (Fig. 7.21).

Vaginal anomalies include bifid vagina, unilateral obstruction of one hemivagina, distal vaginal stenosis or atresia, absence of the vagina, a mislocalized retrorectal vagina, and a bifid vagina communicating widely with the trigonal area of the bladder (Fig. 7.22) (Jaramillo et al. 1990; Tolete-Velcek et al. 1989).

Apart from the incomplete cloaca with two perineal openings, most patients present with a single perineal opening. The perineal anatomy varies from an almost normal female phenotype (Fig. 7.23) to a

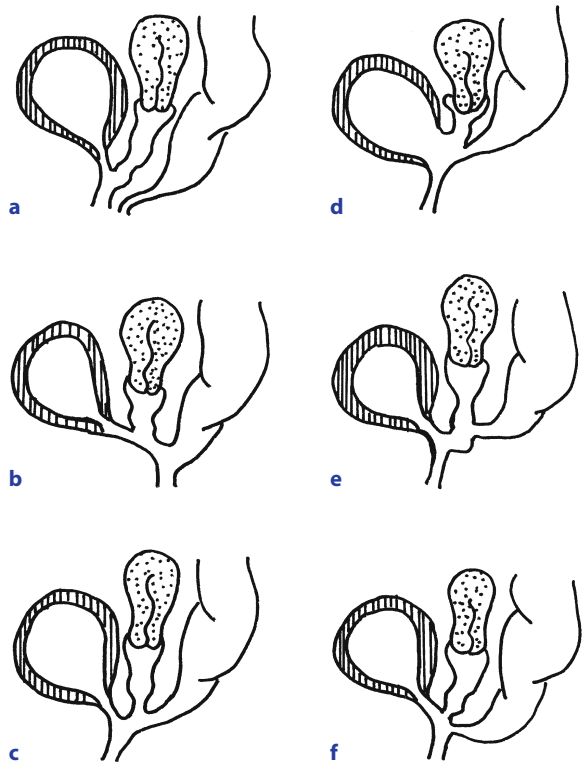


Fig. 7.21a–f. Schematic presentation of cloacal malformation variants. **a** Incomplete cloacal malformation: a persistent urogenital sinus opening is found adjacent to an anteriorly placed anus. **b** Posterior cloaca: the urogenital sinus derives posteriorly and opens in the anterior rectal wall at the anus or immediately anterior to it. Jaramillo et al. (1990) characterize the anatomy of persistent cloaca according to its urinary-cloacal or urinary-rectal communication pattern. Urinary-cloacal communication is called either urethrocloacal or vesicocloacal. **c** Urethrocloacal communication: the urethra empties into the proximal end of the cloaca and is well formed. **d** Vesicocloacal communication: the urethra is rudimentary or absent. Rectal communication is called either vaginal or cloacal. **e** Vaginal communication of the rectum: the rectum usually joins the vagina low on its posterior wall. **f** Cloacal communication of the rectum: the rectum joins the cloaca

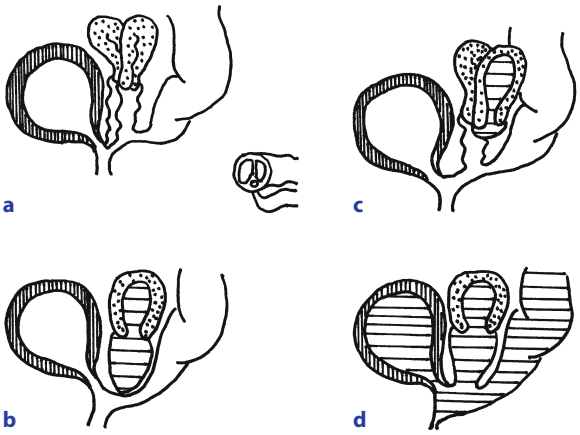


Fig. 7.22a–d. Schematic presentation of cloacal variants and genital anomalies. **a** Bifid vagina and uterus, the rectal fistula enters at the base of the septum dividing the vagina. **b** Distal vaginal stenosis or atresia leading to hydrometrocolpos. **c** Bifid uterus and vagina, unilateral obstruction and hydrometrocolpos. **d** Obstruction of the urogenital sinus resulting in distention of the vagina by a combination of genital secretion, meconium, and urine

rudimentary phallic structure with poorly formed labia (Hendren 1998). Additional pelvic anomalies include fusion defects of the müllerian ducts, with a duplication of the uterus in 55% of patients and obstruction of the genital tract in 25% (Jaramillo et al. 1990; Blask et al. 1991a,b; Tolete-Velcek et al. 1989). Major renal anomalies such as renal agenesis, multicystic dysplasia, or renal ectopia are frequently associated with cloacal malformation. Vesicoureteral reflux usually occurs bilaterally and is sometimes associated with bladder diverticula and ectopia of the ureter (Jaramillo et al. 1990; McLorie et al. 1987). The ureteral ostium might then be found in a lateral or inferior location in the bladder, the vagina, or the cloaca. In cases of functional bladder outlet obstruction, hydronephrosis is common (Rich et al. 1988; Hassink et al. 1996). Furthermore, cloacal malformation can be associated with anomalies of the pelvic osseous structures such as sacral agenesis or hypoplasia, dysraphism, and pubic diastasis. Pubic diastasis, if wider than 4 cm, is frequently associated with either duplication of the bladder or a common vesicovaginal or vesicocloacal chamber. In addition, lower spinal cord abnormalities such as lipomyelomeningocele, high cord, and most frequently (affecting one-third of all patients with cloacal malformation) tethered cord (Karrer et al. 1988; Metts et al. 1997; Barkovich 1999) are found.

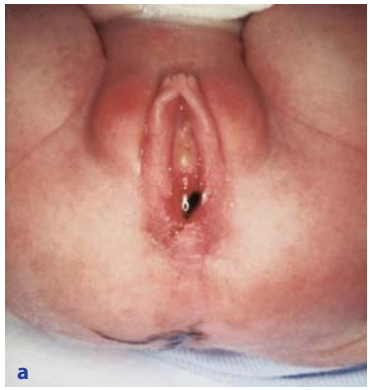
Except for the rare instances of incomplete cloaca, immediate colostomy is required to prevent fecal contamination of the urinary tract and renal damage, which is the most significant potential cause of morbidity and mortality in these patients. Obstruction of the cloaca may occur at any level and determines whether the proximal distended urinary and/or genital system is filled solely with genital secretions or contains urine and/or meconium as well (Fig. 7.22). In patients with hydronephrosis or severe obstruction of the vagina, early drainage is required. Immediate correction of severe vesicoureteral reflux or another life-threatening uropathy is essential. In cases of tethered cord, neurosurgical release can prevent neuronal deficits during growth, but usually fails to alleviate already established neurological deficits.

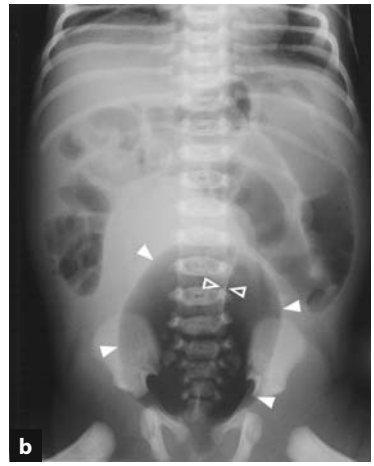
Definitive correction of the cloaca can now be performed between the ages of 6 and 24 months (Hendren 1998), and the prognosis of infants with cloacal malformation has improved significantly during recent years due to surgical repair techniques pioneered by Hendren.

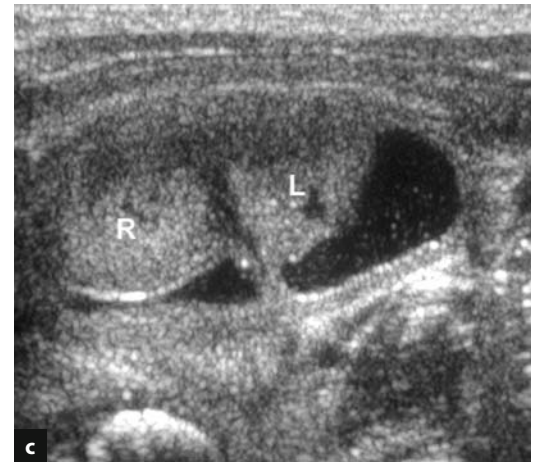
Conclusion

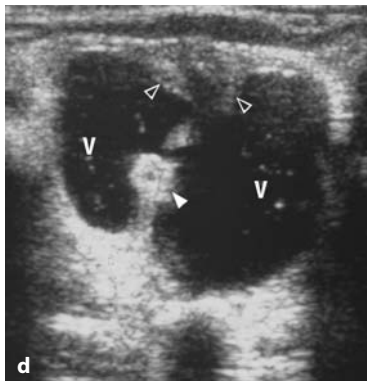
The diagnosis of cloacal malformation includes a wide spectrum of pelvic and perineal anomalies. Associated malformations of the inner genitalia and urinary tract need to be considered.

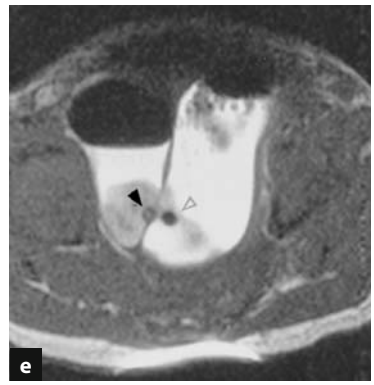
Fig. 7.23a–k. Cloacal malformation with uterus didelphys. **a** The perineal anatomy shows a female phenotype, but only a single perineal opening. Meconium is seen within the ostium of the cloaca. **b** Plain X-ray. The vagina is dilated (*closed arrowheads*) and contains air. A sagittal vaginal septum is visible (*open arrowheads*). **c** Transverse pelvic scan: right (*R*) and left (*L*) cervix uteri behind the empty bladder. **d** Transverse pelvic scan at lower level than **c** shows the right and left vagina (*V*), urethra (*open arrowheads*), and the rectocloacal fistula (*arrowhead*). **e** Axial MR view (T2-weighted) of the gadolinium-filled vagina shows the sagittal vaginal septum with the rectocloacal fistula (*closed arrowhead*) and the dilated vagina halves with air-fluid levels. The *open arrowhead* marks the

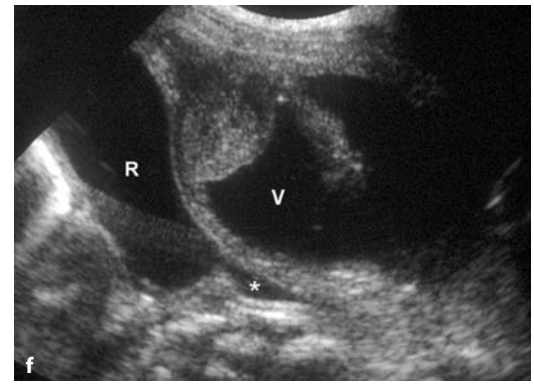


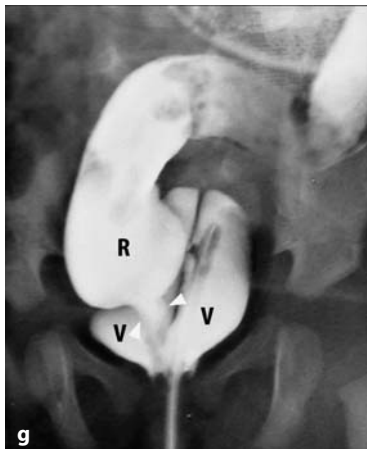


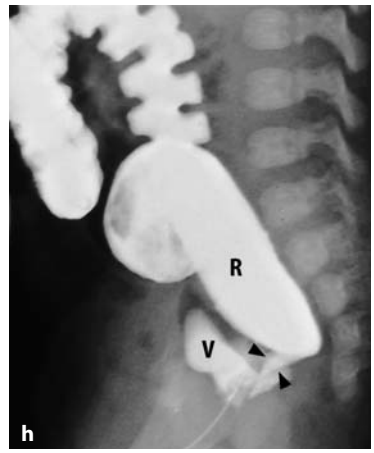


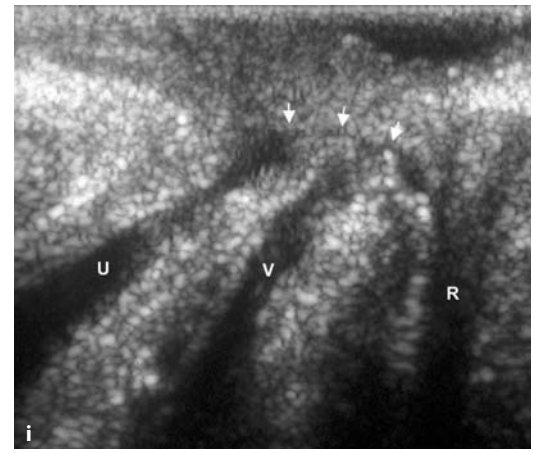




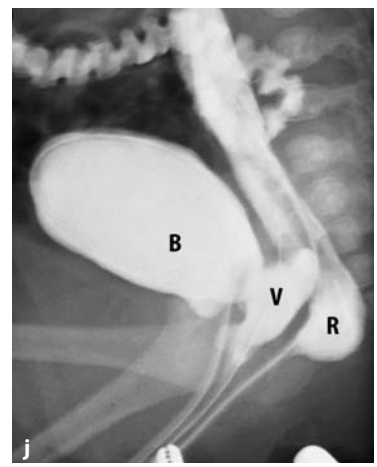


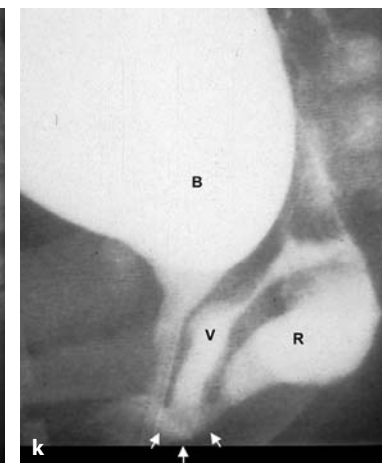






catheter. **f** Longitudinal pelvic scan shows the cloacal fistula (*asterisk*), rectum (*R*), and vagina (*V*). **g**,**h** Frontal and lateral view after contrast filling of the colon via colostomy demonstrates the rectum (*R*), the right and left vagina (*V*), and the rectocloacal fistula (*arrowheads*). **i** Transperineal sagittal scan: urethra (*U*), vagina (*V*), and rectum (*R*) converge to a short common cloacal channel (*arrows*). **j** Lateral view after contrast filling: bladder (*B*), vagina (*V*), and rectum (*R*). Three separate catheters are inserted through the single perineal opening. **k** Lateral view during voiding after removal of the catheters in rectum and vagina. The short common cloacal channel is clearly demonstrated (*arrows*). Bladder (*B*), vagina (*V*), rectum (*R*)





7.5.3.1 Diagnostic Imaging of Cloacal Malformation

Prenatal ultrasound often fails to provide an early diagnosis, and the large, sometimes septated, fluid-filled pelviabdominal mass is often mistaken for the urinary bladder. After delivery the diagnosis of cloacal malformation is made when, in addition to an absent anus, only one perineal orifice is found between the labia (Fig. 7.23). These patients need urgent referral to the pediatric radiology department for early definition of the abnormal anatomy and detection of associated malformations or potential life-threatening complications.

Ultrasound is the most efficient first-step imaging technique in the diagnostic work-up of these patients. Early after birth, no or only a small amount of intestinal gas will be present and a clearer documentation of the intrapelvic structures can be obtained (Fig. 7.23). A pelvic mass, which is almost always a distended vagina and/or uterus, can readily be visualized (Blask et al. 1991a). A fluid-debris level is frequently seen and the level of obstruction can be determined. If there is obstruction of the common outlet, retrograde flow via the fallopian tubes may result in accumulation of intra-abdominal fluid. Depending on the level of obstruction, this fluid may consist of genital secretion only (obstruction lies above the communication between the bladder, rectum, and vagina) or contains urine and/or meconium as well. Vaginal and bladder duplication as well as malformations of the uterus can be visualized. In cases of duplicated genital structures, care should be taken to document any obstruction (Tolete-Velcek et al. 1989; Blask et al. 1991a). The distance between the blind end of the rectum and the perineum can accurately be measured by transperineal ultrasound (Teele and Share 1997). The sonographic evaluation of the newborn is completed by analysis of the kidney and the spinal cord. The result of the sonographic examination of the upper urinary tract is used to choose further diagnostic tests, such as scintigraphy and intravenous urography. If not put in the hands of an investigator highly experienced with MR imaging in young infants, we still regard intravenous urography as superior to MR imaging in delineating all relevant features of urinary tract in cloacal malformation.

In every patient with cloacal malformation, the spinal cord needs to be evaluated, since anomalies of the lower spinal cord occur with an incidence of up to 43%. The spinal cord can either be examined by means of spinal ultrasound during the neonatal period or, if necessary, using MR imaging later in life (Barkovich 1999).

Sonographic features of spinal anomalies in patients with cloacal malformations are either a high-lying plump conus or a tethered cord with a thickened filum terminale (greater than 2 mm at L5-S1), a low-lying conus medullaris (the tip of the conus lies below the level of L2), a posterior position, and a restricted motion of the conus and filum terminale within the thecal sac. In some cases of tethered cord, no distinct filum can be seen, but the spinal cord is markedly elongated, extending downward to the lower end of the dural sac (Fig. 7.24). This feature is particularly common in caudal regression syndrome, frequently associated with anal atresia and cloacal malformation (Barkovich 1999).

After having obtained a good sonographic overview of the pelvic anatomy, radiological examination should then be continued with plain radiographs performed a couple of hours after birth to provide evidence of any distal bowel obstruction due to the accumulation of air (Fig. 7.23). Gas seen in the bladder indicates urinary-intestinal communication. A pelvic mass is usually a distended vagina and/or uterus, secondary to obstruction. If this mass contains gas it is a sign of a rectovaginal communication. Linear calcifications in the abdomen along the peritoneal surface are signs of calcifying peritonitis, which is not necessarily a result of congenital intestinal perforation, but can occur whenever either meconium (Jaramillo et al. 1990) or genital secretion (Nidecker and Humphry 1978; Ceballos and Hicks 1979) spills into the peritoneal cavity via the fallopian tubes. Granular abdominal calcifications suggest calcified intraluminal meconium (enteroliths) due to mixing of urine and meconium that are commonly associated with vaginal atresia or stenosis and rectovesical or rectourethral communication.

The next step in the imaging process is fluoroscopic studies using water-soluble contrast material to visualize the often unpredictable and erratic courses of the communication between the multiple structures and to provide functional information about reflux and competence of the urinary sphincter (Fig. 7.23). Contrast material is injected into the cloaca using an 8-F feeding tube if the perineal opening is small. A wider opening may need partial sealing using the balloon of a Foley catheter or a nipple (the Poznanski technique). Accessory peri-

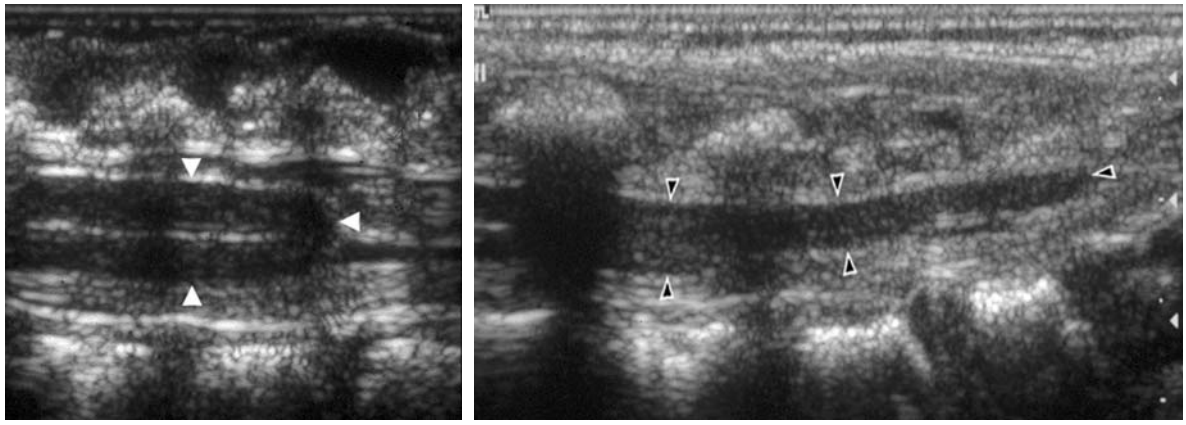


Fig. 7.24a,b. Cloacal malformation with a tethered cord and a high-lying plump conus. **a** Longitudinal scan shows that the cord (*open arrowheads*) extends into the sacral canal. **b** Longitudinal scan shows a high-lying stubby conus (*arrowheads*)

neal openings should be sought. A second rudimentary urethra (phallic urethra) is expected in cases where an additional small opening is found at the base or the tip of the clitoris (Jaramillo et al. 1990). Imaging during injection should begin in the lateral projection to display the various communications. Frontal projections are useful to delineate vaginal or bladder duplications. A competent urethral sphincter can be expected when the bladder fails to opacify, and vaginal obstruction or atresia is documented if contrast material fails to visualize the vagina. It might sometimes be difficult to distinguish between the bladder and the vagina. Reflux into a ureter or a urachal remnant helps to identify the bladder; a cervical impression or a septum identifies the vagina. However, in our experience this cervical impression is often difficult to observe.

Following the injection into the cloaca, an attempt to catheterize the bladder should be made to perform a voiding cystourethrogram, the only way to rule out vesicoureteral reflux. In some cases catheterization of the bladder may be difficult and needs to be supported by the use of a Coudé catheter, cystoscopy, or suprapubic puncture.

The rectum frequently fails to opacify after the injection of contrast material into the cloaca. In patients who have already had a colostomy, contrast material can be directly injected into the distal limb of the colostomy prior to retrograde cloacal injection. This technique regularly demonstrates the level of rectal occlusion and the presence of communication between other pelvic structures, making further cloacal injections unnecessary (Fig. 7.23). Most commonly, a balloon catheter is used to inject contrast material under moderate pressure to demonstrate the narrow communication between the organ systems.

Some authors recommend using MR imaging to delineate the anatomy of the inner genitalia prior to definitive surgical repair of the cloacal malformation (Metts et al. 1997; Tolete-Velcek et al. 1989). We, however, have never obtained much additional information from MR imaging and do not believe that MR imaging, which requires sedation of the patients, should be performed routinely during the work-up of cloacal malformation.

Conclusion

To assess pelvic structures in cloacal malformation, ultrasound should be performed as soon as possible after birth since no or only a small amount of intestinal gas will be present. Fluoroscopic studies to demonstrate the complex anatomy as well as to evaluate the urinary tract and the inner genitalia for diagnostic purposes are mandatory.

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Urinary Problems Associated with Imperforate Anus

8

Michael E. Höllwarth and Erich Sorantin

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8.1 Introduction

The term "imperforate anus" includes all kinds of anorectal malformations from covering of the anus by a thin skin membrane to high anorectal atresia – with or without a fistula, into the urethra or bladder – and to cloacal anomalies in females. It is well known that a high proportion of patients with imperforate anus have this maldevelopment in association with anomalies of one or several other organ systems. Among those, urinary tract anomalies with or without infections, as well as functional disorders of the urinary system, are common and may cause serious complications. Thus, the overall morbidity and mortality of patients with anorectal malformations are considerably influenced by the associated urinary tract anomalies. To facilitate the understanding of the problem, we briefly describe the different types of imperforate anus and the incidence of associated anomalies before we focus on the related urinary tract problems.

M. E. Höllwarth, MD
Professor and Chairman, Department of Paediatric Surgery, University Hospital Graz, Auenbruggerplatz 34, 8036 Graz, Austria
E. Sorantin, MD
Professor, Department of Radiology, Division of Paediatric Radiology, University Hospital Graz, Auenbruggerplatz 34, 8036 Graz, Austria

8.2 Anorectal Malformations

In earlier years anorectal malformations were classified into two subtypes: a high and low form, depending on whether the distal rectal pouch ended above or below the levator muscle level. On the occasion of the international Wingspread workshop meeting in 1984, the different types of imperforate anus were classified into three major groups and into the male and female patterns of the malformation (Stephens and Smith 1986). Briefly, a high-intermediate-low classification was agreed upon, and minor and rare subtypes were omitted. "High" anomalies are characterized by anorectal agenesis or rectal atresia with or without a rectovesical or rectoprostatic fistula in males or a rectovaginal fistula in females. The blind rectal pouch ends definitely above a hypotrophic puborectalis muscle sling. In "intermediate" malformations, the rectal pouch enters that sling; there may be a rectobulbar fistula in males and a rectovestibular or rectovaginal fistula in females. In the "low" forms the rectum passes through a well-developed puborectalis muscle and may end in an anocutaneous fistula in males and an anovestibular or anocu-

taneous fistula in females. The consensus conference placed the female cloaca in a separate group because it may be high, intermediate, or low depending on the length of the common channel. With regard to anal function and continence, it is evident that the high forms of imperforate anus have clearly less satisfying results than the low forms. Beyond that, the high and intermediate forms have a higher incidence of associated malformations and urinary tract functional disorders. In 2005 an international group of experts elaborated the so called "Krickenberg" classification which is not based on anatomical or embryological features but on the frequency of occurence into "major clinical groups" and "rare/reginal variants". Furthermore, an additional grouping of the surgical procedures has been elaborated, with the intention to make them comparable with each other, and uniform methods of assessment of outcome has been aggreed by the participants (Murphy et al. 2006).

8.2.1 Embryology of Imperforate Anus

In the 4-week-old embryo, the hindgut expands to form the internal cloaca, into which issue the large intestine, the allantois, and the Wolffian or mesonephric ducts. The internal cloaca is separated from the external cloaca by the cloacal membrane. The partitioning of the internal cloaca by a craniocaudally growing septum begins at the 4-mm stage and is completed at the 16-mm stage, when the septum reaches the cloacal membrane. Once the septum is completed, the cloaca is divided into a ventral urogenital sinus and the dorsal rectum. The Wolffian ducts become organized into the vasa deferentia and the vesicae seminales in the male, while in the female they are the leading structures for the proceeding of the Müllerian ducts into the vestibule. The external cloaca is a depression of tissue formed by the bilateral genital folds and the genital tubercle on the ventral aspect. When the septum reaches the cloacal membrane, the latter atrophies and both systems enter the common external cloaca. The process of partitioning now extends caudally by the urorectal septum. The high and intermediate groups of anorectal malformation can be seen as the result of a disturbed development of the partitioning of the internal cloaca with the gut ending in a fistula to the verumontanum or higher in males, and into the vagina or fossa navicularis of the vestibule in females. The low forms refer to developmental errors affecting the partitioning of the external cloaca, resulting in a fistula to the perineum or to the female vestibulum or a completely or partially persisting anal membrane (Stephens and Smith 1971).

Duhamel (1961) reported that the most frequent malformations associated with imperforate anus are just those that one finds constantly in the

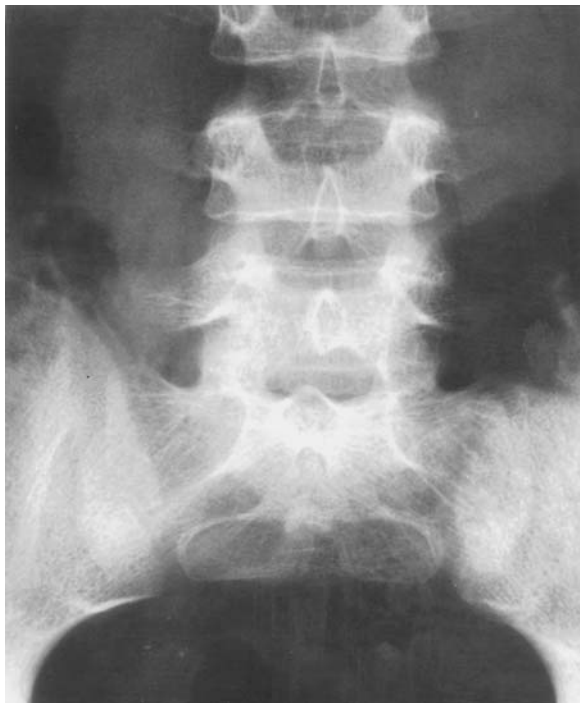

Fig. 8.1. Sacral agenesis–only S1 and parts of S2 are present – indicating a high probability of an associated urologic problem

siren anomaly, and he concluded that the whole pattern of anorectal malformations belongs to the syndrome of caudal regression. This hypothesis is in agreement with the work of Berdon et al. (1966) and Elliot et al. (1970), who explained the common association of lumbosacral vertebral anomalies and hindgut malformations by a disturbed development of the notochordal organizer at a very early stage of embryogenesis (Fig. 8.1).

8.2.2 Associated Malformations

As mentioned above, there is agreement in the literature that anorectal malformations are highly

associated with other anomalies of viscera or the skeletal system. The overall reported incidence varies from 20% to 70%, a range that depends largely on a careful and systematic search for additional anomalies (Stephens and Smith 1971). In a series of 75 patients, we found an overall incidence of 72% further anomalies, reaching nearly 100% in the subgroup of deceased patients (Höllwarth and Menardi 1983) (Table 8.1). These findings confirmed the conclusion from a necropsy study of babies dying with anorectal anomalies (Moore and Lawrence 1952) that there is a nearly 100% association with other malformations.

Very frequently more than one organ system is involved. This is also reflected by the so-called VATER or VACTERL association that combines vertebral anomalies, anorectal atresia, cardiac failure, tracheoesophageal fistula, esophageal atresia, renal dysplasia, and limb malformation.

Stephens and Smith (1971) and others have demonstrated that the incidence of additional anomalies is twice as high in the high and intermediate group of anorectal malformations (85%) as in the low group (46%). These findings have been confirmed by the analysis of our 75 patients with anorectal malformations, which has shown an incidence of 85% in the high and intermediate forms versus 61% in the low forms (Höllwarth and Menardi 1983) (Table 8.2).

Although almost every known malformation has been reported in association with anorectal malformations, analysis of anatomical localization shows that organ systems within the lower part of the body, e.g., the urogenital tract, are significantly more affected than those in the upper part. Similarly, detailed studies of the associated skeletal malformations of our patients showed that vertebral

Table 8.1. Associated malformations in 75 patients with anorectal malformations

Anatomical system	Total (n=75) (%)	Survivors (n=59) (%)	Deceased (n=16) (%)
Urinary tract	41.3	35.5	62.5
Genitalia	12.0	10.1	18.7
Skeletal system	46.6	37.2	37.5
Cardiac system	18.6	11.8	37.5
Intestinal tract	18.6	8.4	62.5
Cerebral	13.3	8.4	25.0
Others	22.6	20.3	31.2
Total	**72.0**	**65.5**	**100**

Table 8.2. Associated malformations in relation to the atresia level

Atresia form	Associated malformations						
	Total	Urogenital	Skeletal	Intestinal	Cardiac	Cerebral	Others
High and intermediate (n=34) (%)	85.0	76.4	52.9	29.4	23.5	11.7	32.3
Low (n=41) (%)	61.0	34.0	41.4	9.7	14.6	24.6	17.0

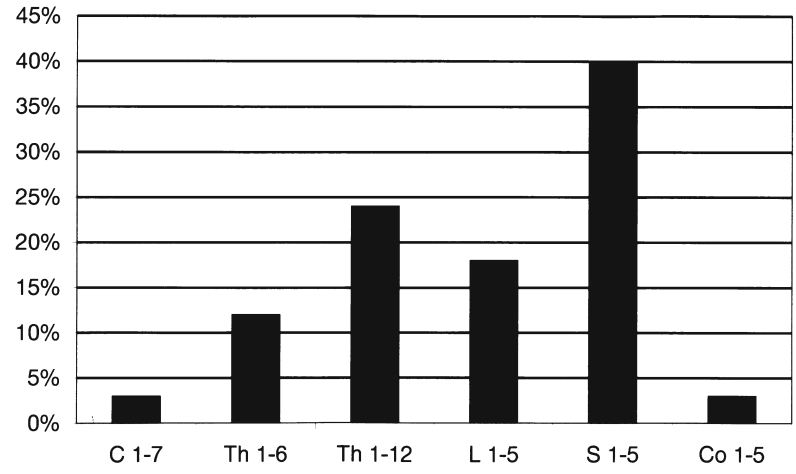

Fig. 8.2. Distribution of associated vertebral anomalies in patients with imperforate anus (n=33)

anomalies are significantly more common in the lumbar and sacrococcygeal spine in patients with imperforate anus (Fig. 8.2), confirming the findings of an earlier study carried out by Pellerin and Bertin (1967).

As mentioned above, partial or complete sacral atresia can be seen as a part of the caudal regression syndrome and may strongly imply additional neurogenic disorders of the bladder. For the radiologist it is important to analyze lumbosacral plain radiographs of patients with imperforate anus carefully, since the presence of lumbosacral anomalies or rachidian-type malformations give rise to strong suspicion of additional urogenital malformations and dysfunctions.

Conclusion

Anorectal anomalies are classified into three types of malformations: high, intermediate, and low. Associated anomalies occur twice as often in the high and intermediate groups as in the low group.

8.3 Urologic Problems

Structural anomalies of the urinary tract, as well as functional disorders and – in a minority of patients – complications after surgical correction of the imperforate anus contribute to a significant degree to the final outcome of those patients (McLorie et al. 1987; Wilcox and Warne 2006). Furthermore, the overall morbidity may be influenced by urinary tract infections, which occur either as a consequence of the rectourinary fistula in males or on the basis of anatomic or neurogenic disorders. A high or intermediate form of imperforate anus and the association of vertebral anomalies have already been emphasized as an important hint that careful radiological/urologic evaluation is required in order to establish the proper plan of management. However, even in patients with low forms of atresia and no additional vertebral malformations, the incidence of associated urologic anomalies, including reflux, is significantly higher when compared to the normal population (Yeung and Kiely 1991). Therefore, it is advisable to perform a careful evaluation of the urinary system in all patients with imperforate anus.

8.3.1 Incidence

Several studies with large numbers of patients have been performed in the past to assess the incidence and type of associated urogenital tract anomalies. The numbers differ from author to author and over the years, depending on how carefully a search has been performed. All authors agree that supralevator anorectal lesions have not only a higher incidence of urologic malformations, but also the more serious forms, especially in males. Out of 200 consecutive patients with imperforate anus Wiener and Kiesewetter (1973) found a 64% rate of urologic anomalies among the high forms (including the intermediate forms) and 18% in the low forms. According to Hoekstra et al. (1983), 71% of the supralevator atresias are associated with urogenital malformations, but also the infralevator malformations have a remarkably high association rate of 34%. McLorie et al. (1987) encountered nonfistular genitourinary abnormalities in 60% of the high and in 20% of the low lesions. All these authors found no gender differences with regard to the incidence of associated urogenital malformations, while Wiener and Kiesewetter (1973) as well as Ralph et al. (1992) described a significantly higher incidence in males. Eighty-four percent of the anomalies in the former authors' series were major, with a potential for serious problems; 18% were incompatible with life.

8.3.2 Structural Anomalies

Fistulas to the urinary tract in patients with imperforate anus can be seen as a part of the malformation itself. Of the male patients with a high or intermediate form of anorectal atresia, 80% have a rectourethral fistula and 8% a rectovesical fistula (Stephens and Smith 1971). Additionally, a number of other malformations of the urologic tract can be found in these patients (Table 8.3). In the upper urinary tract, the most common anomalies are renal dysplasia or renal agenesis, hydronephrosis, duplications, and renal ectopia. Furthermore, 47% of the supralevator group and 35% of the low group showed a vesicoureteral reflux, which might be caused in one-third of the cases by a malformation of the ureterovesical junction, but more commonly by a functional disorder due to a neurogenic bladder (Fig. 8.3) (Ralph et al. 1992). Associated malformations of the

Table 8.3. Incidence of urogenital associated malformations collected from the literature

Malformation	Wiener and Kiesewetter 1973 (*n*=200)	Stephens and Smith 1986 (*n*=246)	Hoekstra et al. 1983 (*n*=150)	Pellerin and Bertin 1967 (*n*=212)
Agenesis				
Both kidneys	5	1	4	
One kidney	15	3	9	8
Hypo-/dysplastic kidney	10	9	7	10
Horseshoe kidney	0	4	8	3
Ectopic kidney	0	0	6	5
Ureteric malformation (including hydronephrosis)	10	12	9	19
Vesicoureteral reflux	11	19	34	0
Bladder malformation	2	3	3	1
Exstrophy/cloaca	10	12	1	1
Urethral malformation (including hypospadias)	15	23	20	11
Others	8	6	6	4

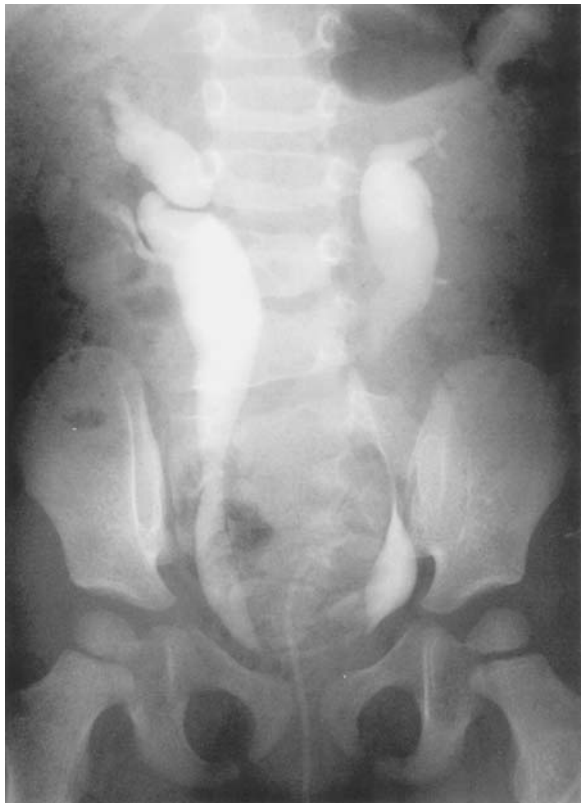

Fig. 8.3. IVU. Bilateral duplicated dysplastic kidney systems with megaureters and ureter dysmotility. Note dysplastic sacrum

lower urinary tract are hypospadias, epispadias and exstrophy, urethral diverticula, valves, strictures, or duplications. While some of these anomalies do not require immediate treatment, others require surgical repair in the newborn period, e.g., exstrophy, or at an appropriate time later on, e.g., obstructions or reflux. Obviously, agenesis of both kidneys is incompatible with life, but just as important are dysplastic or hypoplastic kidneys on both sides. Hoekstra et al. (1983) found that 75% of cases of early death were related to urogenital tract anomalies. The overall incidence of death from renal failure out of a series of 484 infants with imperforate anus was 6.4% with high and intermediate lesions and 1.1% with low lesions, and in each the incidence was higher in male infants (McLorie et al. 1987).

8.3.3 Functional Anomalies

Holschneider et al. (1982) described a urinary incontinence rate of 19% in patients 11 years after the correction of an anorectal atresia, which has been explained by the position of the rectourethral fistula close to the external sphincter region and the surgical trauma of the abdominoperineal pull-through procedure, as well as by additional malformations of the

spine. The latter argument is supported by the fact that two-thirds of the urologic anomalies in patients with imperforate anus are associated with spinal deformities, mainly with sacral anomalies. Among them, occult spinal dysraphism including lipomeningocele, ventral meningocele (Currarino syndrome), and tethered cord are associated with lower urinary tract dysfunction. Boemers et al. (1996a) described a normal urinary tract function in 98% of the children with a normal sacrum, sacral dysplasia only, or sacral agenesis affecting only smaller parts of the segments S4 and S5. Severe dysfunction was observed in all but one patient with a more extended sacral agenesis, indicating that this subgroup of patients needs careful urologic assessment. In contrast, Parrott (1985) found a neurogenic bladder in 7–18% of the cases of imperforate anus, but not all of them had abnormalities of the lumbosacral spine, indicating that excessive dissection and rectal mobilization may cause denervation. Similarly, Greenfield and Fera (1991) and Kakizaki et al. (1994) point to the fact that a significant association of voiding dysfunctions in patients with anorectal malformations can be observed even in the absence of vertebral anomalies. It can be concluded that these children should not be excluded from a urological evaluation including urodynamic studies, video-urodynamics (VUD) if available, or modified VCU (see Chap. 13).

To answer the question of whether the surgical trauma imposes a major insult to the pelvic nerves, pre- and postoperative investigations of bladder function have been performed. Urodynamic studies before any pull-through surgery showed a sphincter-detrusor dyssynergia in 4 out of 14 patients with bladder trabeculation and vesicoureteral reflux or hydronephrosis (Greenfield and Fera 1991). Kakizaki et al. (1994) found a voiding dysfunction in 9 (38%) out of 24 children before anorectoplasty, and partial sacral agenesis was present in only 4 of those 9 babies. Out of 27 patients studied pre- and postoperatively, the urodynamic studies showed minor changes in only four patients when compared with the preoperative results (Boemers et al. 1995). Another three boys had atonic bladder function with loss of the detrusor contractility consistent with autonomic denervation. Two of them had a standard posterior sagittal anorectoplasty combined with a transabdominal procedure with dissection of the distal rectum.

In comparison to earlier studies one has to consider that the surgical strategies have changed considerably over the years. Today the preferred procedure consists of a close rectal dissection by the posterior sagittal anorectoplasty, according to Pena (1988). Boemers et al. (1995) conclude from their study that a posterior sagittal anorectoplasty is followed only in a few patients by an additional bladder dysfunction when special attention is given to the surgical details and a significant rectovesical dissection can be avoided. Furthermore, a hyperreflexive bladder cannot be caused by an iatrogenic injury, because a surgical trauma results mostly in a lower motor lesion with an atonic sphincter followed by incontinence, as three patients in the Boemers et al. (1995) study have shown. A preexisting deficient nerve supply in cases of sacral agenesis might increase the vulnerability to iatrogenic nerve damage. In conclusion, the most common cause of a postoperative bladder dysfunction is not the surgical damage, but a hyperreflexic neuropathic bladder, which is present in up to 55% of the patients, namely in 61% of those with a high anomaly and 36% of those with low malformations (Ralph et al. 1992).

Thus, the high incidence of vesicoureteral reflux in patients with imperforate anus may partly be

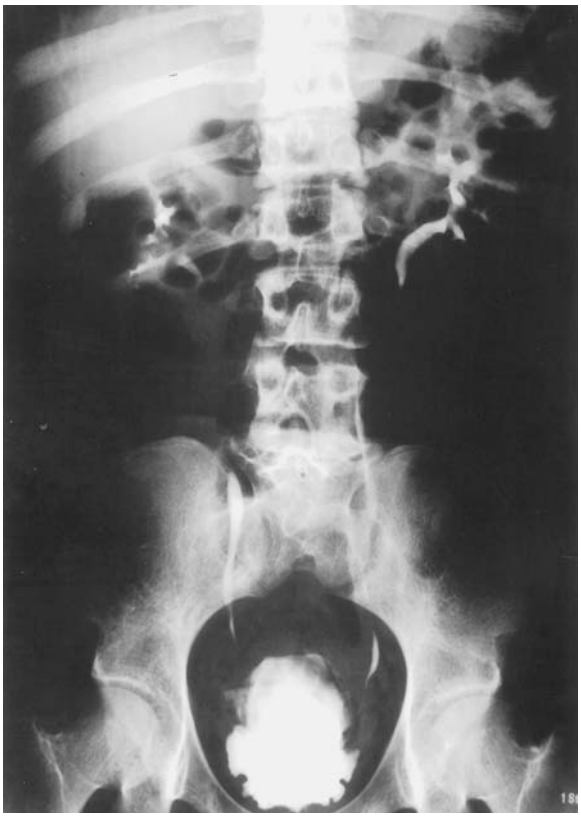

Fig. 8.4. IVU. Sacral agenesis in a patient with hyperreflexive neurogenic bladder and imperforate anus. Vesicoureteral reflux grade 2

caused by a malformation of the ureterovesical junction, but result more often by a neurogenic disorder. Boemers et al. (1996b) showed that 60% of the patients with a neurogenic dysfunction had reflux; additionally 32% had reflux nephropathy. All children with impaired renal function had a neurogenic bladder-sphincter dysfunction (Fig. 8.4).

Conclusion

Structural as well as functional anomalies are reported commonly in babies with anorectal malformations. Therefore, a careful evaluation of the urogenital tract is essential in these cases.

8.4 Imaging

Recently, Boemers et al. (1999) have published detailed guidelines for the diagnostic screening and initial management of babies with imperforate anus. These recommendations are based on the complexity of the malformation and malfunction pattern in patients with imperforate anus and their impact on morbidity and mortality, which calls for a pre- and postoperative evaluation of the vertebral spine and the urogenital tract.

The first issue is to evaluate whether there are skeletal malformations by performing, immediately after birth, an anterior, posterior, and lateral plain X-ray of the whole vertebral column, and the ribs. This makes it possible to count the number and the qualitative anomalies of the vertebral bodies within the different sections and the number and asymmetry of ribs. A careful screening of sacral anomalies is advisable since 75% of the patients with sacral agenesis will have lower urinary tract dysfunction or spinal cord tethering (Boemers et al. 1996a, Pang 1993). If the plain film of the spinal column is abnormal, a careful high-resolution spinal ultrasound study can detect associated intraspinal pathologies. Carson et al. (1984) confirmed in their study that children with coexisting anorectal and sacral anomalies have a high incidence of unsuspected and correctable spinal cord lesions. Therefore, if any associated vertebral malformation can be seen by sonography, an additional MRI can depict the anomaly more clearly. T1-weighted images with 4-mm slices or a continuous stack of 1-mm slices provide excellent images. Rivosecchi et al. (1995), studying 50 patients with anorectal malformations by means of the MRI, found 25 patients with spinal cord abnormalities such as fibrolipoma with or without tethered cord (n=19), syringomyelia (n=4), tethered cord (n=2), and meningocele (n=1). The MRI is, according to Tunell et al. (1987), the single most effective procedure for a preoperative evaluation of spinal cord anomalies and therefore currently the image procedure of choice in these patients.

With regard to the urologic tract, in the newborn period ultrasonography is highly accurate and has been shown to be of great advantage for these patients (Karrer et al. 1988). Except for the first 24 h, when urinary output is low and a dilatation of the collecting system can be missed, ultrasound is the primary screening method for detecting structural urinary tract anomalies. Recurrent opening of the bladder neck and the posterior urethra point to a neurogenic disorder. Any anomaly or dilatation of the upper urinary tract needs voiding cystourethrography for further evaluation. Whether or not an upper tract dilatation exists on ultrasound, Boemers et al. (1999) recommend this investigation in all male patients with no perineal opening. Yeung and Kiely (1991) point to the high incidence of vesicoureteral reflux even in babies with low anorectal malformations and recommend performing voiding cystourethrography in all these patients. Backflow through the fistula in the rectum or reflux in the ductuli can be detected in some male patients. In girls with a persistent cloaca, retrograde genitography with water-soluble contrast medium should be performed.

If voiding cystourethrography has to be performed, the modified technique should be used (see Chaps. 14 and 16); if available, the method of choice is video-urodynamics. In boys with a rectourethral fistula, abdominal pressure can be recorded either through an existing colostomy, or if no colostomy is needed, through a microtip catheter placed in the stomach. If video-urodynamics is not available an additional urodynamic study is recommended in patients with concomitant sacral agenesis during the first 3 months of life. Depending on the type of bladder dysfunction, follow-up urodynamic study has to be done after conservative – anticholinergic – therapy or surgical interventions.

Conclusion

The entire spectrum of imaging investigations and functional studies is necessary to detect urogenital anomalies in anorectal malformations.

8.5 Therapy

The general condition of the baby, the existence of other severe malformations – e.g., esophageal atresia or cardiac failure – the type of the anorectal malformation, and the severity of associated urinary tract malformation govern the timing and the order of the surgical interventions. Low atresia forms in the male can be immediately treated with a cut-back procedure, or in females with primary bouginage or modified translocation of the fistula. High forms may require primary colostomy with postponement of an abdominoperineal pull-through procedure in order to allow the treatment of associated anomalies. Intermediate forms, which can be treated by a simple posterior anorectoplasty, using a perineal approach, without laparotomy. In most cases this procedure may require no time delay.

The treatment of the anatomical urinary tract abnormalities is the same as it would be for similar abnormalities occurring in isolation. The treatment of functional disorders was neglected for many years. Since Boemers et al. (1996b) and other authors showed that a severe hyperreflexive bladder dysfunction may exist even before the operation, early clean intermittent catheterization, either alone or combined with parasympathetic medications or surgical measures, has been recommended for these babies from the beginning in order to avoid later deterioration of the upper urinary tract due to the voiding dysfunction. A paralytic bladder strongly suggests pelvic nerve injury secondary to a surgical pull-through procedure.

Urinary tract infection may be caused by a long rectourethral fistula remnant, as a consequence of urinary stasis with associated anomalies, due to neurogenic bladder dysfunction, and/or vesicoureteral reflux, respectively. Regular monitoring of urine specimens is necessary, with appropriate antibiotic therapy in the case of infection.

Conclusion

The treatment of functional or anatomical urinary tract abnormalities in patients with anorectal malformations does not differ from the treatment of those with isolated malformations.

8.6 Conclusion

Anorectal malformations have a high incidence of associated malformations. Among these, the functional or anatomical abnormalities of the urologic tract are of primary importance because of their impact on the overall morbidity and mortality of these patients. Although urologic malformations can be associated in all patients with imperforate anus, there is a significantly higher incidence in the high forms of atresia and/or when lumbosacral vertebral malformations exist. Careful radiological and urodynamic investigation, including lumbosacral plain radiographs, ultrasound of the bladder and kidneys, a videourodynamic study if available, or a urodynamic study complemented by a modified voiding cystourethrography should be performed before and/or after the pull-through procedure according to recently published guidelines (Bohmers et al. 1999). Additionally, an MRI may be necessary in selected cases to plan a neurosurgical procedure and its appropriate timing.

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Epispadias-Exstrophy Complex

9

Erich Sorantin

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E. Sorantin, MD
Professor, Department of Radiology, Division of Pediatric Radiology, Medical University Graz, Auenbruggerplatz 34, 8036 Graz, Austria

9.1 Introduction

The exstrophy-epispadias complex represents a spectrum of malformations ranging from epispadias to cloacal exstrophy (Wood 1990). The most common entities of this complex and their frequencies are listed in Table 9.1 (Duckett and Cladamone 1985).

Historically, bladder exstrophy was first mentioned in 2000 BC. The earliest description was given in 1597 by Scheuke and Grafenberg, a complete one about 150 years later by Mowat in 1747. The term "exstrophy" was coined by Chaussier in 1780 (Kelly 1998).

Today multistage surgical repair is favored over other treatment alternatives. Due to the complexity of the problem, management of the affected patients requires close interdisciplinary teamwork involving pediatric surgery, pediatric urology, pediatric orthopedics, and pediatric radiology. During all the different stages the pediatric radiologist is responsible for rational use of imaging modalities in order to facilitate treatment planning, to assess therapeutic success, and to detect and monitor complications.

Table 9.1. Types and frequencies of epispadias-exstrophy complex

Types	Frequency
Classical bladder exstrophy	60%
Epispadias (balanitic, penile, subsymphyseal, penopubic)	30%
Cloacal exstrophy, superior vesical fissure, duplicate exstrophy, pseudoexstrophy	10%

9.2 Incidence

Epispadias occurs in 1 in 117,000 of the population, with a 5:1 male predominance. The incidence of classical bladder exstrophy is reported to be between 1 in 10,000 and 1 in 50,000 births (Duffy 1996). There is a 3:1 male predominance. Variants of bladder exstrophy tend to occur more often in females than in males (Duckett and Cladamone 1985).

The risk of occurrence is 400–500 times higher if one parent suffers from bladder exstrophy (Ben-Chaim et al. 1996; Duffy 1996). There is evidence that a slightly increased risk for bladder exstrophy or epispadias exists in children whose mothers are less than 20 years old (Ben-Chaim et al. 1996). In addition, a possible concordance of intrauterine exposure to diazepam and occurrence of omphalocele-exstrophy-imperforate anus-spina bifida (OEIS) complex has been published (Lizscano-Gil et al. 1995). Cloacal exstrophy has an incidence of about 1:200,000 births. For this malformation no sex predominance is reported (Duckett and Cladamone 1985).

Conclusion

Bladder exstrophy is more common in boys. Variants of bladder exstrophy are more common in girls. There is no sex predominance in cloacal exstrophy.

9.3 Prenatal Diagnosis

Bladder exstrophy is diagnosed prenatally in only 13% of cases according to Ben-Chaim et al. (1996). In a retrospective study on 43 prenatal ultrasound scans, they identified five criteria that were related to bladder exstrophy (number in parentheses represents the estimated frequency of each symptom):

- Bladder never identified (71%)
- Lower abdominal bulge representing the exstrophied bladder (47%)
- Diminutive penis and anterior displaced scrotum (57% of males)
- Low set of the umbilicus (29%)
- Abnormal widening of iliac crests (18%)

The urinary bladder can be visualized on prenatal ultrasound scans after 14-weeks of gestation (Ben-Chaim et al. 1996). Therefore, in the absence of the urinary bladder on prenatal ultrasound scans or if any of the other above-mentioned symptoms are present, the diagnosis of bladder exstrophy should be raised.

Conclusion

Bladder exstrophy is an underdiagnosed condition on prenatal ultrasound scans. Absence of the urinary bladder is th e hallmark of bladder exstrophy on those scans.

9.4 Embryology

The defect has to be dated within the first 8 weeks of gestation (Duffy 1996). It is believed to stem from an abnormal mesodermal migration during the development of the lower abdominal wall as well as the urogenital and anorectal canals (Duffy 1996). This mesoderm will later transform to muscles of the abdominal wall and bladder, to the penis or clitoris, to the scrotum or labia as well as to the bones, joints, and ligaments of the anterior pelvic girdle. Muecke (1964) postulated that an overdevelopment of the cloacal membrane causes the abnormal mesodermal migration. After the rupture of the cloacal membrane to produce the urogenital and anal orifices, the entire urogenital tract is exposed, thus producing the exstrophic bladder and the associated epispadias (Sponseller et al. 1995). This theory is supported by the experimental findings in chicks, in which exstrophied bladders could be produced by replacing the cloacal membrane with a foreign body (Muecke 1964).

A recently published immunohistochemical study revealed that specimens of exstrophied bladders reveal fewer myelinated nerve fibers than normal individuals (Mathews et al. 1999). Normally, the innervation of the detrusor determines its ability to contract. Since the exstrophied bladder does not store any urine during intrauterine development, there is no need for contractions and innervation, which may explain the above-mentioned difference in innervation (Mathews et al. 1999). Up to now it is unclear whether this finding can predict contractility of the former exstrophied bladder.

Conclusion

The embryological defect producing the epispadias-exstrophy complex occurs about the 8th week of gestation. Immunohistochemical differenc es between exstrophied and normal bladders exist.

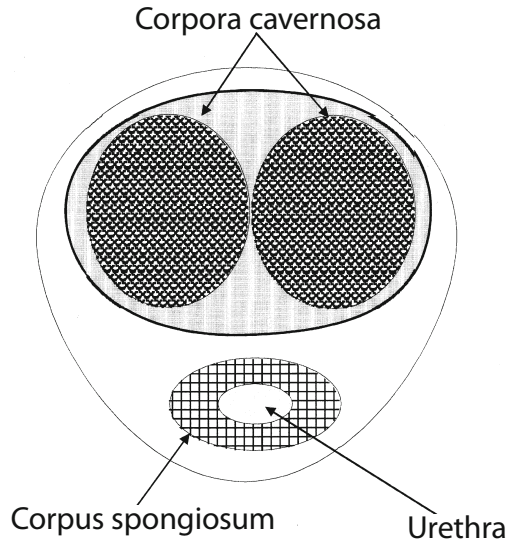

Fig. 9.1. Cross-sectional anatomy of a normal penis: the corpora cavernosa share a common fibrous wall (tunica albuginea corporis spongiosum)

9.5 Anatomy of the Epispadias–Exstrophy Complex

9.5.1 Epispadias

9.5.1.1 Male Epispadias

Normally, the urethra is located on the ventral side of the penis. Both corpora cavernosa are located on the dorsal side of the penis and share a common fibrous wall (Fig. 9.1). In male epispadiac patients, however, instead of the urethra there is a continuous groove extending from the internal urethral orifice to the glans penis, and the corpora cavernosa are separated (Fig. 9.2).

Three different types can be differentiated: balanitic, penile, and penopubic (or complete) epispadias. In balanitic and penile epispadias, continence is present and musculoskeletal deformities of bladder exstrophy are mild or absent. On the other hand, in penopubic or complete epispadias, the whole length of the penis is involved, and these patients are always incontinent to a certain degree. Usually the penis is short and stubby. In addition, this subtype reveals the musculoskeletal deformities of bladder exstrophy, but to a minor degree (Currarino et al. 1993).

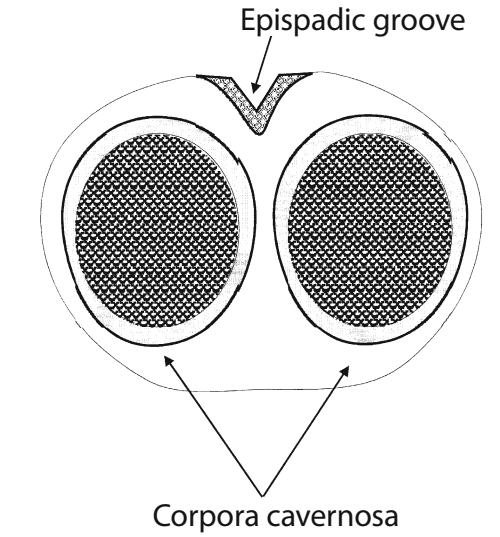

Fig. 9.2. Cross-sectional anatomy of an epispadiac penis: the corpora cavernosa are separated, and there is an urethral groove on the dorsal side of the penis

9.5.1.2 Female Epispadias

Most frequently the complete or subsymphyseal type can be observed (Currarino et al. 1993). In addition, a bifid clitoris exists, and the labia are abnormally separated (Currarino et al. 1993). These patients are always incontinent, and the musculoskeletal deformities of bladder exstrophy are

present (Currarino et al. 1993). Minor, continent forms, exhibiting an absence of the distal urethra or a short patulous urethra, eventually accompanied by a bifid clitoris, may occasionally be seen (Currarino et al. 1993).

In 90% of all patients with epispadias, vesicoureteral reflux (VUR) will be present. This is due to an abnormal trigone and laterally displaced ureterovesical junctions (Duckett and Cladamone 1985) (Fig. 9.3)

9.5.2 Classical Bladder Exstrophy

An excellent overview and a detailed anatomical description are given by Kelly (1998) and Wood (1990), respectively.

9.5.2.1 Urogenital Features

The anterior wall of the abdomen is widely open over the entire dorsal surface of the penis as well as the bladder neck and the anterior bladder wall (Wood 1990). The mucosa of the exstrophied bladder is irritable and becomes hyperemic and polypoid. On histologic examination the mucosa shows cystitis cystica, cystitis granularis, and polypoid changes (Crankscon and Ahmed 1997). If no surgical repair is undertaken, acute and chronic inflammatory changes will lead to squamous metaplasia, and malignancy may occur (Crankscon and Ahmed 1997). In addition, disorganization of the detrusor muscle bundles will occur in this situation, causing bladder dysfunction even after successful anatomical repair (Crankscon and Ahmed 1997). In affected male babies, the penis is short, and a posterior chordee causes it to curve upward to the area of the exstrophied bladder (Currarino et al. 1993). In normal individuals the corpora cavernosa fuse at the penile shaft and share a common fibrous wall with the urethra located at the anterior side of the penis. In contrast, in patients with the epispadias-exstrophy complex, the corpora cavernosa remain separated until the glans penis because of the split symphysis. The epispadiac groove lies between the separated corpora cavernosa at the dorsum of the penis (Kelly 1998) (Fig. 9.4). Unilateral or bilateral cryptorchidism may be present (Currarino et al. 1993).

In females there is a short epispadiac urethra, the clitoris is bifid, and may consist of two widely separated parts. The vaginal introitus is tilted upwards (Crankscon and Ahmed 1997).

In patients with bladder exstrophy, associated anomalies of the upper urinary tract are infrequent (Currarino et al. 1993). After surgical correction VUR will be present in almost all cases of bladder exstrophy (Ben-Chaim et al. 1996). Figure 9.5 depicts the features of bladder exstrophy in a newborn boy.

9.5.2.2 Musculoskeletal Features

The rectus abdominis muscle is deficient and widely separated. The umbilicus is low set and an omphalocele can frequently be observed (Currarino et al. 1993). Inguinal hernias are present in up to 20% of patients, boys being more affected than girls (Connolly et al. 1995). In the later course an incidence of inguinal hernias between 65% and 82% can be expected for males, with rates between 11% and 15% for females (Connolly et al. 1995; Husmann et al. 1990).

One of the hallmarks in bladder exstrophy is the split symphysis, where the width of the split increases with the size of the exstrophy (Currarino et al. 1993). Therefore, in bladder exstrophy the pelvic girdle appears rather C-shaped instead of forming a ring. In detail, the iliac bones are rotated about 12° externally (increasing the iliac wing angle) and the pubic bones about 18° (increasing the ischiopubic angle) (Sponseller et al. 1995). Compared to normal individuals, the pubic bones tend to be shortened by 30%, and the transverse diameter of the pelvis, measured at the level of the intertriradiate cartilage, is increased by 31% (Sponseller et al. 1995). Since the corporal bodies of the penis diverge laterally to the pubic rami, the osseous malformation contributes to the short penis appearance (Sponseller et al. 1995). Figure 9.6 exhibits a pelvic X-ray of a patient suffering from bladder exstrophy. Vertebral malformations can be found in up to 7% (Cadeddu et al. 1997) of cases.

9.5.3 Variants

9.5.3.1 Pseudoexstrophy of the Bladder

This malformation is a rare variant of classical bladder exstrophy. It is characterized by the pres-

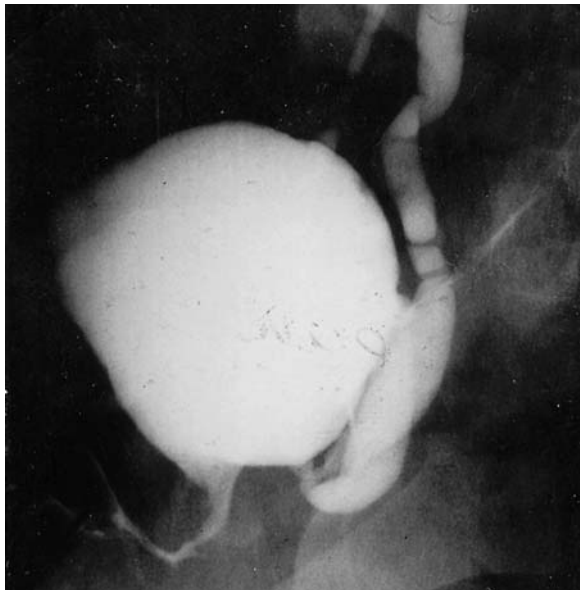

Fig. 9.3. Spot film of VCU in a patient with epispadias: bilateral VUR is present as well as a hook deformity of the ureterovesical junction. The urethra is short and irregular because of surgery

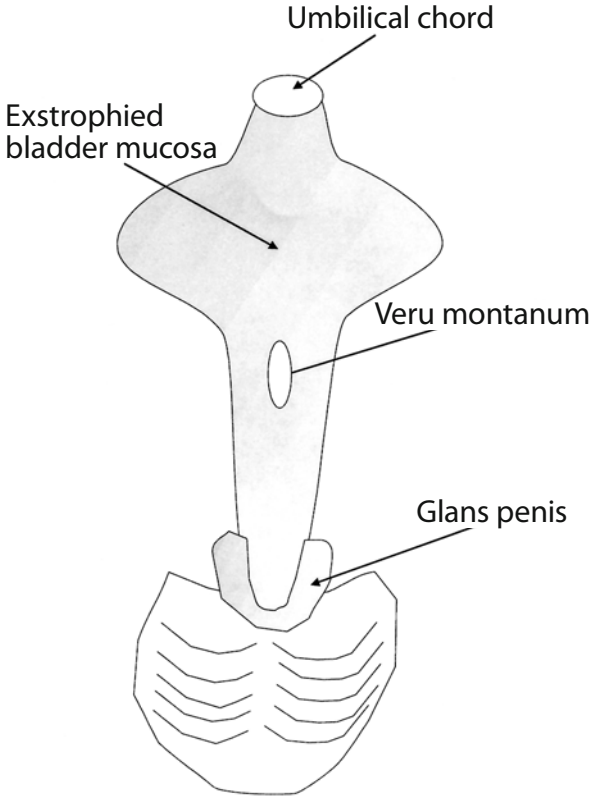

Fig. 9.4. Schematic urogenital findings in a male patient suffering from bladder exstrophy

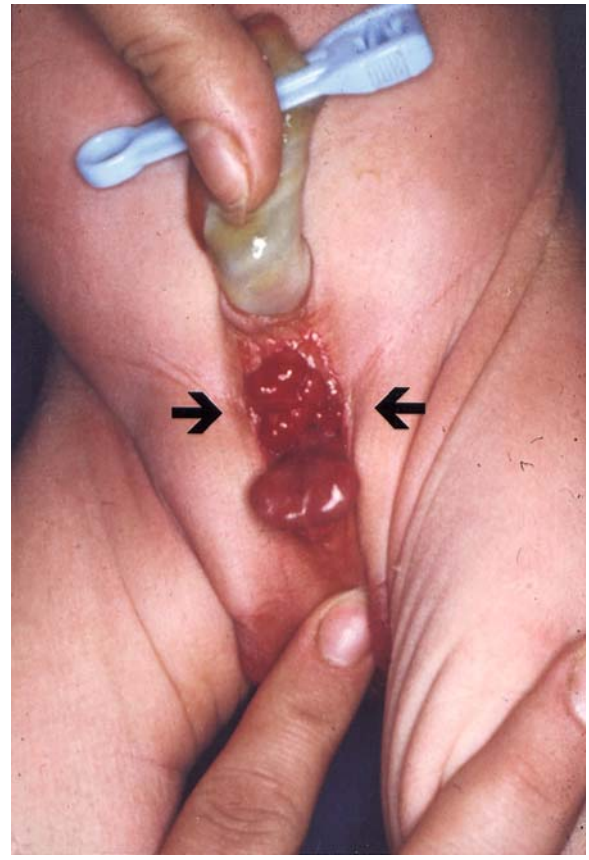

Fig. 9.5. Photograph of a child with classic exstrophy: the umbilicus is low set and the bladder is exstrophied (*solid arrows*). The penis is short, and the corpora cavernosa are separated by the epispadiac groove

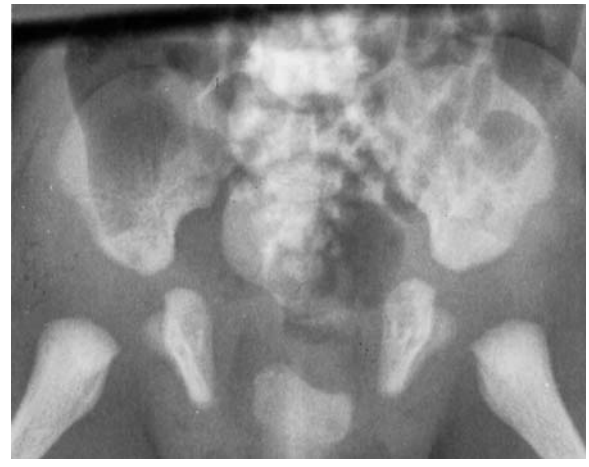

Fig. 9.6. Pelvic X-ray of a male baby with classic exstrophy: split symphysis is present. The pubic and iliac bones are rotated outwards with an increase in the inter-triradiate distance

ence of the musculoskeletal defects of classic bladder exstrophy without the urinary defects. There is a deficient abdominal wall, and the bladder has a subcutaneous position and is only covered by thin epithelial membrane. The umbilicus is low set and the pubic symphysis is widened. At operation the bladder and urethra appear intact (Swana et al. 1997; Ahmed and Abu Daia 1998).

9.5.3.2 Covered Exstrophy of the Bladder

Similar to pseudoexstrophy of the bladder, the same musculoskeletal defects exist, and the closed bladder is protruding through the deficient rectus muscles. In contrast to pseudoexstrophy, the anterior bladder wall is covered by a varying degree of subcutaneous tissue and skin (Borwankar et al. 1998; Sahoo et al. 1997). A female predominance and as well as a high incidence of genital anomalies (bifid clitoris, hypoplastic vagina, stenosed duplicated vagina) have been reported (Sahoo et al. 1997). Anorectal malformations are more common than in classical bladder exstrophy (Sahoo et al. 1997).

9.5.3.3 Superior Vesical Fissure

The musculoskeletal features of classic bladder exstrophy can be observed as well as a minimal bladder eventration below an abnormally low set umbilicus (Borwankar et al. 1998; Sahoo et al. 1997).

9.5.3.4 Inferior Vesical Fissure

To date only a few cases have been reported (Johnson et al. 1995). Bladder exstrophy is limited to the bladder neck, whereas the penis and urethra are normal. Split symphysis is present too.

9.5.3.5 Duplicate Exstrophy

Duplicate exstrophy is comprised of a normal bladder and an additional exstrophied bladder. Complete and incomplete entities have been reported (Perren and Frey 1998).

9.5.3.6 Bladder Exstrophy with Normal Umbilicus and Normal Infraumbilical Wall

Recently a case was reported revealing the above-mentioned features (Sripathi et al. 1997).

9.5.3.7 OEIS Complex

Bladder exstrophy can be part of the OEIS complex (omphalocele-exstrophy-imperforate anus-spinal defects). The OEIS complex is rare and affects only 1 in 200,000 to 1 in 400,000 pregnancies (Smith et al. 1992).

9.5.4 Cloacal Exstrophy (Vesicointestinal Fissure)

9.5.4.1 Urogenital and Intestinal Features

There are two halves of the exstrophied bladder, separated by an exstrophied ileocecal bowel area. On the rostral side of the bowel exstrophy the ileum prolapses. In addition there is imperforate anus, and the colon may be duplicated. Usually a duplicated appendix is found. In males a small, duplicated penis can be seen. In females the vagina is septated and uterine abnormalities are likely. A high proportion of these patients will also present a small to giant omphalocele (Duckett and Cladamone 1985).

9.5.4.2 Musculoskeletal Features

The same skeletal features as in classic bladder exstrophy can be observed. Myelomeningoceles are present in 50% of these patients. Spinal abnormalities are common.

Conclusion

All subtypes of the epispadias-exstrophy complex exhibit a split symphysis to a certain degree. Incontinent epispadias is more common than continent epispadias. In addition to classic bladder exstrophy, covered variants exist. Cloacal exstrophy represents the severe part of the spectrum, comprising urogenital, intestinal, and musculoskeletal malformations.

9.6 Surgical Repair

The overall goal of treatment in patients with the epispadias-exstrophy complex is the well, dry, fertile, and happy (both cosmetically and functionally) adult (Kelly 1998).

Today several treatment options exist including (Kelly 1998):

- Anatomic reconstruction (primary neonatal or staged bladder and urethral reconstruction) with or without pelvic osteotomies
- Permanent urinary diversion
- Bladder augmentations
- Insertion of artificial material and urinary sphincters

The variety of treatment options confirms the how difficult it is to achieve the above-mentioned goals. Detailed descriptions can be found elsewhere in the literature.

Today staged surgical repair is favored, consisting of the steps described in Sections 9.6.1 to 9.6.3 (Wood 1990; Kelly 1998; Ben-Chaim et al. 1996; Ben-Chaim and Gearhart 1996; Canning 1996).

Urinary diversion using bowel segments is no longer the first treatment choice due to its inherent disadvantages such as the need for intermittent catheterization through a reconstructed urethra, mucus plugs, bladder infection, electrolyte disturbances, stones, disruption of the anastomosis, long-term potential for renal deterioration, and bladder or bowel cancer (Kelly 1998; Canning 1996). Bladder augmentation can be regarded as an alternative approach for patients where the staged repair has failed (Kelly 1998). In these patients bladder augmentation can improve the quality of life significantly.

9.6.1 Initial Bladder Closure

Due to improvements in anesthesia and postoperative care, surgical correction of the exstrophied bladder and osteotomies can be done safely within the neonatal period. Since newborns are under the influence of the maternal hormone of Relaxin, bladder closure within 72 h of life is performed. At this age, there is a good chance of achieving pelvic closure without osteotomies in some patients, depending on the size of the symphyseal split (Kelly 1998; Ben-Chaim and Gearhart 1996). In addition, the swelling of the exstrophied bladder mucosa is less severe within the time frame of 72 h. If the male urethral plate is too short it can be elongated by paraexstrophy flaps using the paraexstrophy tissue as described by Duckett and Cladamone (1985; see also Kelly 1998; Ben-Chaim et al. 1996). Follow-ing the principles of plastic surgery is mandatory to maintain good blood supply to the flaps. The urethra is closed proximally in order to stimulate bladder growth, and ureteral stents are placed to prevent obstruction and hypertension (Ben-Chaim et al. 1996). Coexisting omphaloceles and inguinal hernias should also be repaired (Kelly 1998; Connolly et al. 1995; Husmann et al. 1990).

Factors promoting surgical success have been identified (Ben-Chaim et al. 1996; Lottmann et al. 1997):

- Early bladder closure
- Use of osteotomies
- Avoidance of urethral tubes and abdominal distension
- Postoperative antibiotics
- Pelvic immobilization
- Ureteral catheters
- Adequate use of postoperative analgetics

Postoperative complications include ischemia of paraexstrophy flaps, thus leading to urethral strictures (Kelly 1998; Ben-Chaim et al. 1996; Ben-Chaim and Gearhart 1996). Suprapubic leakage is another problem, but usually there is spontaneous closure within several months. VUR is present in almost all cases postoperatively (Currarino et al. 1993). Two children were reported who developed significant hypertension postoperatively after primary bladder closure and pelvic osteotomies followed by immobilization using skin traction (Husmann et al. 1993). In both children hypertension subsided spontaneously after removal of the immobilization.

9.6.2 Epispadias Repair

Epispadias repair is performed at the age of 2–3 years. The goals of the operation are (Ben-Chaim et al. 1996):

- Reconstruction of the urethra and glans penis

- Release of the urethra and penis from the tension caused by the bladder
- Closure
- Correction of the posterior chordee
- Adequate skin coverage

Testosterone can be given 2 weeks preoperatively in order to stimulate penile skin growth, thus making the surgical repair easier.

Currently, the Cantwell-Ranswell urethroplasty is the method of choice (Kelly 1998; Ben-Chaim et al. 1996; Canning 1996; Husmann et al. 1993). Briefly, the urethra is tubularized over a catheter. The corporal bodies are freed completely from the glans and the proximal urethra, then rotated inward and sutured together. The procedure is finished by reconstruction of the glans and moving the distal end of the urethra to the ventral side of the penis. Penile ischemia can lead to an asymmetric appearance of the penis afterwards.

9.6.3 Bladder Neck Reconstruction

Bladder neck reconstruction is undertaken at the age of 4–5 years, where it can be expected that the child can cooperate actively with toilet training. A prerequisite for bladder neck repair is a bladder capacity of more than 60 ml (Ben-Chaim et al. 1996). Since nearly all patients suffer from VUR, new ureteral implantation must also be done. Afterwards muscle flaps are created from the mid-trigone to the prostatic urethra, and these flaps are closed over a catheter in order to produce a bladder neck. In cases where the bladder neck is wide open or continence is inadequate, submucosal injection of Teflon, collagen, or silicone microspheres can be an alternative treatment choice (Kelly 1998).

Conclusion

Management of bladder exstrophy aims to result in a well, dry, fertile, and happy (both cosmetically and functionally) adult. Therapy of bladder exstrophy consists of staged surgical repair. Factors for successful outcome of bladder closure have been identified.
VUR is common after bladder closure.

9.7 Outcome of Bladder Exstrophy

9.7.1 Vesicoureteral Reflux

Vesicoureteral reflux will be present in nearly all patients after bladder closure, thus making antireflux surgery necessary. Pyelonephritis and renal scarring are reported to occur in 25%–50% of patients (Hollowell et al. 1992).

9.7.2 Bladder Function

Generally, besides bladder capacity, urodynamic parameters decline after bladder neck reconstruction, thus leading to the search for alternative surgical strategies (Canning 1996). After bladder closure up to 80% of patients will have normal filling urodynamics before bladder neck reconstruction (Canning 1996; Diamond et al. 1999). Following bladder neck reconstruction only 25% of patients will exhibit normal detrusor function (Canning 1996; Diamond et al. 1999; Stein et al. 1994). Bladder capacity is about one-third of the expected age-matched bladder capacity before bladder neck repair and will be about half of the expected bladder capacity afterwards (Diamond et al. 1999).

9.7.3 Continence

Kelly evaluated achieved continence in a series of 26 patients older than 6 years who underwent sphincter reconstruction at the Royal Children's Hospital Melbourne (Kelly 1998). Patients were classified as being physiologically continent (voluntary urinary control, only sporadic night-time wetting), socially continent (imperfect bladder control, adjustments for daily life such as pads necessary), or incontinent (urine leakage cannot be prevented). Of these 26 patients, 40% belonged to the physiologically continent group, 30% to the socially continent group, and 30% were incontinent. Therefore, it can be expected that about two-thirds of the patients will achieve some kind of continence after surgical repair of bladder exstrophy.

9.7.4 Psychosexual Function and Fertility

It has been reported that about 70% of adolescents and 33% of younger school-aged children will have behavioral, social, and school competency problems (Ben-Chaim et al. 1996). The beginning of sexual activity seemed to be delayed. Following staged repair of bladder exstrophy males will be able to have erections, but about one-third will describe the erections as unsatisfactory due to the small penis appearance. Only a minority will father children, mainly because of obstruction of the ejaculatory ducts and associated infections. Retrograde ejaculation seems to be an additional problem (Ben-Chaim and Gearhart 1996). Similar findings were reported by Stein et al. (1994), who investigated 101 patients after urinary diversion with and without genital reconstruction. No male with genital reconstruction could ejaculate normally and had fathered children, whereas all patients without genital reconstruction could ejaculate normally and 40% had fathered children (Stein et al. 1994). Therefore, genital reconstruction and closure of the urethra in males are burdened with the risk of infertility. However, 92% of women are satisfied with the cosmetic outcome. Nearly all woman can engage in sexual intercourse, but a quarter consider it as unpleasant or painful (Stein et al. 1994). Pregnancies have been reported to occur (Ben-Chaim et al. 1996; Stein et al. 1994).

Conclusion

In up to three-quarters of patients behavioral, social, and school competency problems can be expected. The majority of patients will be sexually active. In males, genital reconstruction seems to be burdened by the risk of infertility. The majority of women will be satisfied with the cosmetic outcome, and pregnancies occur.

9.8 Imaging in Epispadias-Exstrophy Complex

Various imaging modalities are involved during the tortuous course of patients suffering from the epispadias-exstrophy complex (Wood 1990). In newborns with bladder exstrophy chest films are taken as a part of the preoperative work-up within the first days of life. Pelvic X-rays depict the skeletal deformity. Plain films of the lumbar spine should be evaluated with the chest film for vertebral anomalies.

Ultrasound examinations of the kidneys and spinal canal should be performed to assess coexisting malformations. In the case of premature babies, the ultrasound study should be completed by a cranial ultrasound for the evaluation of intraventricular hemorrhage. After bladder closure, voiding cystourethrography (VCU) is the method of choice for demonstration and grading of VUR. Using Fotter's modified VCU technique, functional information regarding detrusor contractions can be obtained during the same investigation (Fotter et al. 1986; Fotter 1992, 1994, 1996) (see Chaps. 14 and 16).

Complete work-up of the lower urinary tract regarding the simultaneous assessment of morphology and functional disorders can be achieved by video-urodynamics, if available (see Chap. 1.4). Since the bladder outlet and urethral morphology are of particular interest in these patients at any time of the staged surgical correction, there is no role for a direct radionuclide cystogram and sonographic VCU.

Renal ultrasound, including 3D-ultrasound and volumetry, will allow noninvasive monitoring of kidney growth. Furthermore, dilatation of the pelvico-caliceal system can be detected. In cases of suspected reflux nephropathy, isotope studies (DMSA scans) or MR urography should be performed (Riccabona 2007).

Added Doppler ultrasound assesses kidney perfusion in the long term. Serial ultrasound examinations of the urinary bladder, including the estimation of the residual urine, gives information about bladder filling capacity and the voiding function. There is a role for 3D ultrasound, which provides the generation of 3D anatomic images and allows more accurate estimations of bladder volume than those derived from two orthogonal sections using the ellipsoid formula.

Intravenous urography (IVU) is still a standard method for the evaluation of the upper urinary tract in terms of morphology, semiquantitative estimation of kidney function, and dynamics of urinary transport. MR urography is on the run to be the method of choice (Riccabona 2007).

After antireflux surgery we do an abbreviated IVU variant on day 14. Two films are exposed: one of the upper abdomen 5 min after bolus injection (p.i.) of the contrast medium, followed by a film of

the whole abdomen at 30 min p.i. These two films of the abbreviated IVU are compared to the preoperative VCU, which depicts the maximal dilatation of the upper urinary tract. A pelvico-caliceal dilatation on the IVU less than or equal to the preoperative VCU indicates a nonobstructed upper urinary tract. If the pelvico-caliceal dilatation on IVU is more pronounced than on VCU, an at least partially obstructed upper urinary tract is suspected.

For the standardized and reproducible assessment of the split renal function and urine drainage isotope studies are performed. Nowadays MR urography represents an alternative, thus avoiding the hazards of radiation (Riccabona 2007).

For imaging of the skeletal features in the epispadias-exstrophy complex, especially in patients who did not undergo pelvic osteotomies, multislice computed tomography or musculoskeletal MR with subsequent 3D reconstructions provides a valuable tool. The underlying skeletal deformities can be assessed and the necessary parameters obtained, as needed for orthopedic correction (Yazici et al. 1998; Gargollo et al. 2005).

Magnetic resonance imaging (MRI) is the best choice for imaging of spinal problems beyond the neonatal period. Patients suffering from cloacal exstrophy and coexisting myelomeningoceles can be evaluated for postoperative complications such as the tethered cord syndrome. In addition, in these patients MRI can be used for assessment of the pelvic floor, bladder, gonads, uterus, and rectum.

Conclusion

In the neonatal period ultrasound can be used for assessment of coexisting renal and spinal malformations. Modified VCU assesses both lower urinary tract function and morphology.
Video-urodynamics, if available, allows complete work-up of the lower urinary tract. After antireflux surgery abbreviated IVU should be used for evaluation of urine transport; in equivocal cases it should be completed by isotope studies.

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Renal Agenesis, Dysplasia, Hypoplasia and Cystic Diseases of the Kidney

10

Michael Riccabona and Ekkehard Ring

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M. Riccabona, MD
Professor, Department of Radiology, Division of Pediatric Radiology, University Hospital Graz, Auenbruggerplatz 34, 8036 Graz, Austria
E. Ring, MD
Professor, Department of Pediatrics, Division of General Pediatrics, University Hospital Graz, Auenbruggerplatz 30, 8036 Graz, Austria

10.1 Introduction

Renal malformations represent the most common manifestation of congenital diseases in childhood. Renal agenesis, dysplasia, hypoplasia and cystic renal diseases are such entities. Causes vary; partially they derive from the complex renal organogenesis, and partially they have genetic and inherited reasons. Furthermore, an acquired disease can be present. Today there is increasing evidence that disturbances of the ciliumcentrosome complex form the pathogenetic base of most or many phenotypically different cystic renal diseases on a cellular level (Guay-Woodford 2006). The knowledge of the individual etiology and development helps to understand the disease process, affects further diagnostic and therapeutic management and helps to properly estimate prognosis of these patients and their families, respectively.

Diagnosis is often easy; gross renal pathology is generally depicted by prenatal ultrasound (US) (Helin and Persson 1986; Cohen and Haller 1987; Patten et al. 1990; Zeijl et al. 1999). However, gradually evolving disease may only manifest later, or subtle pathology can pose some difficulties to imaging. Furthermore, renal pathology may be detected by screening programs after birth, or examinations after clinical symptoms such as urinary tract infection, hematuria, nephrolithiasis, wetting, hypertension and other symptoms of developing renal insufficiency; sometimes unrelated symptoms lead to an ultrasound investigation that depicts renal pathology by chance.

Differentiation of various similar entities can be challenging, indicating the need for a variety of imaging modalities. The known association with other pathology of the urinary tract may also call for additional studies, such as voiding cysto-urethrography (VCU) in babies with multicystic dysplastic

kidneys (MCDK). Postnatal imaging usually is indicated by prenatal findings, family history, known disease likely to be associated with renal abnormalities or clinical/laboratory findings that indicate renal disease in either symptomatic or otherwise healthy patients.

The task of imaging is to reliably define or rule out a disease state in an economic way at minimal harm to the patient. In general, US is used as the first, orienting, non-invasive, non-ionizing imaging for evaluation of the urinary tract and possible associated malformations, for example, in syndromal conditions. If US, including the modern techniques such as color Doppler (CDS), power Doppler (= amplitude coded color Doppler sonography, aCDS) and harmonic imaging (HI) sufficiently answer the clinical query, no further imaging is needed. Otherwise, scintigraphy for evaluating renal (relative) function, VCU for evaluation of vesico-ureteral reflux (VUR), intravenous urography (IVU) and MRI/CT for assessing calyceal cysts/diverticula, duplex systems, evaluation of complications and cystic renal tumors, or (US/CT-guided) renal biopsy are used. Once the diagnosis is established, follow-up depends on the course of the disease and can often be accomplished by repeated US.

10.2 Renal Agenesis

Causes of renal agenesis are aplasia of the Wolfian duct or absence of the ureteral bud with consecutive lack of induction of metanephrogenic tissue (McCrary 1972; Thüroff and Frohneberg 1986; Woolf 1997; Sadler 1998; Avner 1998). In these patients one usually finds no ipsilateral ureter, as well as associated aplasia, hypoplasia or anomalies of genital structures originating from the ipsilateral Wolfian and Muellerian duct. The renal vessels are missing. Unilateral renal agenesis has no significant impact on the patient with only a small risk of accompanying malformations (Cope and Trickey 1982). Bilateral renal agenesis, also called Potter's syndrome, is lethal with a reported incidence of approximately 1:40,000 (Potter 1972; Churg et al. 1987; see also Chap. 23). The incidence of unilateral renal agenesis is reported to be 1:1,100 on autopsy series, with aplasia of the ipsilateral adrenal gland in 10% (Hoyer 1996; Frohneberg 1986). The contralateral kidney may be ectopic, malrotated and usually presents with compensatory hypertrophy. However, if hypertrophy is not present, dysplastic or hypoplastic changes of the remaining single kidney must be considered, and these patients need close nephrologic follow-up since prognosis is worse. Close relatives have a slightly increased risk of renal malformations.

The purpose of postnatal imaging is to search for ectopic kidney parenchyma, to evaluate the contralateral kidney (e.g., to differentiate crossed dystopia), to assure normal renal function and to evaluate associated abnormalities, particularly of the genital structures. In general, US is used as the first step (Fig. 10.1). Then scintigraphy – including an anterior acquisition with a catheterized urinary bladder – and VCU are performed. No additional imaging is used routinely. However, MRI and three-dimensional US (3DUS) can be helpful for evaluating associated genital anomalies, e.g., to find an ectopic testis (MRI) or to confirm a bicornuate or septate uterus (3DUS) (Beomonte-Zobel et al. 1990; Jurkovitz et al. 1995; Landry et al.1999; Nelson et al. 1999; see also Chap. 7 and Fig. 10.7c).

Conclusion

In renal agenesis imaging (primarily US, VCU and scintigraphy) is used for confirming the diagnosis and for evaluating and monitoring the contralateral kidney.

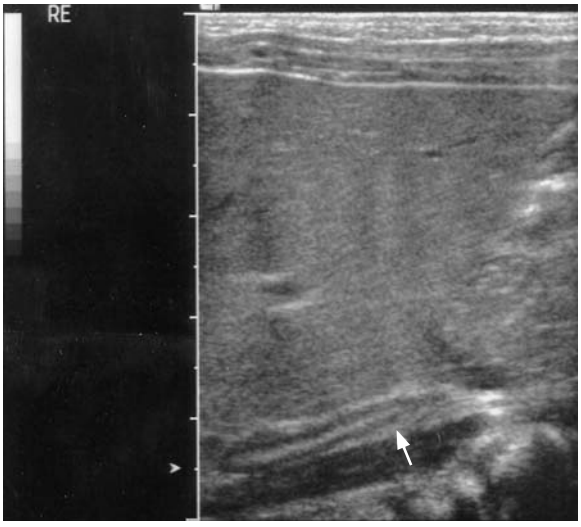
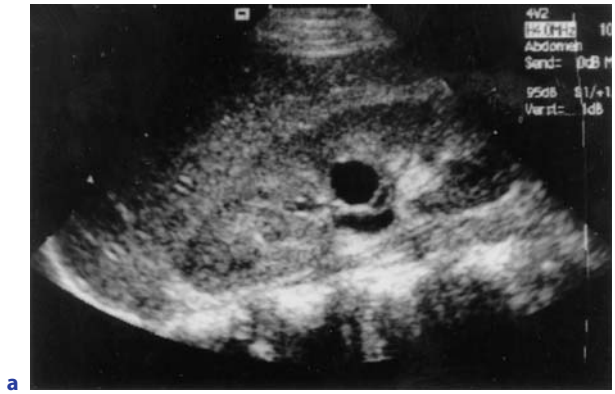
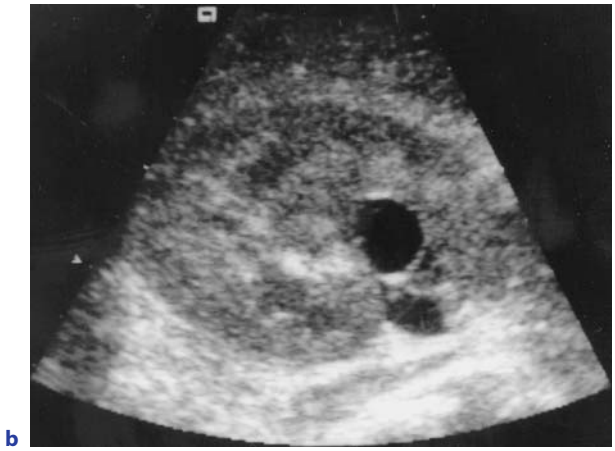
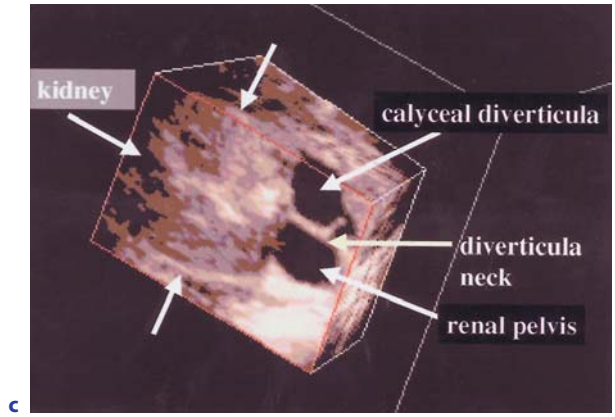
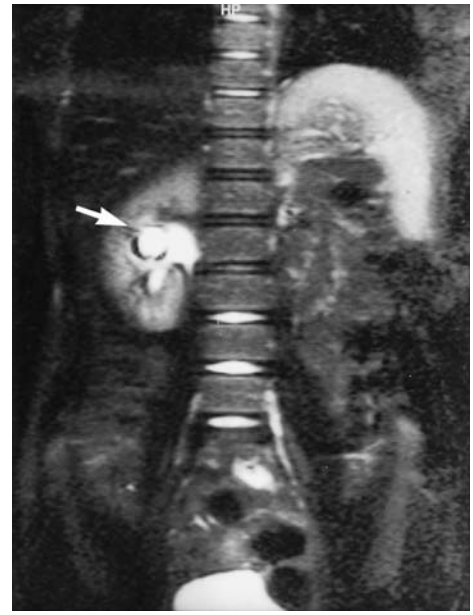


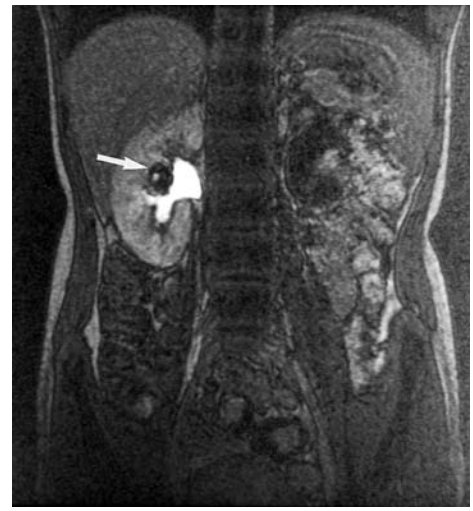
Fig. 10.1. Renal agenesis: US of renal agenesis showing the empty renal fossa with a somewhat atypically shaped adrenal gland (*arrow*) in this longitudinal view of the *right upper* quadrant











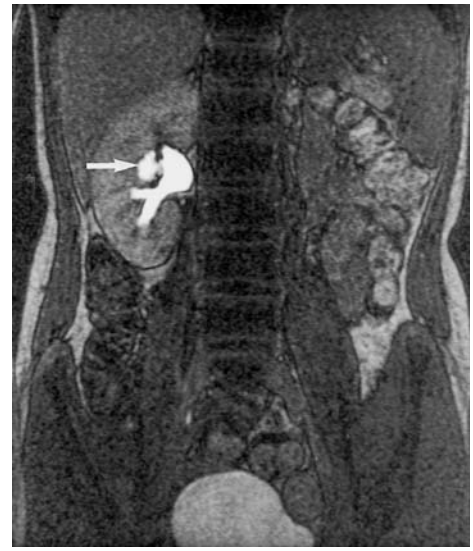


Fig. 10.2a–f. Calyceal diverticula: **a**,**b** US of a simple renal cyst close to the renal pelvis in longitudinal and transverse images. **c** 3DUS of the same cyst suggesting a connection of the cyst to the urinary collecting system (diverticula neck). **d–f** Dynamic MRI urography images of this calicyeal diverticula (*arrow*) demonstrating initially the topographic anatomy of the cyst (T2-weighted coronal image, **d**), then the delayed contrast extravasation into this calyceal diverticula (T1-weighted fast angio 3D sequences/acquisitions; *e* = early phase, no contrast in the cyst; *f* = delayed scan with gadolinium coming from the collecting system into cyst)

10.3 Renal Hypoplasia

The radiological appearance of a small kidney (less than 50% of the normal size) led to the confusing and misleading expression of "acquired hypoplasia," meaning a small kidney secondary to renal artery stenosis, radiation, compression by adjacent structures and other rare entities, whereas renal hypoplasia in its original meaning is defined as a congenital condition. Embryologically, renal hypoplasia originates from disturbed differentiation of metanephrogenic tissue or problems with the induction of tissue differentiation, e.g., by quantitative deficiency of metanephric primordia or disorders in formation and growth of the ureteral bud (Frohneberg 1986; Bernstein 1968). Histologically, it is defined by reduction in the number and/or size of nephrons, mostly in combination with dysplastic elements (Watkins et al. 1997). In oligomeganephronia these few nephrons are grossly enlarged. Renal hypoplasia can be found unilaterally, as an unipapillary kidney or even segmental–e.g., in duplex systems–and bilateral, which then often leads to early renal insufficiency (Fetterman and Habib 1969; Peterson et al. 1982; see also Chaps. 21 and 23). Segmental manifestation in a single system is known as Ask-Upmark kidney and is probably due to segmental/regional arteriitis, incidental or secondary to VUR, and/or dysplastic parenchyma with regional ectatic calyces (Arant et al. 1979). Close relation to renal dysplasia is observed that may lead to manifestation as a mixed entity in one patient (Bernstein 1992; Watkins et al. 1997) (Table 10.1). Incidence is reported to be 1:500 in adults (Bengtsson and Hood 1971).

Clinically, the signs and symptoms vary with the degree of hypoplasia and the underlying cause or associated disease. Many children are otherwise healthy, and renal hypoplasia is detected by chance; others with a more severe disease state may suffer from urinary tract infection, hypertension–predominantly in Ask-Upmark kidney, renal acidosis or signs of chronic renal failure.

Imaging usually starts with US. US volume calculations show a small kidney with otherwise often normal sonomorphologic appearance (Fig. 10.3). However, renal growth charts reflect the changes in renal size depending on age and bodyweight, but do not account for regional variations (Avni et al.1985; Hoyer 1996; Churg et al. 1987; Schnieder and Fendel 1995; Dinkel et al. 1985; Kasiske and Umen 1986). In segmental manifestation aCDS may demonstrate segmental vessel rarefaction in dysplastic areas (see also Fig. 10.4c). Scintigraphy confirms the lack of focal parenchymal defects in diffuse hypoplasia. IVU is rarely used nowadays and is restricted for situations with suspicion of a duplex system, an unipapillary kidney, possible segmental manifestation, or in an additionally dilated urinary tract. It shows a small kidney with reduced concentration of contrast both in the parenchyma and in the otherwise normal urinary tract in diffuse disease, or regional parenchymal narrowing with reduced parenchymal

Table 10.1. Renal hypoplasia. Classification and forms of renal hypoplasia, adapted according to Bernstein (1973, 1992) and Watkins et al. (1997)

Simple renal hypoplasia
• Isolated
• Syndromal (branchio-oto-renal syndrome, fetal alcohol syndrome, Turner syndrome, Goldenhar syndrome, autosomal syndromes)
• Unipapillary kidney and segmental hypoplasia (Ask-Upmark kidney)
Mixed renal hypoplasia (with dysplastic and cystic elements)
Oligomeganephronia
• Isolated
• Syndromal (branchio-oto-renal syndrome)

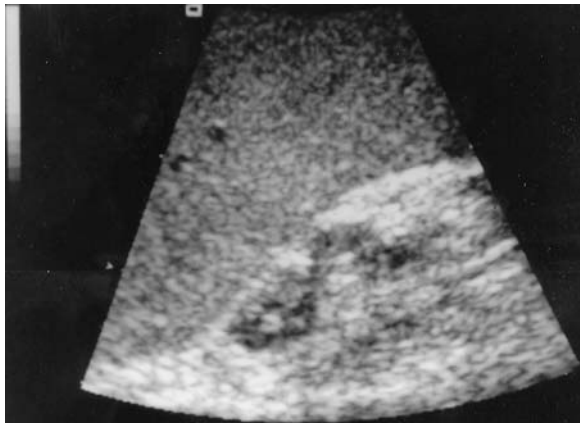


Fig. 10.3. Renal hypoplasia: US of the right upper quadrant showing a small, but otherwise sonomorphologically normal kidney in a longitudinal section, consistent with renal hypoplasia

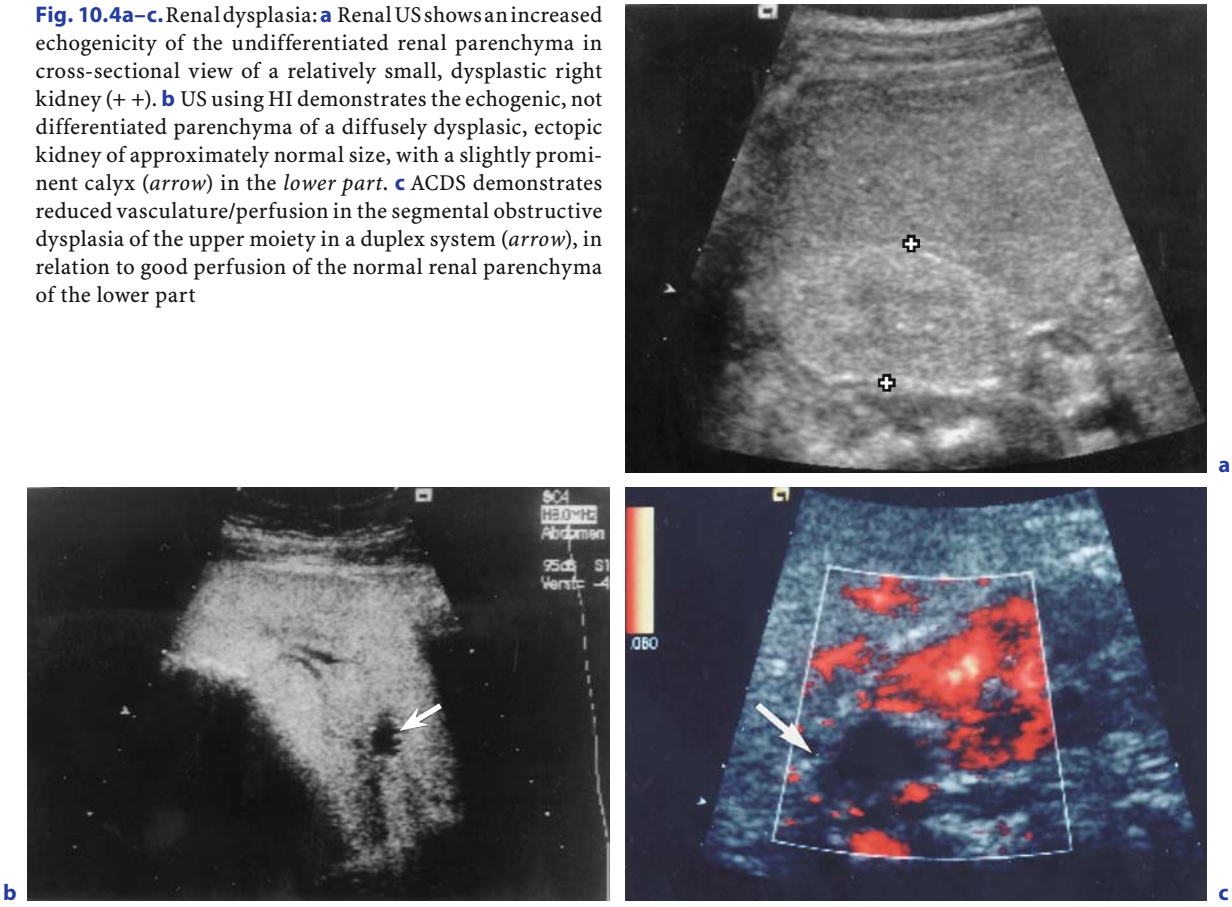


Fig. 10.4a–c. Renal dysplasia: **a** Renal US shows an increased echogenicity of the undifferentiated renal parenchyma in cross-sectional view of a relatively small, dysplastic right kidney (+ +). **b** US using HI demonstrates the echogenic, not differentiated parenchyma of a diffusely dysplasic, ectopic kidney of approximately normal size, with a slightly prominent calyx (*arrow*) in the *lower part*. **c** ACDS demonstrates reduced vasculature/perfusion in the segmental obstructive dysplasia of the upper moiety in a duplex system (*arrow*), in relation to good perfusion of the normal renal parenchyma of the lower part

contrast in segmental manifestation. Where available, MRI is starting to replace IVU.

Additional workup is performed with VCU to rule out VUR as a possible cause for a radiologically small kidney and scintigraphy for determination of relative (split) renal function. Various entities have to be considered for the differential diagnosis, especially when disease is discovered later in childhood (conditions including reasons for acquired or secondary renal hypoplasia). These include renal artery stenosis, renal dysplasia, Alport syndrome, chronic glomerulonephritis or postpyelitic cirrhotic kidney/end-stage renal disease (ESRD). CT or MR angiography and Captopril scintigraphy are performed in suspected renal artery stenosis. In Alport syndrome and chronic lomerulonephritis, US-guided biopsy may be indicated. Catheter angiography is performed to confirm renal artery stenosis or regional vascular disease and often combined with balloon dilatation/angioplasty in the same session if applicable.

Conclusion

Imaging is used to differentiate hypoplasia from other entities such as acquired disease, dysplasia and refluxnephropathy. It starts with US and then generally is accomplished by VCU and isotope studies.

10.4 Renal Dysplasia

There is a wide range of manifestations and underlying causes for renal dysplasia (Stockamp 1986). The causes start with genetic and embryological disorders, including links to cystic renal disease and to hypoplasia, span to changes secondary to developmental disturbances, and reach to dysplasia secondary to fetal VUR. New genetic insights indicate that VUR may be

associated with genetically predefined connatal dysplasia, but itself is not the cause for disturbed renal development (Bernstein 1992; Hohenfellner et al. 1999). Furthermore, obstruction of the urinary tract such as in posterior urethral valve, prune belly syndrome, vesico-ureteric junction obstruction (VUJO), uretero-pelvic junction obstruction (UPJO) and ureteric atresia may lead to renal dysplasia (Huland 1986; Bernstein 1992) (Table 10.2; see also Fig. 23.2).

The manifestation can vary from focal/segmental dysplasia, such as in duplex kidneys (with or without ectopic ureteroceles), or subtle tissue changes over diffuse severe disease to even non-functioning renal units such as in MCDK (see also Sect. 10.5.2). In general, a disturbed renal ontogenesis results in the presence of structures not present during normal nephrogenesis such as immature spindle cells, dilated epithelial structures, secretory cells or dysontogenetic tissue; particularly cartilaginous metaplasia is considered to be essential and–when present histologically–diagnostic (Persky et al. 1967; Potter 1972; Kissane 1990). These changes can be associated with cystic changes and with various syndromes (syndromal dysplasia for example in trisomy 13–15 and 18, or in Meckel-Gruber syndrome) (Table 10.2; see also Sect. 10.5.1.6).

Table 10.2. Renal dysplasia. Various manifestations of renal dysplasia, including cystic and syndromal forms, adapted according to Bernstein (1992), Kissane (1990), Hoyer (1996) and Watkins (1997)

Multicystic renal dysplasia
Obstructive renal dysplasia:
• With lower urinary tract obstruction
• With upper urinary tract obstruction
• Segmental renal dysplasia
Diffuse renal dysplasia
• Syndromal:
– Autosomal dominant: tuberous sclerosis, von Hippel-Lindau syndrome
– Autosomal recessive: Meckel-Gruber syndrome, oro-facial-digital syndrome, Zellweger syndrome, short limb-polydactyly syndrome, Jeune syndrome
– Aneuploidies: trisomy 13–15, 18, 21, Turner syndrome
– Non-inherited syndrome: nail patella syndrome, prune belly syndrome, Ehlers Danlos syndrome, branchio-oto-renal syndrome
Non-syndromal and miscellaneous
Focal renal dysplasia
• Miscellaneous
• Hereditary:
– Angiomyolipoma (tuberous sclerosis)
– Neurofibroma (von Recklinghausen's neurofibromatosis)

Clinical symptoms vary depending on the individual manifestation, the underlying disease and the amount of renal functional impairment. Diagnostically – besides assessing renal function by blood and urine analysis and checking for hypertension – imaging plays the most important role in the initial workup.

US can detect tissue changes: it usually shows echogenic renal parenchyma with reduced cortico-medullary differentiation. Cysts of varying sizes, mostly small, may be present (Fig. 10.4a,b; see also Fig. 23.2). Duplex Doppler may show elevated renal resistance in poorly functioning units; aCDS helps to evaluate reduced peripheral renal vasculature and perfusion, most convincingly displayed in segmental manifestation (Fig. 10.4c). Additionally, VCU–to detect the often-associated VUR (in up to 30% of patients)–and scintigraphy are performed routinely. In some patients with complex urinary tract abnormalities MR urography may be helpful (Terrier et al. 1986; Krestin 1990; Hattery and King 1995; Sigmund et al. 1991; Avni et al. 1997; Borthne et al. 1999).

Genetic tests may be performed in those patients and families suspicious of an underlying inherited renal disorder. In some equivocal situations, when disease is found only during later childhood and imaging remains inconclusive, diagnosis is made by renal biopsy. Focal dysplasia as found in tuberous sclerosis (renal angiomyolipoma) and von Recklinghausen's neurofibromatosis is discussed in Chapter 3 and 24, as they rather present as a renal mass or tumor than as a focal dysplasia or a renal cyst, and usually are listed as benign renal masses (Dodat et al. 1988; Bernstein 1993).

Conclusion

US can be suggestive of dysplasia. Histology establishes the definite diagnosis, particularly in patients with disease detected later in life and not in early infancy. VCU is obligatory. Other imaging methods are used for additional workup, to confirm an otherwise normal urinary tract and to evaluate (split) renal function (isotope studies).

10.5 Cystic Renal Disease

This includes a variety of entities; numerous classifications exist that have changed over time. The causes vary. Inherited diseases as well as a disturbed renal embryogenesis and renal development create a wide spectrum of manifestations that spans from diffuse, severe, bilateral congenital disease to simple, single renal cysts occurring in the adult (Tanagho 1975; Stockamp 1986) (Table 10.3). The main mechanism is a disturbance at the junction between the metanephrogenic tissue and the ureteral bud (Osathanondh and Potter 1964, 1966; Devine 1983). Isolated disturbances lead to isolated defects and cysts; multilocal or diffuse involvement of tubules creates a diffuse and progressive disease such as in polycystic kidney disease. Disorders in the continuity of the tubules cause medullary sponge kidneys. Most (inherited) cystic diseases seem to have a genetic or chromosomal background, with gene defects that center on the development and function of the cilium-centrosome complex, with a number of gene defects having been localized during the past years (Guay-Woodford 2006). Disturbances of this cilium-centrosome complex may possibly form a common base in the pathogenesis even of non-hereditary or acquired cystic disease; as well, this pathogenetic model offers an explanation for potentially associated systemic conditions such as cysts in other organs. Sometimes it can be difficult to differentiate a hemorrhagic renal cyst or a segmental polycystic abnormality from cystic renal tumors. The various forms and clinical presentations may have different prognoses and may imply different diagnostic and therapeutic strategies. The following pages discuss the most important entities separately.

Table 10.3. Cystic renal diseases. Classification according to the proposal of the American Academy of Pediatrics, Urologic Section (Glassberg et al. 1987)

Hereditary disease
• Polycystic kidney disease
– Autosomal recessive polycystic kidney disease (ARPKD)
– Autosomal dominant polycystic kidney disease (ADPKD)
– Juvenile nephronophthisis and medullary cystic disease complex (MCDC)
– Glomerulocystic kidney disease (GCKD)
– Congenital nephrotic syndrome (Finish type, autosomal recessive)
– Syndromal cysts: Meckel syndrome, Lawrence-Moon-Biedl-Bardet syndrome, Ivemark syndrome, Zellweger syndrome, tuberous sclerosis, Hippel- Lindaus' disease
Non-hereditary cystic renal disease
• Multicystic dysplastic kidney disease (MCKD)
• Multiloculated cyst and similar entities
• Simple renal cyst
• Medullary sponge kidney
• Secondary or acquired renal cyst (post-traumatic, chronic renal failure)
• Cystic renal tumor

In general, imaging again starts with US, including Doppler facilities and HI, which significantly improves tissue differentiation and detection as well as delineation of cysts, particularly in difficult scanning conditions (Thomas and Rubin 1998; Shapiro et al. 1998; Wittingham 1999). VCU is used to evaluate potentially associated VUR. IVU or MRI (when available) is performed in a suspected calyceal diverticula, medullary sponge kidney or duplex systems and obstructive uropathy. Scintigraphy allows for quantification of split renal function that is essential for follow-up of these patients. Contrast-enhanced multiphasic spiral CT is helpful for evaluating complicated cysts, complex cystic masses or cystic renal tumors (Bosniak 1986; Urban 1997; Szolar at al. 1997). MRI is excellent for cyst detection using T2-weighted sequences. In some situations MRI can be applied to detect small lesions and to confirm existing disease, or to compare complex changes during follow-up (Hattery and King 1995; Bilal and Brown 1997; Borthne et al. 1999).

Therapeutically, no real medical treatment of these diseases is yet established–in general, adequate management of the patients in order to delay onset and progression of chronic renal failure is of importance, including nutritional management and medications for various secondary symptoms. However, early differentiation of the various entities might become more important, not only for family counseling, but as new therapeutic approaches based on new molecular genetic knowledge and discoveries leading to a more profound understanding of the disease processes are being investigated. Mediator substance and cytokines already showed remarkable

results in animal experiments on polycystic kidney diseases by reducing cyst development and inducing regression of cysts (Avner et al. 1999; Sweeney et al. 2000). Therefore, besides genetic diagnosis, imaging will become more essential particularly for treatment and follow-up of these patients.

10.5.1 Polycystic Kidney Disease

10.5.1.1 Autosomal Recessive Polycystic Kidney Disease (ARPKD)

ARPKD, or infantile polycystic kidney disease, is a heredito-familial disorder with a gene-defect on chromosome 6 (Zerres 1994). The incidence is 1:10,000 to 1:40,000 of live births (Kissane 1990; Zerres et al. 1984). It is associated with mutations of the PKHD1 gene (Zerres et al. 1998). The manifestation and the course of the disease may vary. In general, ARPKD manifests in early infancy or during childhood, although clinical onset may be delayed into adulthood in some patients with less severe manifestation (Shaikewith and Chapman 1993; Lieberman et al. 1971; Kaplan et al. 1988). However, this entity is often referred to as infantile polycystic disease as it leads to renal insufficiency during childhood in 90% of affected patients. Potter's syndrome-like changes secondary to oligohydramnios may be present at birth in severe cases with fetal renal insufficiency. Many of these neonates die from respiratory failure due to pulmonary hypoplasia. Children surviving the neonatal period may have a prolonged course and may become adolescents before renal replacement therapy is needed (Roy et al. 1997).

Histologically, there are growing numbers of initially very small cysts deriving from dilated collecting tubules with a flattened epithelium. Areas of normal renal structures diminish during the course of the disease, whereas the cysts grow less in size than in number (Cole et al. 1987; Hoyer 1996; McDonald et al. 1997). The severity of renal disease correlates with the number of affected nephrons. Hepatic involvement is frequently associated with ARPKD, cysts can be found in other parenchymal organs, and histological signs of liver fibrosis are considered obligatory (= congenital hepatic fibrosis). Liver histology shows a disc-shaped dilatation of dysgenetic periportal biliary ductules (extreme form = Caroli disease), with periportal fibrosis and duct proliferation, but otherwise normal hepatocytes, leading to portal hypertension mostly in adult patients (Liebermann et al. 1971; Alvarez et al. 1981; Cole et al. 1987; Kaplan et al. 1989).

Clinically, onset may vary even within one family. Beyond infancy, patients may present with a palpable abdominal mass, hypertension, cardiac failure or symptoms deriving from liver disease (particularly bacterial cholangitis and portal hypertension) depending on the variation, variability and expression of the disease (Barth et al. 1992). Sometimes ARPKD is diagnosed by chance or by family screening, as kidneys may look normal during prenatal and neonatal screening US in less severe cases. Prenatal diagnosis is difficult except for molecular genetic techniques (Barth et al. 1992; Zerres et al. 1994).

The first step in imaging usually is US. It may show initially sonomorphologically normal kidneys that become bilaterally enlarged, with normal presentation of the collecting system, but some very small subcapsular cysts of up to 3-mm diameter (Boal and Teele 1980; Zerres et al. 1988; Worthington et al. 1988; Hoyer 1996; Manish et al. 1997). The cysts can be seen unilaterally or bilaterally, and often they initially are too small to be detected, creating a bilaterally speckled increased echogenicity of the renal tissue, with inhomogenously reduced tissue differentiation, also called the pepper-salt kidney (Fig. 10.5a–c). During the course of the disease, the cysts constantly increase mainly in number, but also in size. After a period of regression with reduction of renal size a constant enlargement is noted with progressive disease, eventually leading to an end-stage kidney.

US is unable to definitely distinguish between ARPKD and ADPKD; only suggestive contributions to diagnosis may be made (Fig. 10.6). Furthermore, enlarged echogenic kidneys can also be seen in a variety of conditions such as congenital nephrotic syndrome, fetal malformative syndromes, renal vein thrombosis or acute renal failure. However, in conjunction with family history diagnosis can be suspected. With established diagnosis, no further imaging is needed. In equivocal cases CT/MRI can be used. CT with optimized technique is more sensitive and standardized in evaluating and detecting cysts; MRI may offer new perspectives in assessing the progress of the disease and associated liver disease (Kern et al. 1999). IVU is less specific and rarely used. If applied it shows markedly enlarged kidneys with prolonged, persisting, radial streaks

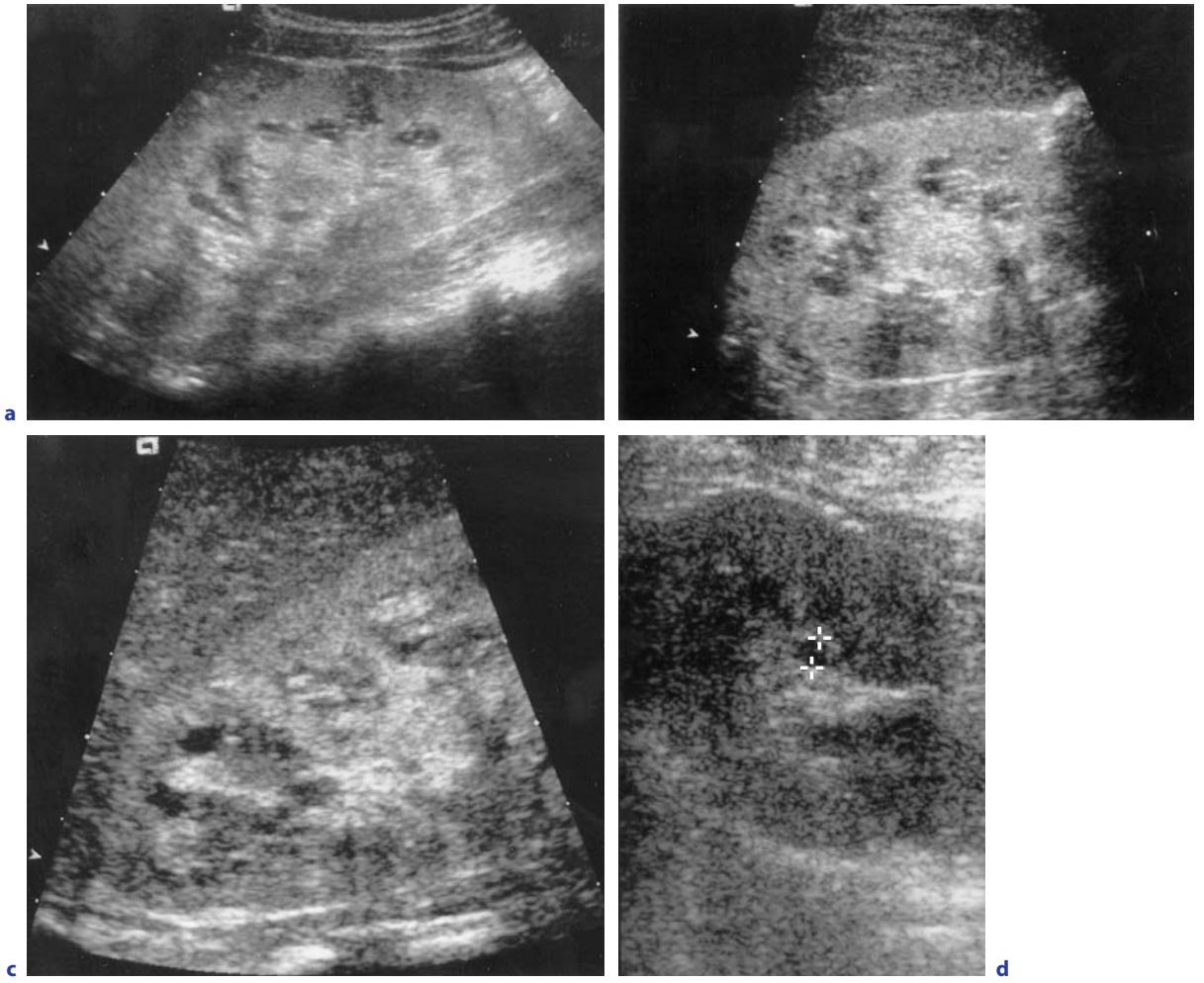


Fig. 10.5a–d. ARPKD (**a–c**) and ADPKD (**d**): **a–c** Longitudinal (**a**), cross-sectional (**b**) and augmented US view (**c**) of an enlarged kidney demonstrating multiple small parenchymal cysts with inhomogenously reduced cortico-medullary differentiation of the very echogenic renal parenchyma in a young girl with ARPKD. (**d**) US demonstrates one (+ +) of a few unspectacular renal cysts – others are scattered throughout the kidney, but not imaged in this section – in a child with early onset of ADPKD. Note some reduction in cortico-medullary differentiation and regional inhomogenicity of the renal parenchyma

and tubular striation as well as delayed cortical brush pattern (Schneider and Fendel 1995). In all patients with ARPKD, imaging of the liver and evaluation of possible portal hypertension are mandatory.

10.5.1.2 Autosomal Dominant Polycystic Kidney Disease (ADPKD)

With an incidence of 1:400 to 1:1,000 life births, ADPKD (infantile polycystic kidney disease) represents one of the most common inherited diseases. The defect is located on the short arm of chromosome 16 (the PKD1 gene) in over 85% of patients; some show a gene defect on chromosome 4 (the PKD2 gene) (Reeders et al. 1985; Romeo et al. 1988; McDonald et al. 1997; Ong and Harris 2005). Although manifestation usually takes place during adulthood – therefore also called adult polycystic kidney disease – ADPKD may be detected even prenatally or during infancy and childhood by selective family screening or by chance (Porch et al. 1986; Kääriäinen et al. 1988; Journel et al. 1989; Estroff et al. 1991; Fick et al. 1993). Some families as well as siblings of affected patients are predisposed to early manifestation (Sedman et al. 1987; Kaplan et al. 1977; Fick et al. 1994).

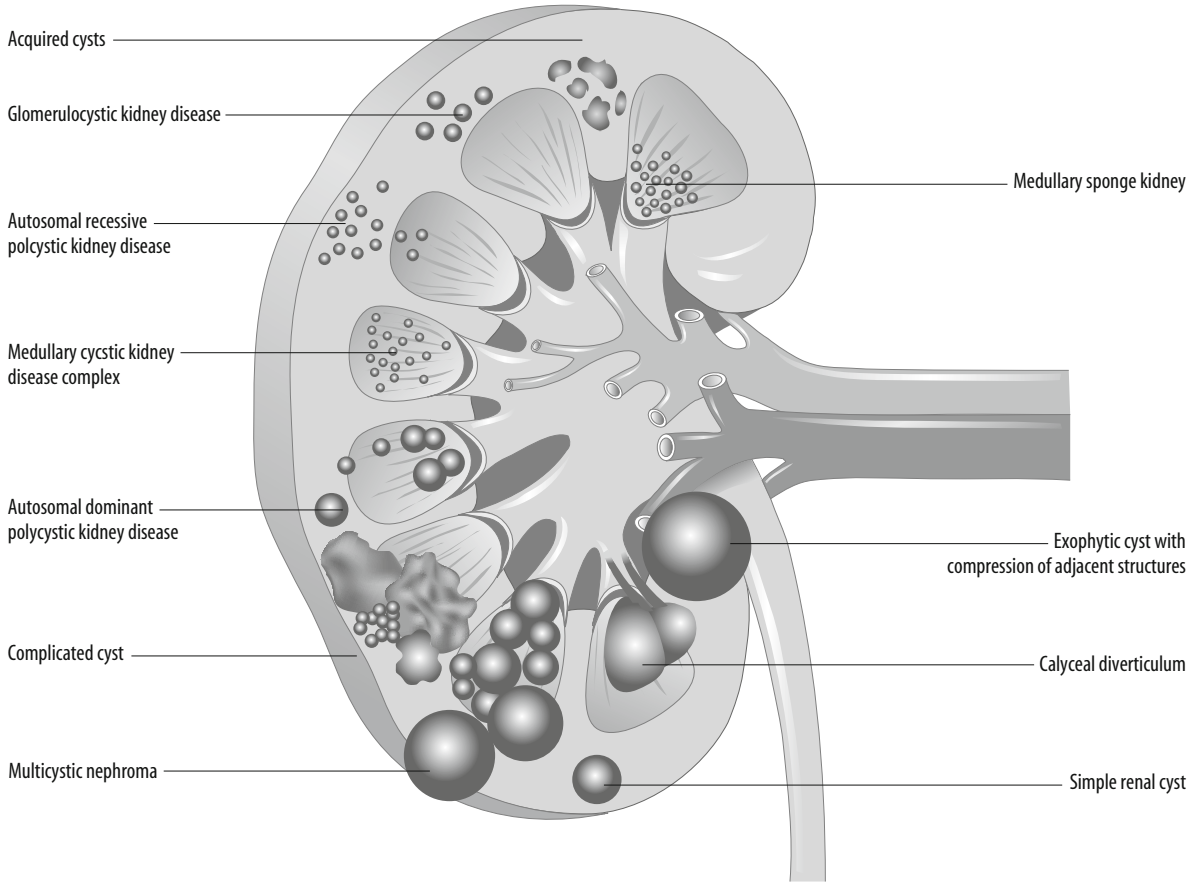


Fig. 10.6. Graph of typical cystic renal changes: Schematic drawing of typical cyst forms and locations in various cystic kidney diseases, with explanation of abbreviations and subcaptions: *ARPKD* autosomal recessive polycystic kidney disease (multiple small cysts, early manifestation, situated mostly cortical or at the corticomedullary border). *ADPKD* autosomal dominant polycystic kidney disease (some big cysts, usually during late childhood/adulthood, in all parenchymal areas); *GCKD* gomerulocystic kidney disease = predominantly small cortical or subcapsular cysts; *MCDC* medullary cystic disease complex (medullary microcysts, centered close to the cortico-medullary junction); *MCDK* multicystic dysplastic kidney; *MSK* medullary sponge kidney (medullary cystic changes, in a more or less radial pattern, centered towards the papilla)

Histologically, ADPKD shows cystic dilatation of all parts of the nephron including Bowman's space. Initially, only a few macrocysts may be present with an irregular distribution. Later on, both kidneys are enlarged, with a growing number of large cysts both in the cortex and the medulla. Accompanying cysts of the liver, the pancreas and other organs are common, but congenital hepatic fibrosis is rare. A high incidence of cerebral vessel malformations – particularly of aneurysms of the big cerebral arteries – is reported (in up to 70 % of adult patients!) and has been described in pediatric patients as well (Proesmans et al. 1982). Furthermore, some relationship to tuberous sclerosis and the gene localization for tuberous sclerosis is described (Brook-Carter et al. 1994).

Clinically, ADPKD usually manifests with loin pain, hematuria, urinary tract infection, nephrolithiasis, hypertension and chronic renal insufficiency. For evaluation of theses symptoms, various imaging modalities depending on the individual, unspecific symptoms, from US and/or IVU to CT and MRI, are used. Chronic renal insufficiency usually develops gradually after the age of 30 years; earlier severe disease is rare (Worthington et al. 1988).

On US, the kidneys in general look normal during (early) childhood; sometimes one or two parenchymal (unilateral) renal cysts may be found (Fig. 10.5d). Some rare cases of early manifestation (enlarged fetal kidneys or neonatal renal cysts) have been described (Cole et al. 1987; Boal and Teele 1980; Kääriäinen at al. 1988). In early stages, two

or more cysts in a child with positive family history are considered diagnostic (Zerres 1987; Hoyer 1997). Later on, multiple cysts of varying size, mostly large, in irregular distribution, with varying amounts of normal renal tissue in otherwise hyperechoic renal parenchyma of both enlarged kidneys, represent the typical US finding. These cysts may become complicated by secondary hemorrhage, sedimentation and infection, sometimes necessitating further imaging or US/CT-guided puncture/drainage. IVU is no longer considered to be indicated for this query today; if performed it may show indirect signs of calyceal splaying around macrocysts and lucent areas due to cysts replacing normal renal tissue. CT and MRI are very sensitive in depicting the varying number of cysts. They may be used during follow-up for quantification and comparison, for evaluation of complications and for differentiation of complicated cysts in cases where US, including CDS and contrast-enhanced studies, is inconclusive (Kääriäinen et al. 1988; Bosniak 1986; Riccabona et al. 1999; Kim et al. 1999)

10.5.1.3 Medullary Cystic Disease Complex (MCDC) and Juvenile Nephronophthisis (NPHP)

Medullary cystic disease is an autosomal-dominant inherited disease with a late onset of chronic renal failure. Familial juvenile nephronophtisis (NPHP) is usually transmitted recessively; five genes (NPHP 1–5) have so far been identified (Hildebrandt and Otto 2005). The sporadic form most probably represents a new mutation (Gadner 1976; Donaldson et al. 1985; Hildebrandt et al. 1992; Avner 1994). Histology shows glomerular cysts with thickening of the multilayered membrane, accompanied by some tubular cysts. Depending on the disease state, a growing amount of interstitial fibrosis, chronic inflammation and tubular atrophy with consecutive chronic sclerosing tubulointerstitial nephropathy is observed (Fanconi et al. 1951; Gadner 1976; Waldherr et al. 1982). The adult form of MCDC is reported to be rare and difficult to diagnose even on renal biopsy specimens, whereas juvenile nephronophthisis is one of the most common genetic causes for ESRD necessitating dialysis and renal transplantation in children and adolescents (see also Chap. 21). The overall incidence is reported to be 1: 1,000,000 to 1:50,000 of births (Potter et al. 1980; Waldherr et al. 1982).

Clinically, MCDC is characterized by the insidious onset of chronic renal failure, with symptoms such as polydipsia, polyuria, secondary enuresis, weakness, pruritus, growth retardation and a relentless progression to ESRD. In 10% of patients with juvenile nephronophthisis, additional liver fibrosis or dysplasia of the bile ducts can be observed similar to the changes seen in ARPKD (Boichis et al. 1973).

On US, no specific changes are seen in early MCDC. In NPHP, some reduction in cortico-medullary differentiation may be observed initially (Hildebrandt 1997). Then the kidneys become slightly hyperechoic, and renal size decreases, eventually leading to a cirrhotic kidney, with detectable cysts in the cortico-medullary junction zone or subcapsular, predominantly in advanced chronic renal failure (Garel et al. 1984; Blowey et al. 1996) (Fig. 10.6). MRI and CT may be helpful in detecting small medullary cysts earlier than US and for standardized documentation (Elzouki et al. 1996). In general, however, no additional imaging is needed, as it does not contribute significantly to the diagnosis, which is made by family history and molecular genetics (Hildebrandt 1997).

10.5.1.4 Glomerulocystic Kidney Disease (GCKD)

GCKD is a rare congenital condition. It can be categorized into a group with hereditary syndromal changes (such as Zellweger syndrome, tuberous sclerosis or trisomy 13), a group of hereditary non-syndromal diseases transmitted autosomal dominantly and sporadic forms (Sellers et al. 1978; Joshi et al. 1984; Kaplan et al. 1989; Bernstein 1993). Some authors also include dysplastic cystic renal disease (see Sect. 10.4 and 10.5.2) (Kissane 1990). Histology reveals bilateral cystic dilatation of the renal glomeruli with widening of the Bowman spaces and consecutive dilatation of the proximal tubule (Baxter 1965; Bernstein 1993).

On US, these tiny cysts are visualized predominantly in the renal cortex and subcapsular, with a normal-appearing medulla. Possibly signs of interstitial nephropathy can be seen (i.e., accentuated cortico-medullary differentiation) in the bilaterally grossly enlarged kidneys with generally increased echogenicity, which is even more prominent in the cortex (Hoyer 1996; Manish et al. 1997) (Fig. 10.6). Secondary changes may be observed: inflammation, punctuate calcification, secondary medullary fibro-

sis or relative loss of renal size may then confuse the image (Fitch and Stapleton 1986; Fredericks et al. 1989). Differentiation against other entities with bilateral widespread small cysts may be difficult, and imaging may present very similar to polycystic kidney disease, particularly ARPKD (Fitch and Stapleton 1986). As diagnosis is made by histology and family history, no additional imaging is performed except for follow-up investigations.

10.5.1.5 Congenital Nephrotic Syndrome (Finnish Type)

This is a rare autosomal-recessive inherited disease that manifests at birth and endemically exists in Finland, with an incidence in this area of 1:8,200 live births (Hallmann et al. 1956; Huttunen 1976). The gene defect has been localized to chromosome 19 (Kestilä et al. 1994). Histology shows cortical changes ranging from just some dilated tubules in fetal renal specimen to severe tubulo-interstitial and glomerular abnormalities in older patients. Numerous radial dilatations of the tubules (microcystic kidney disease) with mesangial hypercellularity and some degenerative changes with interstitial fibrosis and glomerular sclerosis are considered the typical finding in infants (Holmberg et al. 1997).

The disease is not sensitive to any medication used to treat nephrotic syndrome. Death is mostly related to lack of nutritional support or intercurrent disastrous infections even before ESRD starts at approximately 2–4 years of age. The currently most accepted treatment includes vigorous parenteral nutrition and protein replacement from birth on, bilateral nephrectomy and starting peritoneal dialysis during late infancy, and early planning of renal transplantation (Mahan et al. 1984; Holmberg et al. 1995).

Clinically the neonates present with severe proteinuria, edema and abdominal distension; other changes may develop depending on lack of nutritional support. Diagnosis is made clinically and is very often established prenatally based on high alpha-fetoprotein concentration of the amniotic fluid and the maternal serum, an enlarged placenta, severe proteinuria of the fetus or infant, and gene analysis (Kjessler et al. 1975; Kestilä et al. 1998).

On US, the initially and prenatally normal kidneys are enlarged with increased cortical echogenicity with disappearing of the cortico-medullary differentiation during the course of the disease. Other changes such as disturbance of flow pattern, increase of resistive index or variations of cortico-medullary differentiation are influenced by renal function, cardiac situation and medication. Only rarely US-guided renal biopsy is performed. Additional imaging is not necessary except for extrarenal queries related to chronic renal failure and ESRD and for ore-transplantation workup.

10.5.1.6 Syndromal Cystic Renal Disease

There are a number of hereditary and non-hereditary syndromal cysts as well as cysts in aneuploidies, with partially autosomal recessive, partially autosomal dominant transmission (Table 10.3). Some important syndromes such as orofacial syndrome type 1, Meckel-Gruber syndrome, Bardet-Biedel syndrome and Joubert syndrome also exhibit gene defects that can be linked to the cilium-centrosome complex development and malfunction (Guay-Woodford 2006). They usually are part of a complex systemic disease with disturbance of nephrogenesis, combined with dysplastic features. They can present as multiple renal cysts, as GCKD, MCDC, or as ARPKD and ADPKD (Bernstein 1973, 1976, 1979, 1992; Donaldson et al. 1985; Kissane 1990; McDonald et al. 1991, 1997; Hoyer 1996; Watkins et al. 1997). The pediatric radiologist needs to consider these entities for differential diagnosis and further diagnostic imaging of associated malformations or abnormalities; otherwise the presentation and imaging of syndromal renal cysts does not differ from the imaging of the other cystic renal entities.

Conclusion

Cysts within enlarged kidneys and cystic abnormalities of other abdominal parenchymal organs are suggestive of a hereditary polycystic kidney disease. Many of these cystic diseases seem to converge on a common pathogentic pathway centered at the cilium-centriosome complex. However, a broad variation in onset, clinical manifestation and radiological features can make early differential diagnosis difficult. Imaging in pediatric patients usually is accomplished by US; for evaluation of complications, differential diagnosis and evaluation of extrarenal disease, MRI is becoming the method of choice.

10.5.2 Multicystic Dysplastic Kidney (MCDK)

This entity represents a subgroup of renal dysplasia (Bernstein 1971). MCDK is the most common cystic renal lesion in pediatric patients and the most common cause for an abdominal mass in neonates. The incidence is 1:4,300 of live births with a male predominance (2:1) except for the rare segmental manifestation, which is more common in the right kidney of girls (Longino and Martin 1958). The ipsilateral ureter commonly is abnormal, atretic, sometimes even absent, supporting the theory that MCDK results from early ureteral pathology during nephrogenesis (Huland 1986; Woolf 1997). Depending on the time of manifestation (most common during the 7th to 10th week of gestation) of the ureteral abnormality, a varying number of poorly differentiated, immature nephrons may be found in the MCDK. Floating borders exist to high grade UPJO. It usually affects the entire kidney, but rarely can also involve only a portion, e.g., in a duplex system, with atresia of the ureter of the upper moiety (Diard et al. 1984; Jeon et al. 1999). It is a sporadic malformation, but incidental reports exist on MCDK in siblings, twins and families (Srivastava et al. 1999).

The contralateral kidney is normal in 66% except for compensatory hypertrophy (if absent, hypo-/dysplasia must be suspected). However, contralateral kidneys are slightly more disposed to positional or rotational anomalies. Associated urinary tract anomalies are present in one third (low degree UPJO in 12%, VUR in 20%). Furthermore associated ipsilateral genital anomalies are found in up to 50%, such as cystic dysplasia of the rete testis or the seminal vesicle (Greene et al. 1972; Ring et al. 1990, 1993) (Fig. 10.7c,d). Rare bilateral manifestations (in some series up to 20%) are incompatible with extra-uterine life and may have some underlying genetic preposition (Griscom et al. 1975). Associated additional anomalies of other organs may be present such as atresia of the gastrointestinal tract, impaired cardiac septation or myelo-meningocele. These extrarenal malformations relate to the time of an insult during ontogenesis rather than to the nature of that hypothetical event.

Clinically, MCDK is commonly detected by prenatal US screening or presents neonatally as a palpable abdominal/flank mass. The natural history of MCDK may vary. The mass often shrinks and disappears, making surgery unnecessary (Gordon et al. 1988; Orejas et al. 1992; Ring et al. 1990, 1993) (Fig. 10.7e). Management focuses on monitoring spontaneous regression and/or on detection of complications such as continuing growth with compression of adjacent structures, inflammation, hemorrhage or even tumors arising within the mass then necessitating surgery (Hoyer 1996; Krull et al. 1990; Kullendorff 1990).

Imaging is initially focused on establishing the diagnosis, to confirm a normal contralateral renal unit and to rule out associated anomalies. This usually is achieved by US, scintigraphy and VCU. In case of duplex systems or a dilated contralateral collecting renal system or segmental MCDK, as well as in patients with complex malformations, MR urography (MRU) has become the accepted imaging tool, replacing IVU if available (Borthne et al. 1999) (Fig. 10.7c). Conventional grey-scale US shows a multicystic structure with some big and some smaller cysts that do not communicate and possibly some central echogenic, non-differentiated tissue components (Avni et al. 1986; Hoyer 1996) (Fig. 10.7a). Duplex Doppler and (a) CDS may be helpful to depict areas with persisting perfusion, which may be prone to create complications, or may help to establish the differential diagnosis (Riccabona et al. 1993; Hendry and Hendry 1991) (Fig. 10.7b). Follow-up is usually performed by US. Additional complications or arising suspicion of malignancy may necessitate further imaging (CT, MRI).

Conclusion

The task of imaging is to establish diagnosis (US, scintigraphy), to evaluate the contralateral system and associated disease (VCU, MRU) and to follow-up MCDK (monitoring involution = US, evaluating complications = US, CT, MRI).

10.5.3 Medullary Sponge Kidney (MSK)

MSK is rare in pediatrics, and only 5% of cases are familial; it can be segmental or may affect the whole kidney (Yendt 1990; Kissane 1990; Avner 1994; Watkins et al. 1997). Usually MSK manifests in adults showing multiple medullary, peripapillar centered cysts with secondary calcifications, hypercalciuria with nephrolithiasis and hematuria, and infection (Fig. 10.8).

US may lack sensitivity in the very early stages: the kidney may look sonomorphologically normal,

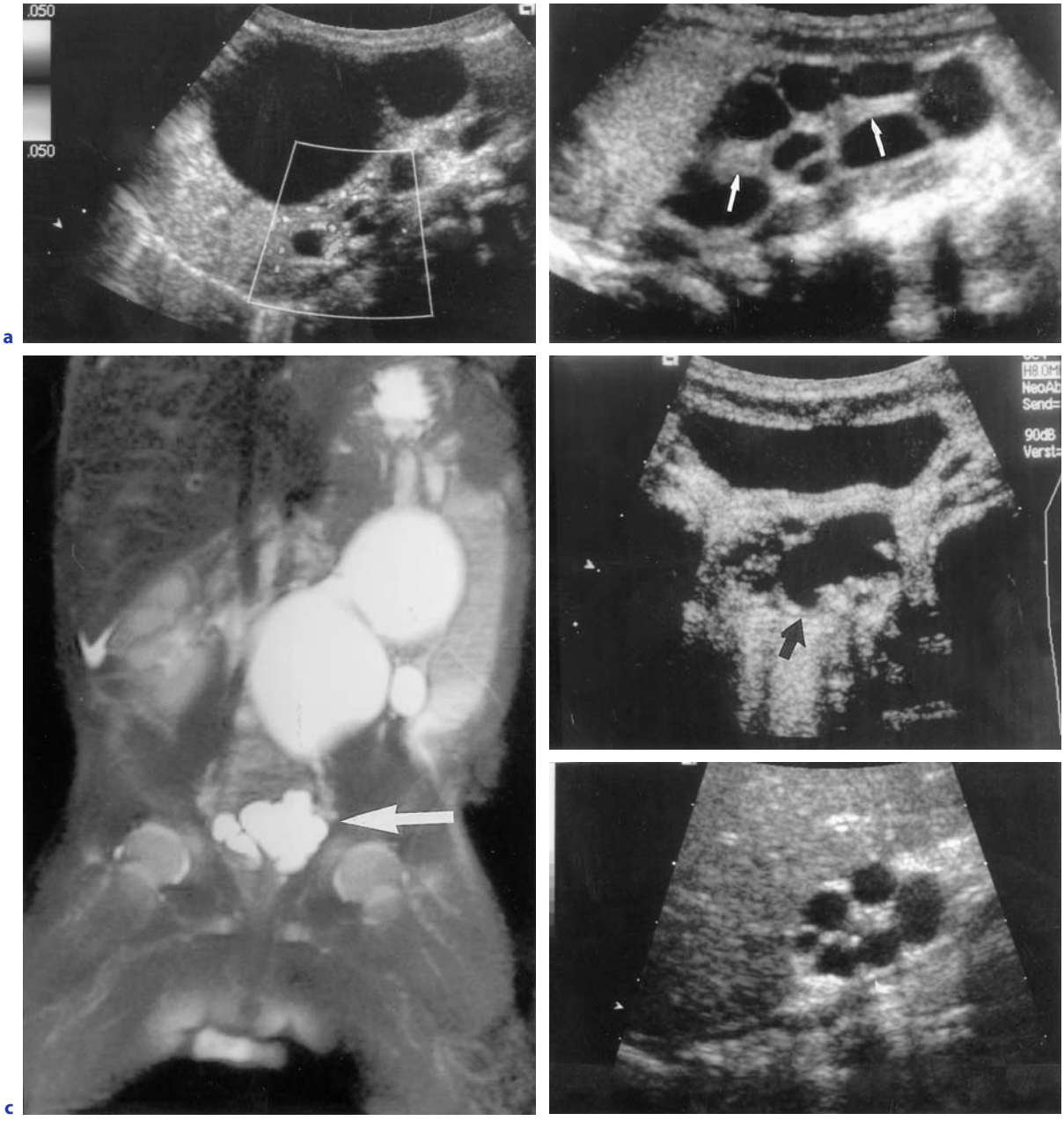


Fig. 10.7a–e. MCDK: **a** US images showing longitudinal section of multiple, non-corresponding cystic masses and some echogenic-dysplastic, non-differentiated parenchyma (*arrow*). **b** CDS demonstrates vasculature in the echogenic dysplastic parenchymal part of this MCDK. **c** 3D reconstructed MRI image of a MCDK with associated cystic dysplastic malformation of the ipsilateral seminal vesicle and rete testis, also demonstrated by US on a transversal section behind the bladder (*arrow*) (**d**). **e** US of spontaneous regression/involution of an already relatively small MCDK (*arrow*) in a longitudinal section

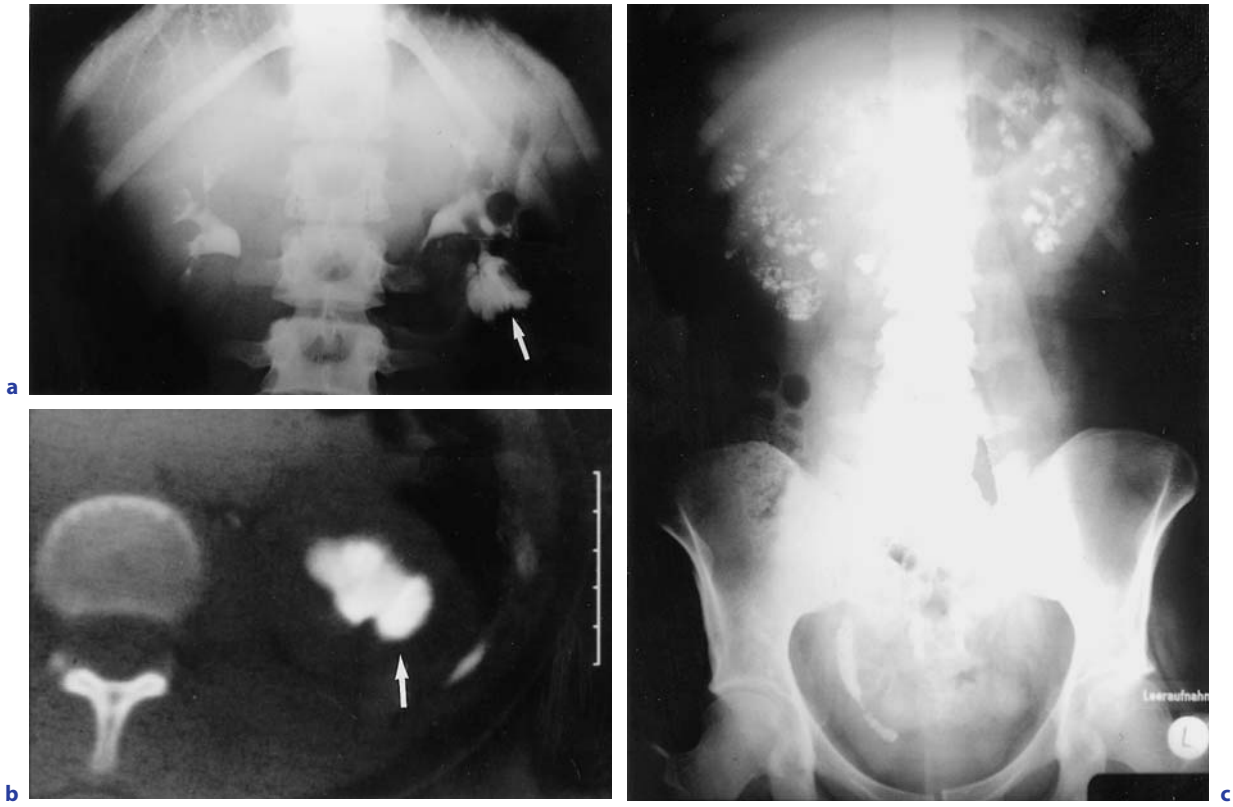


Fig. 10.8a–c. MSK: **a** IVU of a segmental MSK (*arrow*) in a child, with corresponding late phase CT image (**b**). **c** Plain film of severe diffuse disease with bilateral clotty medullary calcifications and distal ureteral calculi in an adolescent patient

or – at a slightly delayed stage – the kidney may look similar to early stages of medullary nephrocalcinosis, with normal sonomorphology of the cortex and hyperechoic patches throughout the medulla focusing on the papilla (Christmas-tree phenomenon, Patriquin et al. 1985). Later on, multiple calcifications as well as nephrolithiasis with or without obstruction may be observed on plain films and on US (Fig. 10.8c). As IVU is an excellent diagnostic tool in the diagnosis of MSK and of its complications such as obstructing calculus, US and IVU/plain film form the mainstay of imaging in this query–other imaging is used routinely (Palubinskas 1963) (Fig. 10.8a,c). CT shows a typical pattern, with radial patchy contrast in the pyramids on the excretory (late) phase of a multiphasic, contrast-enhanced scan (Fig. 10.8b). MRI is very sensitive towards detecting even small cysts that might be missed on US, but has restrictions in visualizing small calcifications. Furthermore, CT and MRI may become necessary during follow-up, as MSK may be associated with hemi-hypertrophy syndromes and as such bears a slightly higher risk of Wilms' tumor (Hoyer 1996).

Conclusion

MSK is diagnosed by US and IVU/plain film, but US may miss subtle changes only in the very early disease. If complications and malignancy occur, CT and MRI become useful.

10.5.4 Simple Renal Cyst and Acquired Renal Cyst

Simple renal cyst can occur spontaneously or be familial. They are rare in childhood with a reported incidence of 0.22% (Baert and Steg 1977; McHugh et al. 1991). Simple cysts do not bare any consequences or associated risks except for a few occasions, where growing cysts lead to hypertension, compression of adjacent structures and possibly

obstruction of the collecting system (Churchill et al. 1975). In these rare cases, US-guided puncture/drainage with instillation of sclerosing agents (alcohol, tetracycline, Gelet et al. 1990; Reiner et al. 1992) may be an alternative to operative treatment or endoscopic surgery (Fig. 10.9d). In adults, cysts are much more common (up to 50%); therefore, the development of simple renal cysts may be seen as a normal ageing phenomenon (Baert and Steg 1977; Tada et al. 1983).

Acquired cysts can occur in post-traumatic and post-inflammatory (tuberculous, etc.) settings or spontaneously develop in kidney parenchyma during chronic renal failure and dialysis (Dunill et al. 1977; Leichter et al. 1988; Hogg 1992; see also Chap. 21). As in kidneys with acquired cysts such as in ESRD, malignancy may develop, even in the wall of such cysts, and they need to be monitored (Bretan et al. 1986; Levine 1992).

On US, simple cysts show clear, sharp margins and central anechoic fluid, with dorsal gain amplification. Some compression of the adjacent tissue may occur in big cysts (Fig. 10.9a). Usually they are detected incidentally; only rarely do they present with clinical signs of a renal mass (Siegel and McAlister 1980). However, if cysts are multilocal, multiloculated or bilateral, differentiation against ADPKD may be difficult (Davidson and Hartman 1994; Hoyer 1996b). IVU only demonstrates indirect signs of tissue or calyceal distortion (Fig. 10.9b). On CT, the localized spherical fluid accumulation has between 0 to 20 Hounsfield units (HU) and

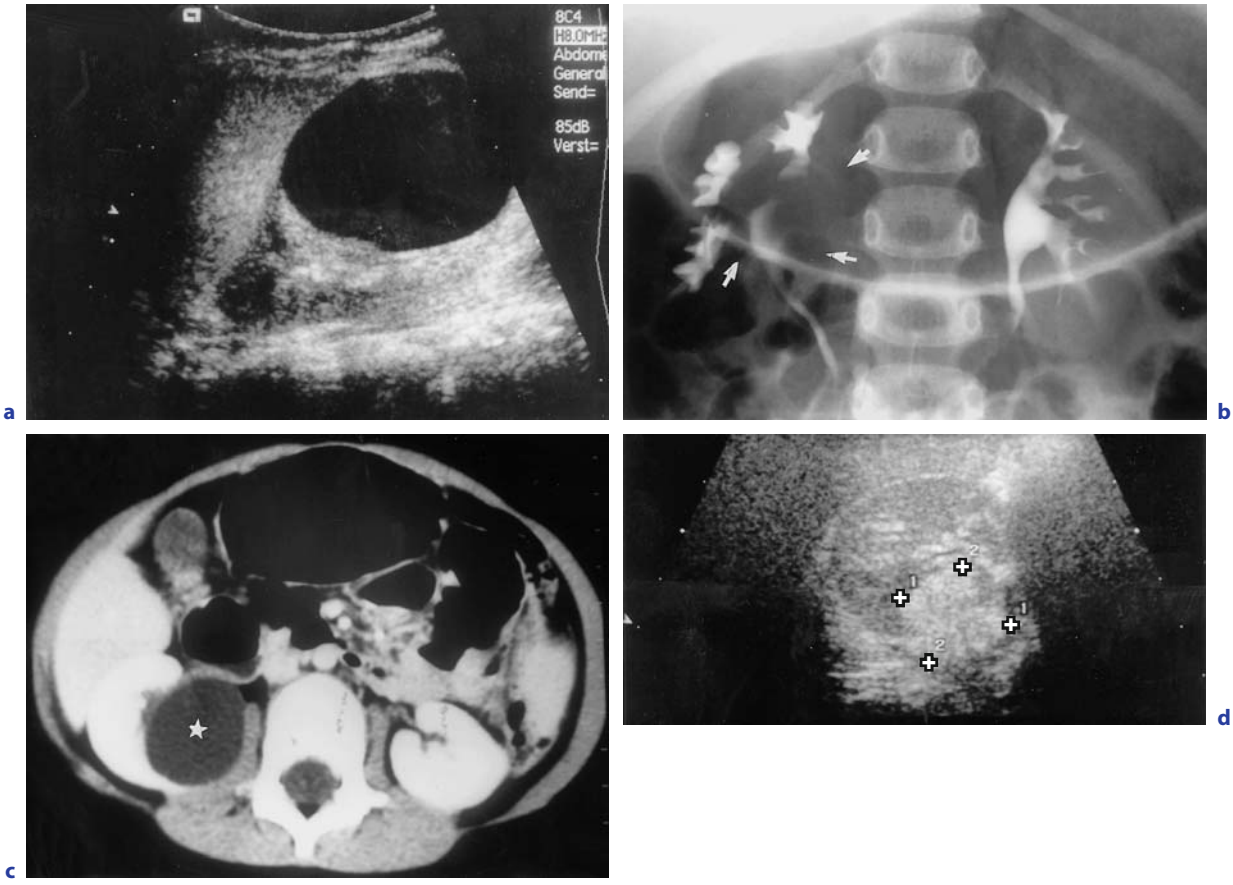


Fig. 10.9a–d. Simple renal cyst: **a** A radiologically simple, but big renal cyst of the lower pole of the left kidney on US with compression of parenchyma, in a longitudinal section, in a 4-year-old boy. **b** IVU of a central cyst of the right kidney demonstrates distortion and elongation the calyces by the cyst seen as an area of increased radiolucency (*arrows*). **c** Corresponding CT demonstrates the simple cyst (*asterisk*) with compression of the renal hilus/hilar structures in an 8-year-old girl who was consecutively operated on. **d** US of the postoperative situation with echogenic (= fatty) tissue in the former cyst (+ +) on a transverse section

sharp borders without any contrast enhancement (Bosniak 1986) (Fig. 10.9c). On MRI, the typical fluid signal without gadolinium enhancement is observed (Bilal and Brown 1997).

Differentiation against a calyceal cyst may be difficult on US. IVU, CT or MRI may be helpful for this differential diagnosis demonstrating a slightly delayed filling (of the cyst) with contrast material relative to the renal excretion into the collecting system. On CT and MR delayed scans are therefore necessary to avoid missing the contrast filling of such a calyceal cyst (Fig. 10.2a–f).

Acquired cysts look similar to normal cysts on US, except for post-traumatic and inflammatory cysts–the latter two may be multiloculated or septated, may show sedimentation and may demonstrate somewhat irregularly shaped margins (Hoyer 1996a,b; see also Figs. 10.6 and 10.10). These cysts must be treated like complicated renal cysts necessitating follow-up or–in cases without adequate history–CT/MRI. Definite differentiation against cystic renal tumors may sometimes only be achieved by (CT- or US-guided) biopsy, particularly in case of (secondary) hemorrhage into the cyst with consequently higher HU values on CT (Fig. 10.10) (see also Chap. 19 and 24).

Conclusion

Simple and acquired renal cysts are rare in infancy and childhood. US usually detects them as an incidental finding. Possible manifestation of a polycystic or dysplastic renal disease must be considered necessitating at least regular follow-up and nephro-urologic check-up.

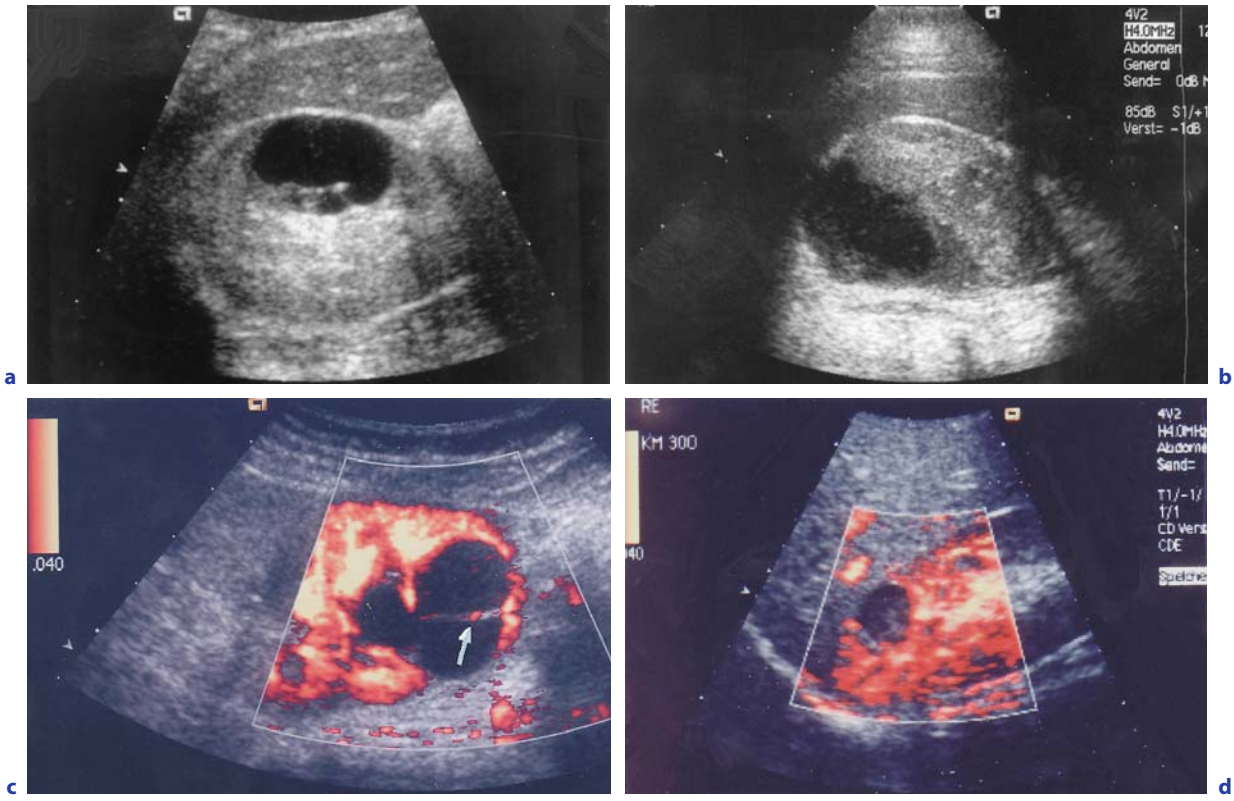


Fig. 10.10a–d. Complicated renal cyst: **a** US demonstration of a complicated cysts with septations and internal daughter cysts; **b** US demonstrates sedimentation and inhomogeneity within a complicated renal cyst after hemorrhage into a septic embolic renal infarction; **c** vascularization within a septum in a septated renal cyst, demonstrated by aCDS (*arrow*); **d** contrast-enhanced aCDS (Levovist) demonstrates lack of perfusion and – much better than initial grey scale US – delineates the small renal abscess (= complicated cyst with echogenic material, without perfusion) in the upper pole of a right kidney on this longitudinal section

10.5.5 Complicated Renal Cyst, Multiloculated Cyst and Cystic Renal Tumor

"Complicated cyst" is a term deriving from descriptive radiology. The exact definition varies depending on the imaging modality applied and the age of the patient. A complicated cyst is defined as a cystic lesion with some abnormalities, therefore not matching all criteria necessary for a simple cyst. These are: small size, clear and sharp margins, no echoes or contents in the clear fluid, no parenchymal part or inclusion (Figs. 10.2, 10.6). The radiological changes of such a complicated cyst may originate from secondary hemorrhage or sedimentation of proteins and of membrane cells. Calcifications may occur, or infection may be present (Fig. 10.10). Differentiation of these cysts, usually discovered by US, is essential and achieved in part by CT/MRI, in part in conjunction with clinical and laboratory findings (Table 10.4).

On CT, a renal cyst is usually categorized into three classes of suspicion using the Bosniak classification (Bosniak 1986): a single, sharp bordered cyst with clear fluid (= I°, = simple cyst); a slightly complicated cyst with either septations or complicated fluid (HU > 20), but without parenchymal structures and without contrast enhancement (= II°); and an already very suspicious cyst with additional nodular wall irregularities (= III°). A cystiform structure with contrast enhancement is a solid mass and should be handled as a renal mass (= IV°) (Bosniak 1991). As even CT can sometimes not rule out malignancy, only histology can precisely categorize the lesion in these situations and then is compulsory to find or rule out malignancy.

The multicystic nephroma and multiloculated cysts often pose a diagnostic problem; various classifications of these closely related entities have been suggested (Takeuchi et al. 1984; Theissig et al. 1986; Upadhyay and Neely 1989; Strand et al. 1989; Domizio and Risdon 1991; Wood 1992). Histology is not definite and is only used to rule out malignancy; often it demonstrates some amount of dysplasia, thus suggesting a form of cystic dysplasia with secondary changes similar to segmental MCDK or Ask-Upmark kidney. There are no clinical symptoms, although microscopic hematuria may occur, or an abdominal mass may be palpable.

In multiloculated cysts, US shows multiple, nonconfluent, cystic areas, with relatively sharp margins, and compression of the adjacent tissue creating an increased echogenicity of the less differentiated adjacent tissue that may be difficult to evaluate and differentiate even on multiphasic contrast-enhanced CT (Fig. 10.11). The remaining rest of the kidney has a normal parenchyma, yet may show disturbed perfusion due to compression; sometimes these changes are detected prenatally (Riccabona et al. 1999).

Various renal tumors may present as a cystic renal mass (Takeuchi et al. 1984; Fitch et al. 1985; Dodat et al. 1988; Babut et al. 1993; Hoyer 1996). Unclear or nodular margins, increased echogenicity of the content or areas of (atypically) perfused tissue and septations within the cystic mass, as well as (local) contrast enhancement on CT, may indicate a cystic renal tumor and necessitate further diagnostic workup. Sonographic methods such as CDS and aCDS as well as HI or the use of sonographic

Table 10.4. Differential diagnosis of a complicated renal cyst. This table lists the most important entities that have to be considered for differential diagnosis of complicated renal cysts

"Simple cyst" aggravated by:
• Secondary hemorrhage
• Sedimentation
• Inflammation
Acquired cysts
• Posttraumatic
• Inflammatory cyst (abscess, tuberculoma)
• Infected calyceal cyst with sedimentation and calculi
• Partially thrombosed vascular aneurysm
• Necrotic area after infarct, abscess
Cystic malformation:
• Segmental MCDK
• Dysplastic cysts (obstructive dysplasia)
• Multilocular cyst and multilocular cystic nephroma
Manifestation of congenital (poly-)cystic kidney disease (particularly ADPKD)
Cystic renal tumor
• Necrotic harmatoma, capillary hemangioma, vascular malformation, bleeding in an angiomyolipoma, and other cystic benigne renal tumors
• Cystic Wilm's tumor, cystic mesoblastic nephroma
• Cystic carcinoma and other, partially necrotic or cystic, malignant renal tumors

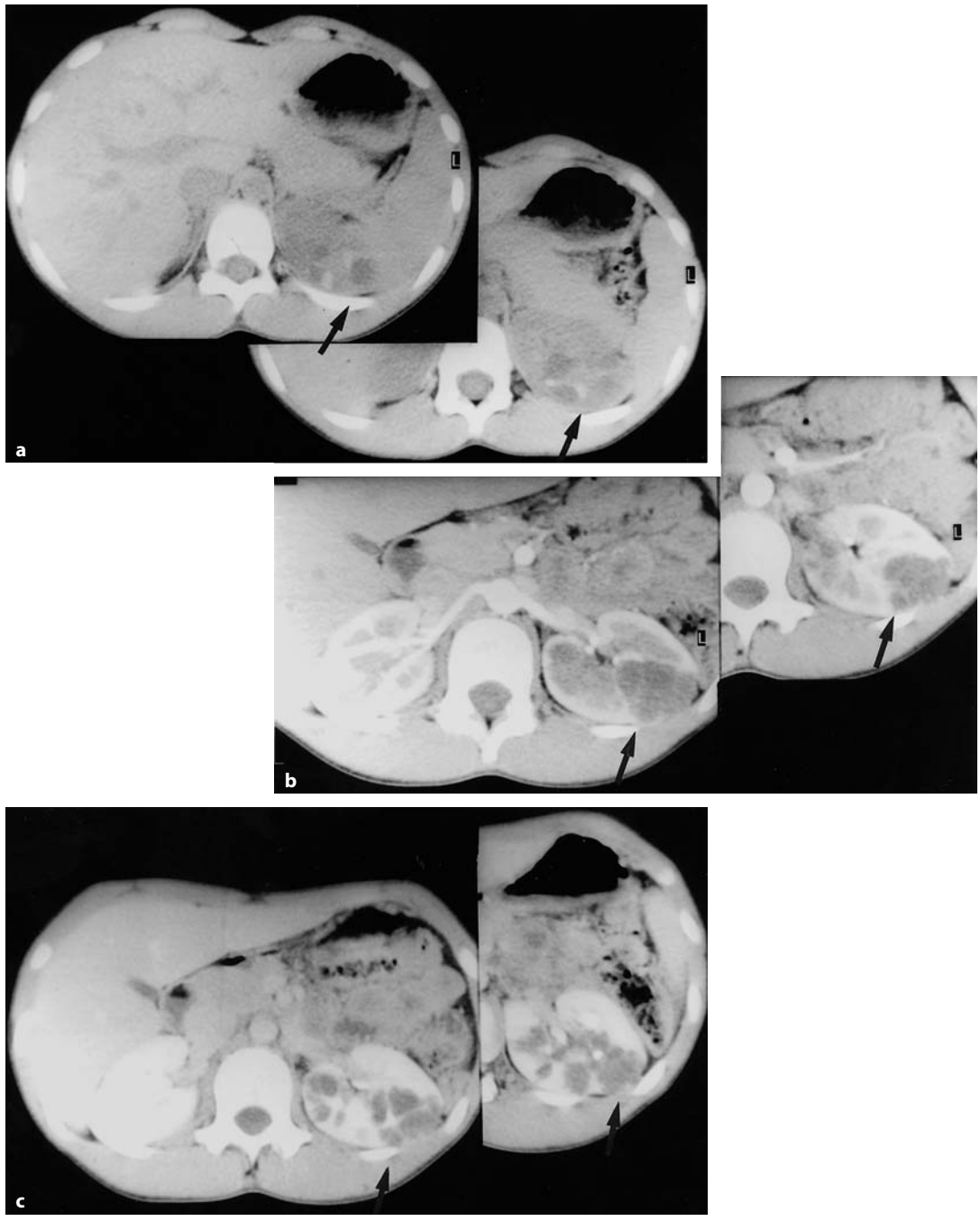


Fig. 10.11a–c. Cystic nephroma: traumatically complicated segmental cystic nephroma (*arrows*) on multiphasic contrast-enhanced CT

contrast-enhancing agents can be helpful already in the initial sonographic workup (Riccabona et al. 1999, 2000; Kim et al. 1999) (see also Fig. 10.10d). The important task of imaging is to help to differentiate other similar entities such as unilateral presentation of polycystic kidney disease, inflammation, cystic aneurysm of the renal artery, arteriovenous fistula or arteriovenous malformation, abscess formation or hemorrhage into a renal infarction. It is used to rule out progressive disease or malignancy. Differentiation of sonographically questionable findings usually is addressed by performing additional

dynamic contrast-enhanced MRI. In modern pediatric imaging, multiphasic contrast-enhanced helical CT is used more reluctantly due to the relatively high radiation exposure. US is then again used for monitoring these patients. In cases with equivocal findings, US- or CT-guided biopsy and puncture/drainage may be of diagnostic value; sometimes primary surgical intervention, open biopsy and removal become necessary (see Chap. 19 and 26).

Tumors have to be recognized and imaged/treated appropriately. Many tumor entities can present as a cystic renal tumor; the histology ranges from benign renal neoplasm to cystic Wilm's tumor, cystic mesoblastic nephroma and cystic renal adenocarcinoma (Theissig et al. 1986; Babut et al. 1993; Upadhyay and Neely 1989). The detailed and definite diagnosis is often only made histologically as imaging features may not be characteristic in the individual case (see Chap. 24).

Conclusion

In pediatric patients, renal cysts are generally detected by US. If they look like complicated cysts and do not match any entity of congenital polycystic renal disease, they should be studied by additional imaging such as CT or MRI (for complicated cysts and suspected malignancy or for differentiation of a calyceal diverticula). If there are still equivocal findings, they should be monitored or–particularly when showing growth or atypically vascularized areas–should undergo biopsy/operation.

narrow the list of differential diagnoses (Fig. 10.6); still suspicion of chronic glomerulonephritis with ESRD or of a renal cystic tumor/malignancy may necessitate US- or CT-guided biopsy.

Usually US and VCU are sufficient as a first imaging step; only sometimes CT and MRI or even angiography may become necessary. IVU has been replaced by MRI; only rarely it is still used for differential diagnosis – particularly if MRU is not available. New findings in molecular genetics will further improve non-imaging diagnostic capabilities, but variations in expression of the same genetic condition will still necessitate individual imaging in assessing the state of a disease. Furthermore, rapid improvement in MRI techniques will probably more and more entitle these entities to MR diagnosis in the pre- and postnatal setting. Once the diagnosis is established, the task of imaging is to help monitor these patients – either the progression or resolution of disease, or the state of the contralateral kidney. Although no curative treatment exists for many cystic renal disorders to date, modern treatment and supportive means help avoid complications in most children, thus enabling adequate growth and delayed onset of renal insufficiency, and in ESRD improving the chances for dialysis and renal transplantation.

Conclusion

As the "simple renal cyst" is–unlike in the adult population–rather uncommon in pediatric cystic kidney disease, a thorough workup and follow-up of even incidental findings are compulsory.

10.6 Summary

Renal hypoplasia, dysplasia and cystic renal diseases comprise many entities that sometimes are diagnostically challenging. However, there is increasing evidence that on a cellular and genetic level many or most of them have a common pathogenetic pathway centered at the cilium-centrosome complex. With the help of the clinical information, the onset and patient age, the family history and the genetic results, diagnosis can be made in the majority of cases without invasive procedures such as renal biopsy. The location and size, distribution and onset of cysts and parenchymal abnormalities can help to

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Vesicoureteric Reflux

11

Fred E. Avni, Khalid Ismaïli, Marie Cassart, Nash Damry, Michelle Hall and Thierry Schurmans

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F. E. Avni, MD, PhD
M. Cassart MD, PhD
Department of Medical Imaging, Erasme Hospital, 808 Route de Lennik, 1070 Brussels, Belgium
K. Ismaili, MD, PhD
M. Hall, MD
T. Schurmans, MD
Department of Nephrology, Children's Hospital Queen Fabiola, Av JJ Crocq 15, 1020 Brussels, Belgium
N. Damry, MD
Department of Medical Imaging, Children's Hospital Queen Fabiola, Av JJ Crocq 15, 1020 Brussels, Belgium

11.1 Introduction

Vesicoureteric reflux (VUR) is considered a significant factor for the development of progressive renal damage in the presence of urinary tract infection (UTI). Optimizing its detection is therefore of utmost importance for the identification of patients at risk. This necessitates a good knowledge of the pathogenesis, the circumstances of occurrence, and the natural history of the disease. In addition, the techniques used for demonstrating VUR must be used at their best and for good purposes (Mouriquand 1995; Garin et al. 1998; Hellström and Jacobsson 1999; Jakobsson et al.1999; Ismaili 2006).

VUR results from the lack of a normal valve-like mechanism of the vesicoureteric orifice (Thompson et al. 1994). Many factors contribute to the competence of the vesicoureteral orifice, e.g., the location of the orifice, normal renal function with downhill diuresis, and good hydration of the patient. Reflux-

ing ureters have a larger diameter and a more lateral or caudal position. Furthermore, the competence of the vesicoureteric junction is also influenced by the length of the intravesical segment of the ureter: a shorter distance is likely to result in VUR. Primary VUR occurs mainly in neonates and in infants, whereas secondary VUR results from or is associated with various uronephropathies. It occurs more often in school-age girls. The exact prevalence of VUR in healthy children is unknown, but apparently is between 1% and 2% (Verrier-Jones 1999)

11.2 Diagnosing VUR

11.2.1 Voiding Cystourethrography

To date, voiding cystourethrography (VCU) is the preferred method for the initial diagnosis of VUR in children with UTI or in the workup of an antenatal diagnosis of fetal uropathy (Lebowitz 1986; Lebowitz 1992; Blickman et al. 1985; Fernbach et al. 2000). It is the only method that allows precise grading of VUR and the detection of intrarenal reflux. Grading of reflux is based on the work of the International Reflux Study Group and includes VUR from grade I–V (Table 11.1) (Figs. 11.1–11.6) (Lebowitz et al. 1985). VUR of higher grades is associated with a greater degree of dysplasia/reflux nephropathy. Also, VUR from higher grades tends to resolve more slowly than milder grades of VUR. A special type of VUR, intrarenal reflux, occurs more often at the upper and lower poles of the kidney (Fig. 11.4). It is related to the particular anatomy of the medulla-calyx complex in these poles that renders reflux more prone to occur and scars more likely to develop (Ransley and Risdon 1975; Rolleston et al. 1974).

VCU is also useful because it provides a simultaneous evaluation of the bladder and urethra. The demonstration of voiding dysfunction, bladder wall thickening, or diverticula may help to characterize and understand VUR (Fotter et al. 1986; Koff 1992). Urethral obstruction, whatever its origin, may also be associated with secondary VUR (Fig. 11.7).

The drawbacks of the method are that the procedure is invasive, necessitating bladder catheterization or puncture, and that it is an irradiating technique. Fortunately, the newer pulsed fluoroscopy cystographic technique reduces the radiation dose as low as radionuclide studies (ovarian dose 0.017–0.052 mGy, mean dose: 0.029 mGy) (Kleinman et al. 1994; Hernandez and Goodsitt 1996).

Table 11.1. VUR grading

Grade	Findings
Grade I	VUR limited to the ureter
Grade II	VUR up the renal cavities without dilatation
Grade III	VUR into the renal cavities inducing dilatation and eversion of the calyces
Grade IV	Moderate to marked dilatation of the ureter and pyelocalyceal system
Grade V	Marked tortuosity and dilatation of the ureter and pyelocalyceal system

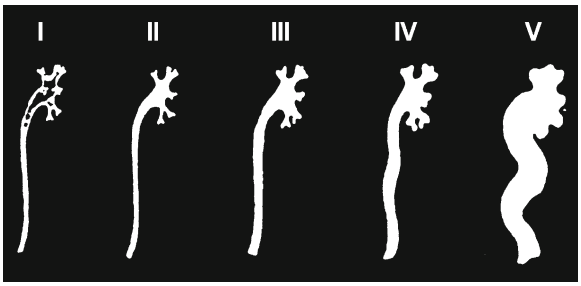


Fig. 11.1. VUR grading

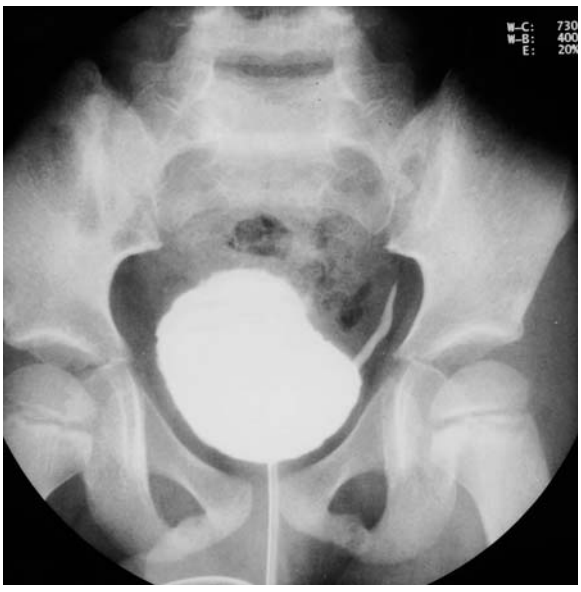


Fig. 11.2. VCU: left VUR grade I

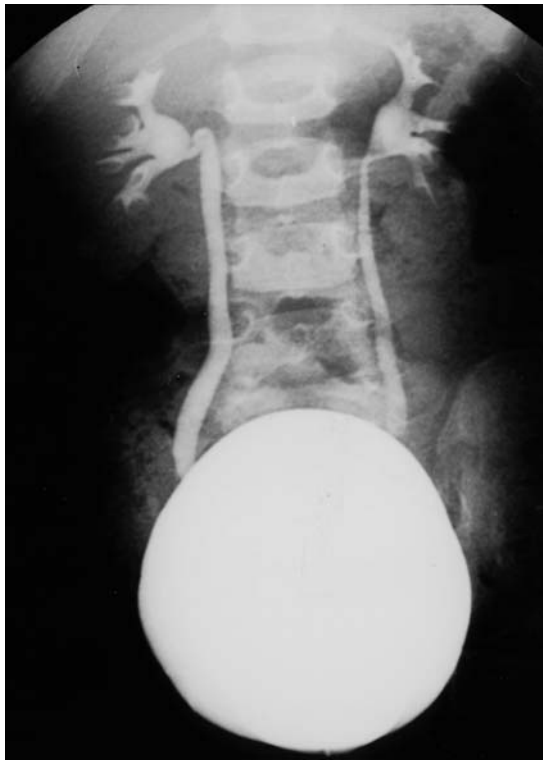


Fig. 11.3. VCU: bilateral VUR grade II

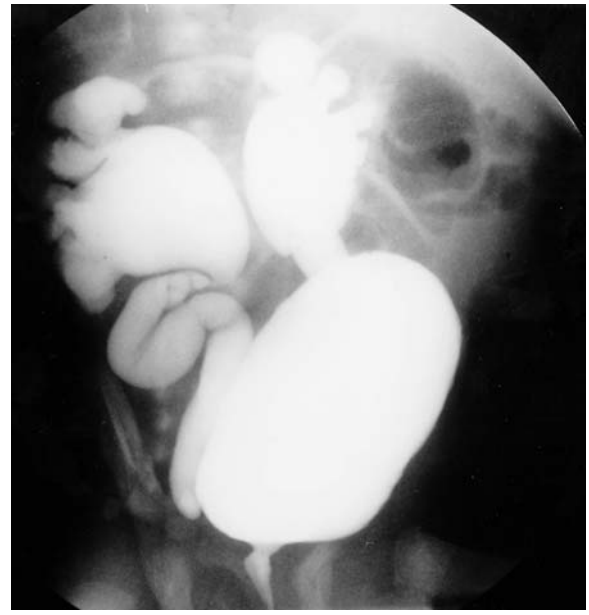


Fig. 11.5. VCU: bilateral grade IV VUR

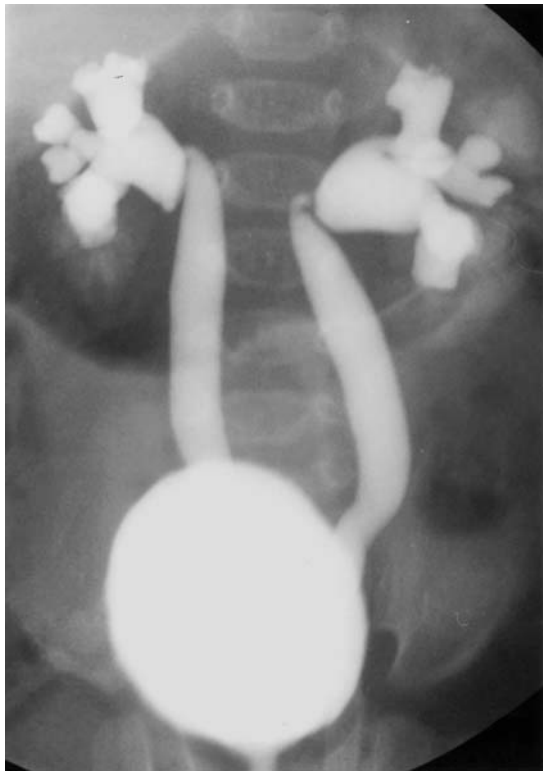


Fig. 11.4. VCU: bilateral grade III with intrarenal reflux

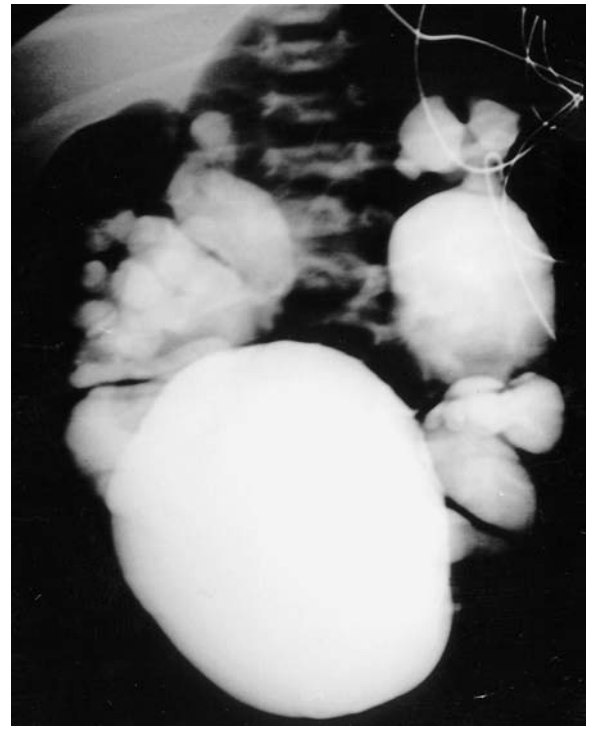


Fig. 11.6. VCU: bilateral grade V VUR

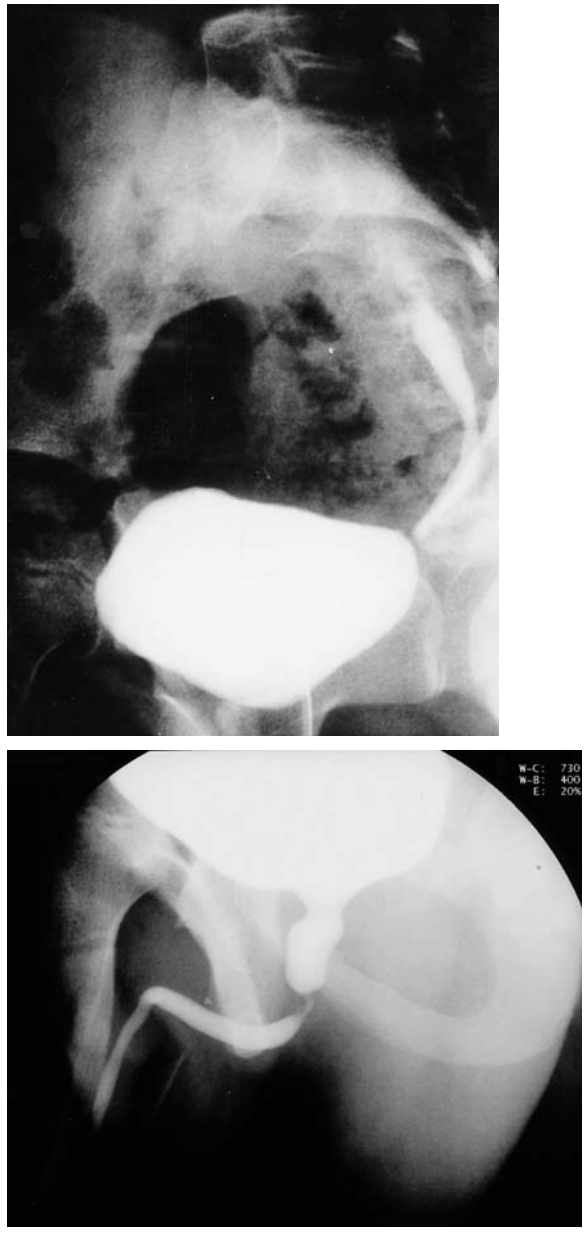


Fig. 11.7. a Left grade I VUR and **b** posterior urethral valves seen during the voiding phase

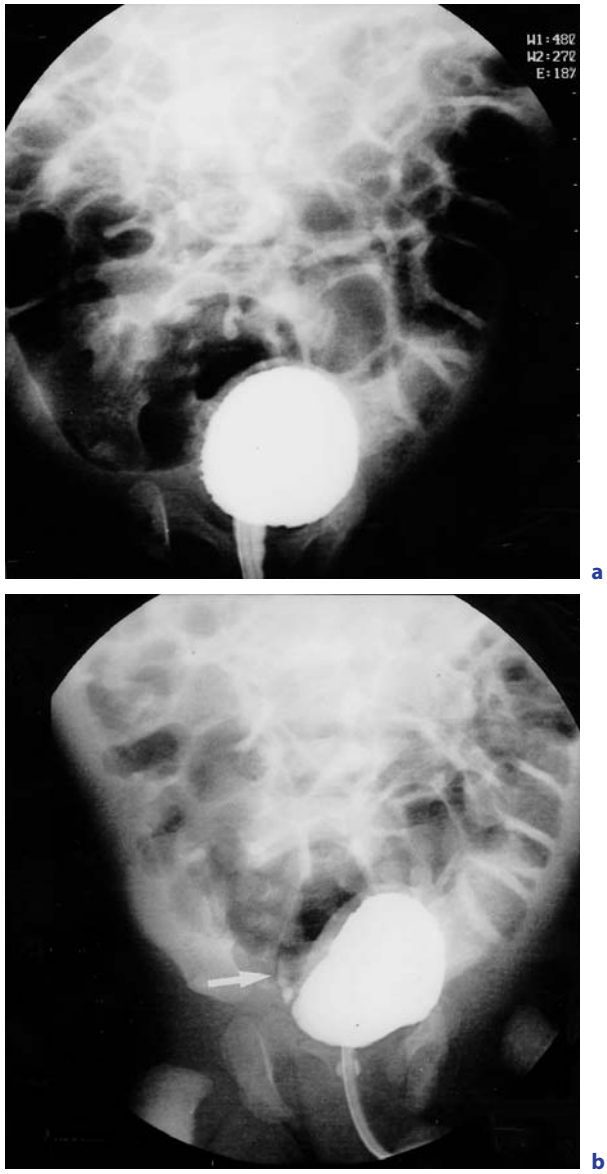


Fig. 11.8a,b. Cyclic VCU. Right grade I VUR (*arrow*) is detected on the second filling. **a** First voiding. **b** Second filling

Another limitation of the technique is that conventional VCU underestimates the occurrence and degree of VUR (Jécquier 1989). More recently, cyclic filling of the bladder has been shown to improve the detection rate of VUR by 3% in a second and by 4% in a third filling. This is of particular interest in neonates or in other patients with low vesicle capacity (Fig. 11.8) (Paltiel et al. 1992; Gelfand et al. 1999).

Pitfalls of VCU include underestimation of the degree of VUR in case of reflux into an already dilated and obstructed ureter (refluxing megaureter) (Blickman and Lebowitz 1984), or when VUR and ureteropyelic obstruction coexist (Lebowitz and Blickman 1983; Bomalaski et al. 1997); due to the obstruction, the refluxing urine may not reach the pyelocalyceal system (see below). Finally, reflux of contrast within the vagina during the micturi-

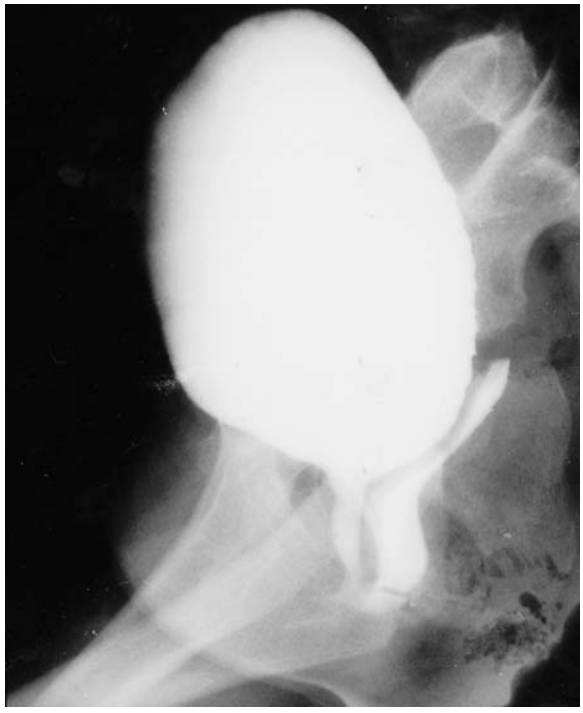
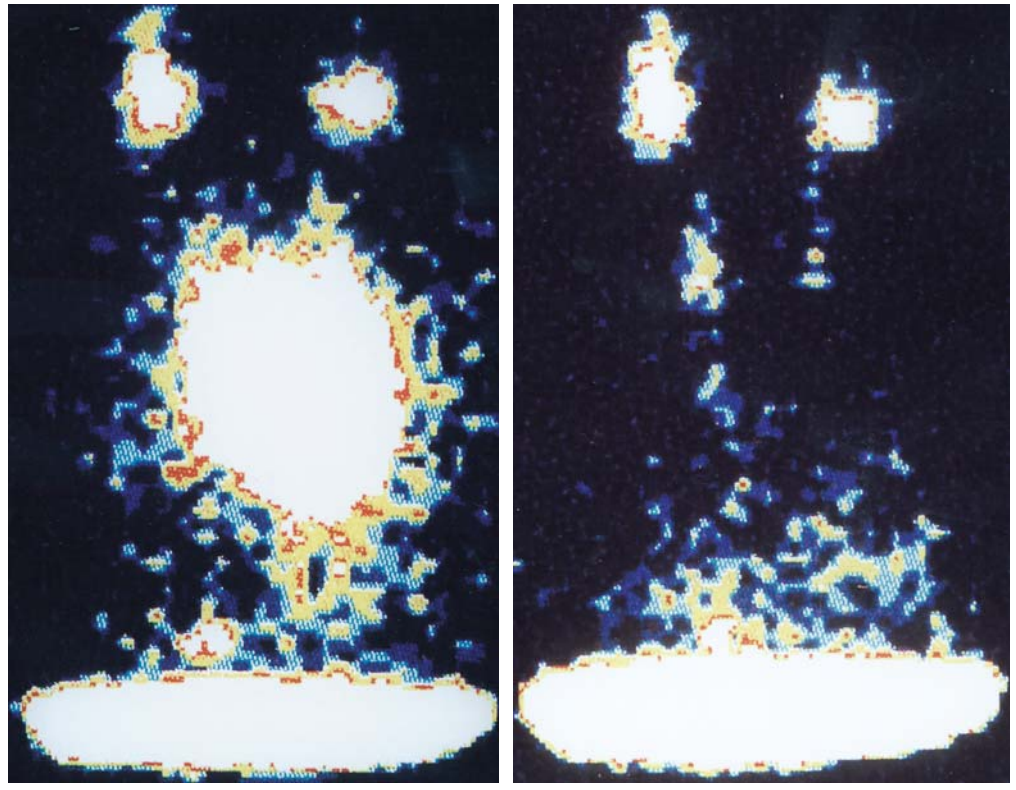


Fig. 11.9. VCU (voiding phase): retrograde filling of the vagina

tion phase of the VCU is commonly observed and should not be regarded as a sign of ectopic insertion or of fistula (Fig. 11.9) (Lebowitz and Avni 1980) unless the refluxed contrast fills a distended vagina or unless there is no clear separation between the vagina and urethra. In such cases a variant of urogenital sinus must be suspected (Lebowitz and Avni 1980; Marshall 1979).

11.2.2 Direct Radionuclide Cystography

Direct radionuclide cystography has good and somewhat better results than conventional VCU for the demonstration of VUR at lesser irradiation levels (Fig. 11.10). The longer duration of the examination allows better monitoring and a higher rate of VUR detection. The technique does not provide information about the bladder or the urethra. It misses intrarenal reflux and may miss grade-I VUR (Chapman et al. 1988; Mozley et al. 1994). Its best indications are the follow-up of patients with previously known VUR and the screening of siblings of patients with



a b

Fig. 11.10a,b. Direct isotopic cystogram: bilateral VUR. **a** Filled bladder. **b** Postvoiding

VUR: VUR may be present in 25%–45% of these siblings (Noe 1992; Noe 1995; Wan et al. 1996; Piepz and Ham 2006).

11.2.3 Indirect Radionuclide Cystography

The isotopic tracer is injected intravenously and the presence of VUR is evaluated in the late phase of this examination, after micturition. This technique requires good cooperation from the child and is not suitable for children under the age of 5. It has the same drawbacks as direct radionuclide cystography; its only advantage is that it does not require bladder catheterization (Piepz 2006).

11.2.4 Ultrasound

Ultrasound (US) has gained popularity for the evaluation of the urinary tract in children. It is easily performed and, since it is a non-irradiating technique, it is well accepted by the parents. Because the patients are small, high-resolution transducers can be used and the urinary tract is nicely displayed.

The role of the technique for screening patients at risk of having VUR has been very controversial. Many authors suggest that conventional US in no way replaces VCU in patients at risk; for these authors, US detects only 25%–45% of patients with VUR (Blane et al. 1993; DiPietro et al. 1997; Zerin et al. 1993). Unfortunately most of the studies rely on the presence of urinary tract dilatation as the only sign of VUR; consequently, they underestimate the value of US. Many other US signs have been described in association with VUR (Table 11.2) and should be looked for (Bergius et al. 1990; Avni et al. 1997; Hiraoka et al. 1994; Hiraoka et al. 1997; Tsai et al. 1998). Renal pelvis dilatation is certainly an important sign of VUR, but the problem is to determine the degree of dilatation that should be considered abnormal: 7 mm in the newborn and 10 mm in older children seems to be a good cut-off for diagnosing dilatation (Stocks et al. 1996; Marra et al. 1994; Walsh and Dubbins1996). The detection of calyceal or ureteral dilatation is an important supplementary finding, and both have been shown to be associated with VUR (Newell et al. 1990). A varying dilatation of the pelvis is suggestive of VUR (Fig. 11.11a, b). Lack of corticomedullary differentiation is also commonly associated with VUR. This sign, as well as an overall increased cortical hyperechogenicity, could result from high intravesical pressure and ischemic damage, which lead to glomerular ischemic damage and renal dysplasia (Fig. 11.11c) (Hulbert et al. 1992; Steinhardt et al. 1988). Small kidneys or renal cortical thinning, features of renal dysplasia, may also be associated with VUR and with high pressure damage already in utero (Sanders et al. 1988; Najmaldin et al. 1990a; Gobet et al. 1999). Another interesting US sign that can be associated with VUR is pelvic and ureteral wall thickening (Fig. 11.12).The sign is not specific as it can be encountered in cases of urinary tract infection, renal transplant rejection, or in postoperative ureteropelvic junction (UPJ) obstruction. Yet once the other etiologies such as postoperative status are excluded, a VCU seems justified (Avni et al. 1988; Alton et al. 1992; Robben et al. 1999). Using all the US data, one should be able to detect 65%–85% of patients with VUR and particularly the high-grade cases (III–V) (Avni et al. 1997; Tsai et al. 1998; Hiraoka et al. 1997).

Table 11.2. US signs that can be associated with VUR

- Renal pelvic dilatation
- Variable dilatation
- Ureteral dilatation
- Calyceal dilatation
- Loss of CMD
- Signs of dysplasia
- Pelvic and ureteral wall thickening
- Hyperechoic medulla (Diard et al. 1987)
- Color Doppler turbulence in dilated ureters
- Enlarged bladder

Color Doppler US has been proposed as an adjunct to conventional US for the detection of VUR. First, the visualization of the ureteric jet by means of color Doppler US was thought to mean there was no VUR (Salih et al. 1994; Jecquier et al. 1990). Although it might be interesting to localize the ureteric orifices (Strehlau et al. 1997), other studies did not confirm this hypothesis. The use of color Doppler for the demonstration of VUR in dilated ureters has also been reported: with VUR, the refluxing urine displays different colors related to the variable direction of flow. Unfortunately this can only be obtained when the ureters are dilated (Matsumo et al. 1996).

Over the past few years, several authors have suggested replacing radiological or radionuclide cys-

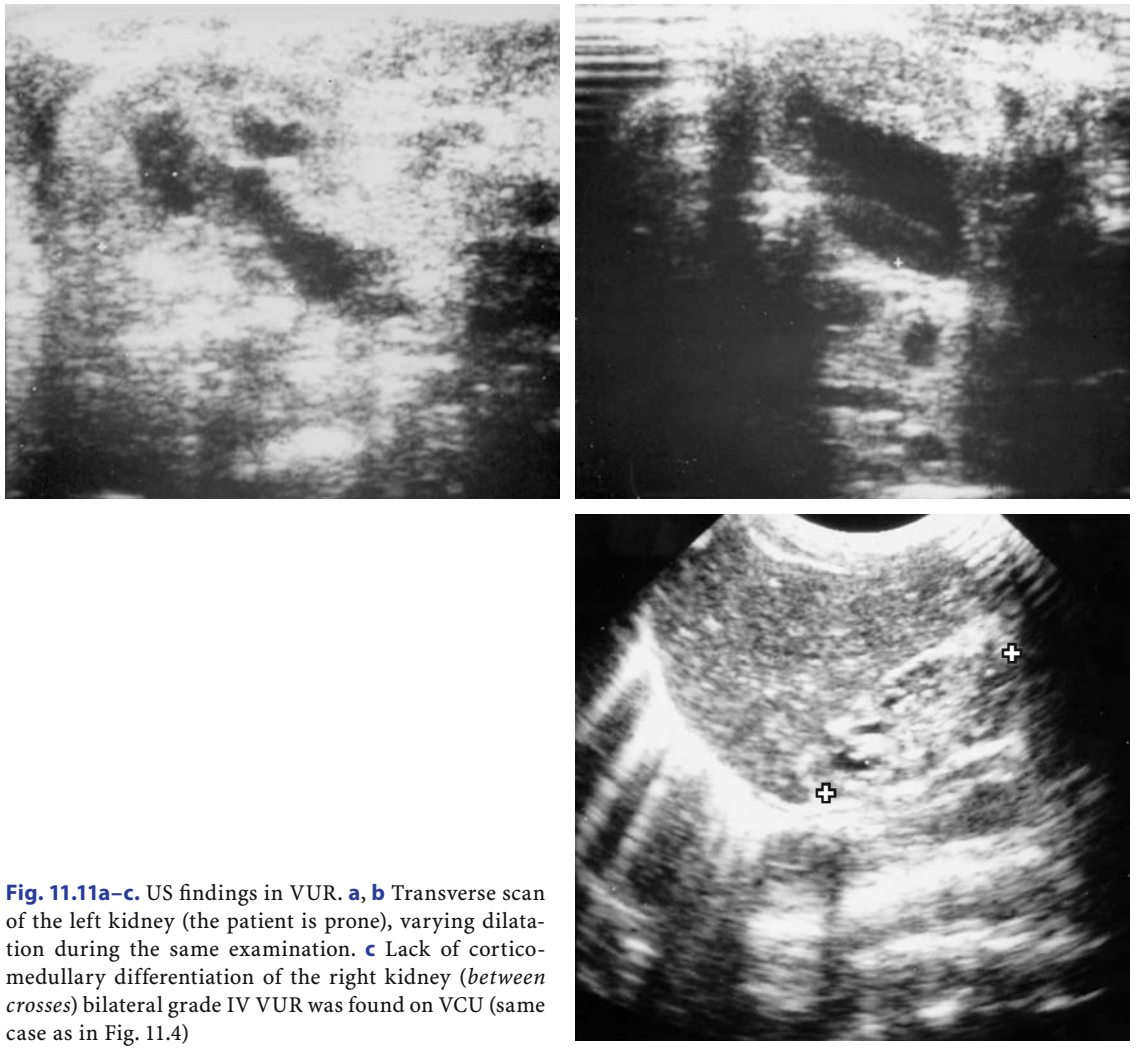


Fig. 11.11a–c. US findings in VUR. **a**, **b** Transverse scan of the left kidney (the patient is prone), varying dilatation during the same examination. **c** Lack of corticomedullary differentiation of the right kidney (*between crosses*) bilateral grade IV VUR was found on VCU (same case as in Fig. 11.4)

tography with US cystography. For this purpose, air or fluids with echogenic bubbles are introduced into the bladder. US of the ureters and kidneys is performed during and after introducing the echogenic bubbles into the bladder. In cases of VUR, echogenic fluid is demonstrated within the collecting systems (Fig. 11.13). The detection rate of VUR using this method is very satisfactory, especially compared to conventional (noncyclic) VCU. The advantage of the method is that it requires no irradiation; the disadvantage is that catheterization is still needed and that there is no or little information on the bladder and the urethra. It is also dependent upon the national acceptance of the contrast used (Alzen et al. 1994; Hanbury et al. 1990; Atala et al. 1993; Darge et al. 1998; Mentzel et al. 1999; Riccabora 2002; Vassiou 2004; Darge et al. 2005).

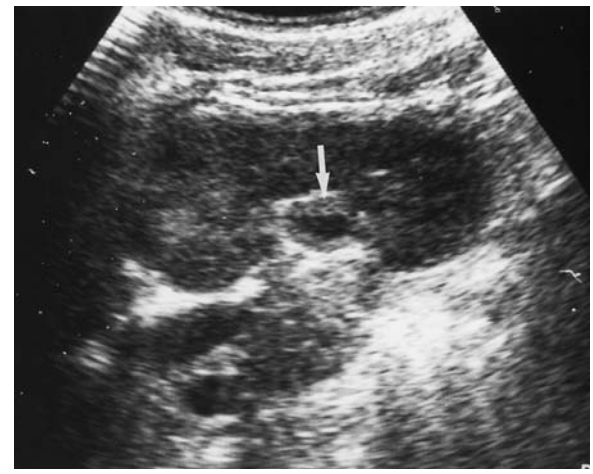


Fig. 11.12. US findings in VUR. Pelvic wall thickening (*arrow*) in case of grade III VUR

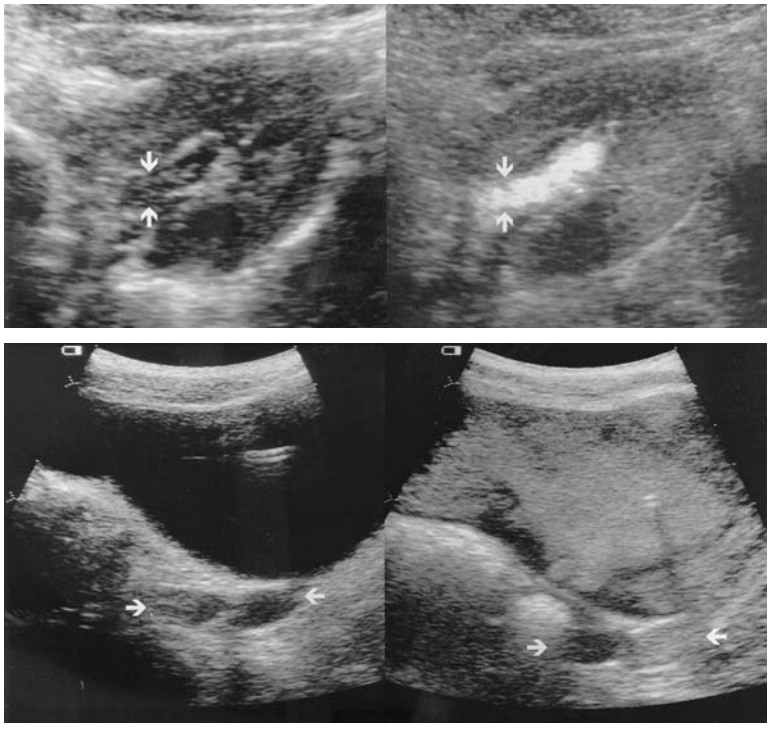


Fig. 11.13a,b. VUR on sonographic cystogram (courtesy of K. Darge). **a** Sagittal scan of the bladder before and after contrast introduction through a catheter; the *arrows* point to the dilated ureter. Echogenic bubbles reflux within the ureter. **b** Transverse scan of the right kidney before and after contrast introduction showing reflux

11.2.5 Intravenous Urography

Intravenous urography (IVU) should no longer be performed. IVU greatly underestimates the occurrence and degree of VUR. However, on the IVU, several features may suggest VUR in patients examined for other urological reasons: the discovery of a small irregular kidney, striations on the pelvis and ureter walls, dilated and clubbed pyelocalyceal system, and dilatation of the ureters without obstruction (Fig. 11.14). When such findings are encountered, a VCU should be performed in order to confirm the presence of VUR (Lebowitz and Avni 1980; Ginalski et al. 1985). It is worth noting that massive VUR occurring during an IVU may fill the renal cavities of a nonfunctioning kidney and mimic function. Therefore, a catheter should be introduced into the bladder prior to an IVU performed in a patient with known high-grade VUR (Lebowitz and Avni 1980).

Conclusion

VCU, using the newest pulsed fluoroscopy technique, is the most suitable technique for characterizing VUR. US, with all its potential applications, should be utilized as a screening method in patients at risk.

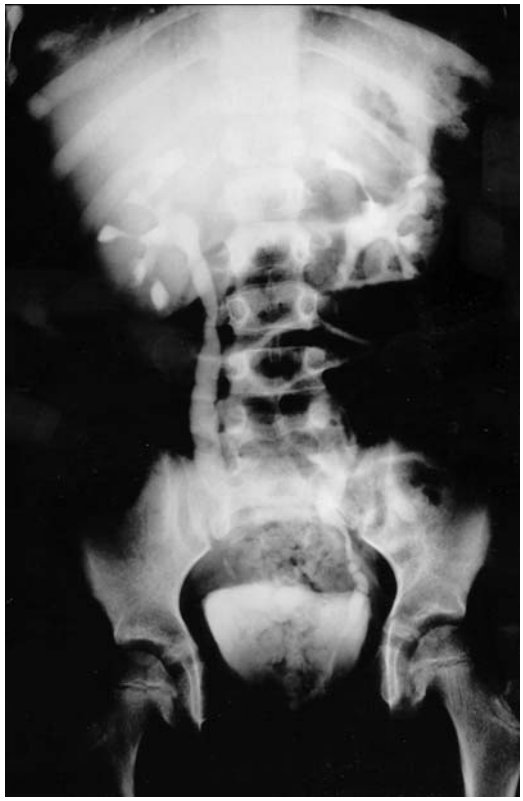


Fig. 11.14. Intravenous urography in a case of bilateral reflux nephropathy showing thinned parenchyma and clubbed calices

11.3 Detection of VUR–Circumstances

11.3.1 Postnatal Workup of Antenatally Diagnosed Fetal Uropathies

Antenatal diagnosis of fetal anomalies by obstetrical US has led to the detection of an increasing number of fetal uropathies (Gunn et al. 1995) (see also Chap. 13). The attitude towards antenatally diagnosed uropathy has now been standardized (see Chap. 13), leading to increased detection of VUR (Avni et al. 1998; Zerin et al. 1993; Van Eerde 2007; Lee 2006; Ismaili 2006), and VCU is performed routinely in the neonatal period.

Primary VUR is demonstrated more and more frequently and has become one of the leading causes of neonatal urinary tract dilatation (Zerin et al. 1993). In utero, making a precise diagnosis of VUR is difficult, unless variability of the pelvic dilatation is observed during the obstetrical US examination (Hiraoke et al. 1994; Walsh and Dubbins 1996). Another circumstance under which VUR is directly diagnosed is the so-called megacystis-megaureter association (see below).

Perinatal VUR differs notably from VUR detected in older children, which occurs mainly in girls. Among patients with perinatal VUR, two groups are encountered: a group with mild VUR and usually normally functioning kidneys and a second group with severe VUR with massively dilated ureters, which is associated with kidney damage at birth (the so-called fetal reflux nephropathy). This has led to the CA KUT concept or syndrome (congenital anomalies of the kidneys and urinary tract) describing the association between renal dysplasia and hypoplasia with urinary tract malformation (Fig. 11.15) (Najmaldin et al. 1990a; Anderson and Rickwood 1991; Yeung et al. 1997; Mana 2004; Ismaili 2006). The first type of VUR is often an incidental finding during neonatal VCU; it is encountered equally in girls and boys. The second most severe type is almost exclusively detected in baby boys already during fetal life, and this particularity has led to a theory associating this frequent occurrence of severe VUR in baby boys with a transient fetal bladder outlet obstruction (Avni and Schulman 1996; Sillen 1999a,1999b). Whatever its grade, VUR in children is prone to resolve more spontaneously than VUR detected in older patients.

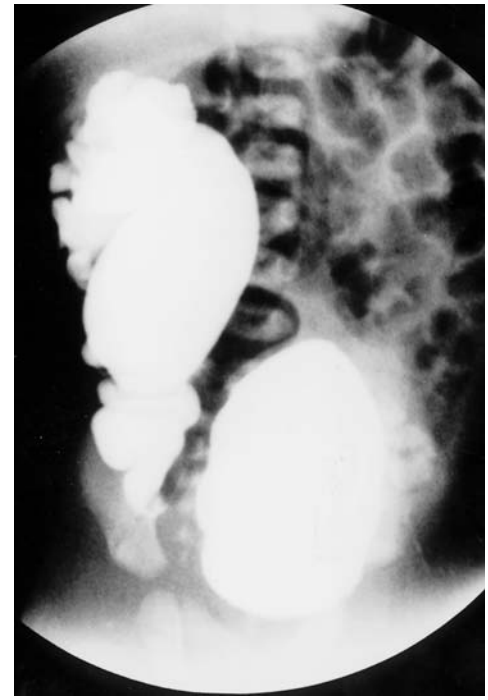


Fig. 11.15. Massive right grade V VUR in a baby boy. The renal function was already impaired

11.3.2 Nonneurogenic Bladder-Sphincter Dysfunction

Voiding dysfunction is another circumstance in which VUR is often detected (see Chap. 11). Voiding dysfunction is a frequent disorder mostly occurring in school-age girls. Most recent theories hypothesize that in such patients, VUR is not primary, but secondary to the bladder-sphincter dysfunction. Treatment of this type of VUR is unsuccessful unless the dysfunction is treated as well (Seruca 1989; Snodgrass 1998; Sillen 1999a; Nielsen 1989).

Urodynamic studies coupled to a VCU are mandatory for the proper management of severely affected patients (Fotter et al. 1986; Sillen 1999a; Pfister 1999). On VCU, the bladder wall appears trabeculated and thickened, diverticula may be present, the urethra is large (spinning top urethra), and the bladder neck appears tightened (Baunin 1993).

11.3.3 Urinary Tract Infection

The relation between VUR and UTI has been largely debated (Gordon 1995). It seems that UTI does

not cause VUR and that VUR does not cause UTI (Shanon and Feldman 1990). Yet the association between both entities is too frequent to be ignored. In cases of UTI, a VCU should be performed systematically in order to detect associated VUR (which occurs in about 40% of cases), whereas in VUR, a prophylactic chemotherapy should be undertaken in order to prevent superimposed infection. Similarly, it seems reasonable to perform VCU under prophylactic chemotherapy (Greenfield et al. 1997; Bollgren 1999; Sargent and Stringer 1995) (see Chap. 15).

11.3.4 Familial VUR

As mentioned above, the frequent familial occurrence of VUR justifies the use of a screening procedure in order to detect affected siblings (40%–65% will be affected). For this purpose, direct radionuclide cystogram and cystosonography appear to be the most appropriate techniques (Heale 1997; Noe et al. 1992).

11.3.5 Secondary VUR

As mentioned above, VUR may be associated with voiding dysfunction; furthermore, VUR is frequently associated with bladder outlet obstruction whatever its origin, or with neurogenic bladder disorders (Figs. 11.16, 11.17). Therefore, a VCU is the best-adapted examination for evaluating these patients; furthermore, analysis of the micturition phase and evaluation of the urethra must be part of every VCU (Van Gool 1995).

Conclusion

VUR is mainly detected during the workup of congenital uropathies, UTI, or bladder dysfunction.

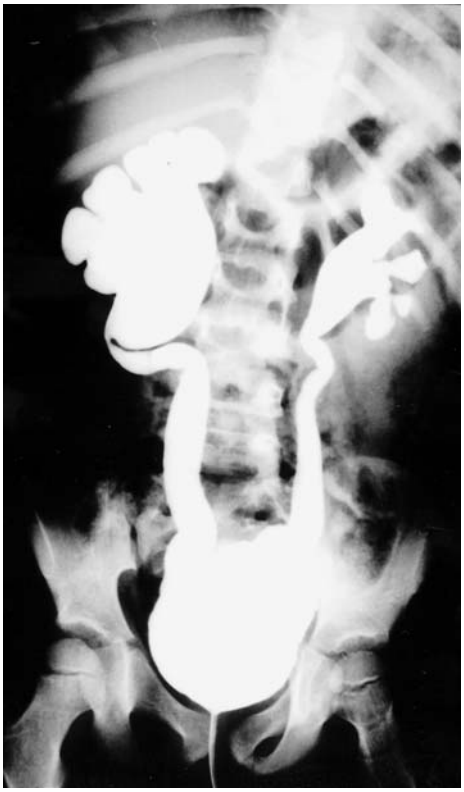


Fig. 11.16. Bilateral grade III VUR in a 12-year-old boy with neurogenic bladder on the IVU

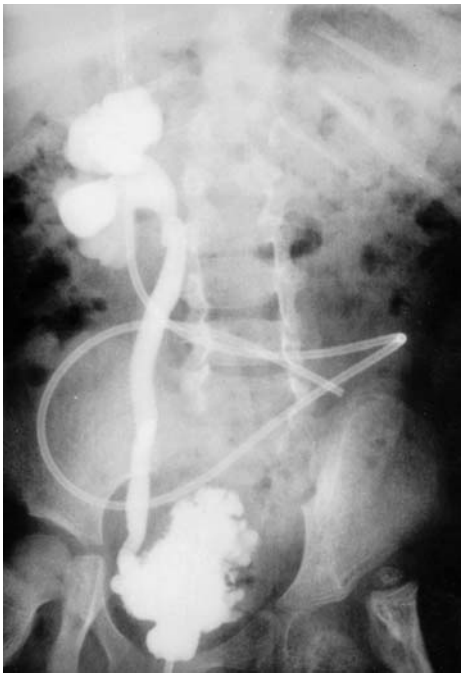


Fig. 11.17. Right grade III–IV VUR in 8-year-old patient with neurogenic bladder and ventriculoperitoneal shunt

11.4 Particular Presentations of VUR

11.4.1 Reflux and UPJ Obstruction

The coexistence of VUR and ureteropelvic junction (UPJ) obstruction occurs in 10%–14% of patients undergoing surgery for UPJ and in 1% of patients in whom VUR is detected (Fig. 11.18). In these patients proper medical management will depend upon the accuracy of the evaluation. Imaging has to differentiate between a true UPJ obstruction associated with VUR (in which case, pyeloplasty should be performed first) and a pseudo-UPJ secondary to severe VUR, in which case ureteral reimplantation should be performed first (Lebowitz and Blickman 1983; Maizels et al. 1984; Hollowel et al. 1989; Bomalaski 1997). On the VCU, the VUR may hardly reach the dilated pyelocalyceal system. In case of complete obstruction, no urine will opacify the collecting system, whereas in pseudo-obstruction, some contrast will reach the dilated pyelocalyceal system (Fig. 11.19). In such patients, IVU and MR urography at best shows the obstructed UPJ. On IVU, upright post-voiding film may help to determine the degree of obstruction at the UPJ (Lebowitz and Avni 1980).

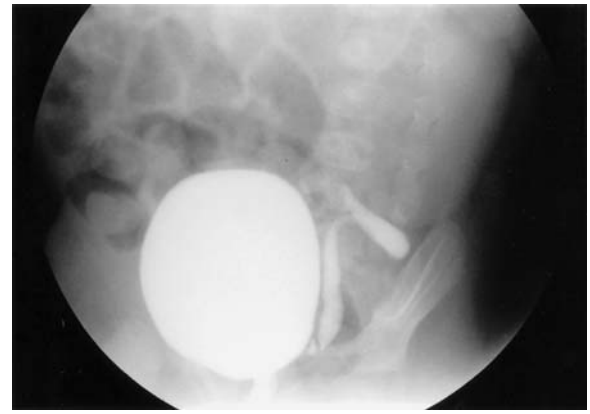
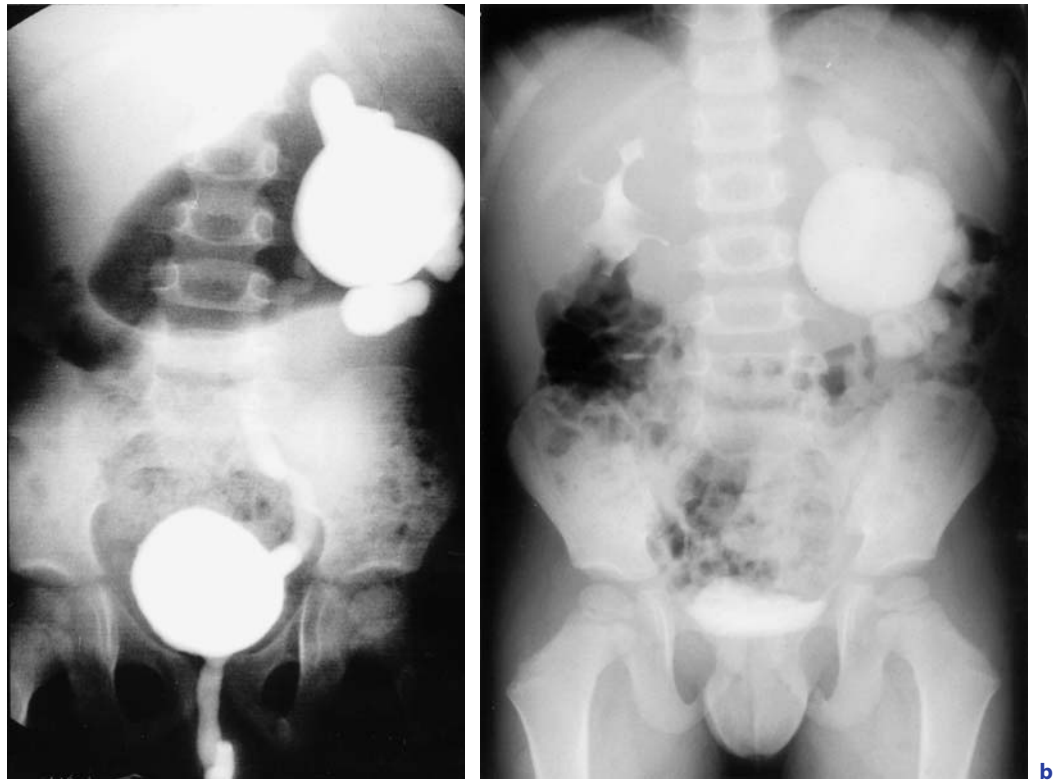


Fig. 11.19. Neonatal left UPJ obstruction and VUR (antenatal diagnosis of UPJ obstruction). The refluxed urine barely reaches the dilated pyelocalyceal system due to the severe UPJ obstruction. This should not be misdiagnosed as grade I VUR



a **b**

Fig. 11.18a,b. Left UPJ obstruction and VUR. **a** VCU: VUR into the renal cavities. **b** IVU: upright postvoiding film. Typical UPJ obstruction

11.4.2 Reflux and UVJ Obstruction

VUR and obstruction at the ureterovesical junction may coexist; therefore, a VCU should be part of the workup of every megaureter. Also, the presence of an obstruction at the UVJ may lead to an underestimation of the degree of VUR; the refluxing contrast may show fluid levels and will dilute within the urine already present in the obstructed ureter, and it may not be detected at all (Fig. 11.20). Furthermore, the VUR may not reach the pyelocalyceal system due to the marked ureteral dilatation. The proper management of this association should include ureteral modeling along with reimplantation using an antireflux procedure (Blickman and Lebowitz 1984).

11.4.3 Reflux and Lithiasis

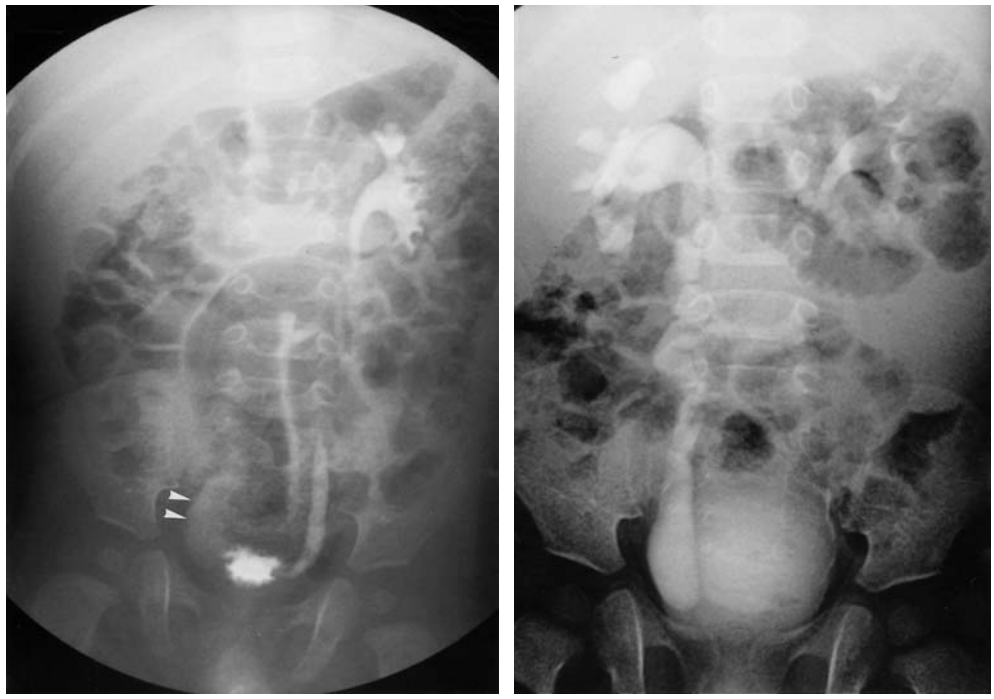
The incidence of calculi among patients with reflux is approximately 0.5%, whereas the incidence of VUR among patients with lithiasis is about 8%. Any functional or anatomical abnormality of the urinary tract that favors stasis of the urine facilitates the development of lithiasis (Fig. 11.21). Removal of the stone alone or removal together with a ureteral reimplantation must be discussed case by case (Roberts and Atwell 1989; Kraus et al. 1999).

11.4.4 Reflux Into an Unused Ureter

The normal downhill flow of urine from the kidney towards the bladder is one of the mechanisms preventing VUR. In case of diversion, renal transplant, or partial nephroureterectomy, urine may reflux from the bladder into the ureteral stump (Teele et al. 1976; Cain et al. 1998). It is best visualized on VCU, but the condition may be identified on US (Fig. 11.22). In most cases, no further complication occurs. Rarely, suprainfection may occur, and in such cases the stump may have to be removed.

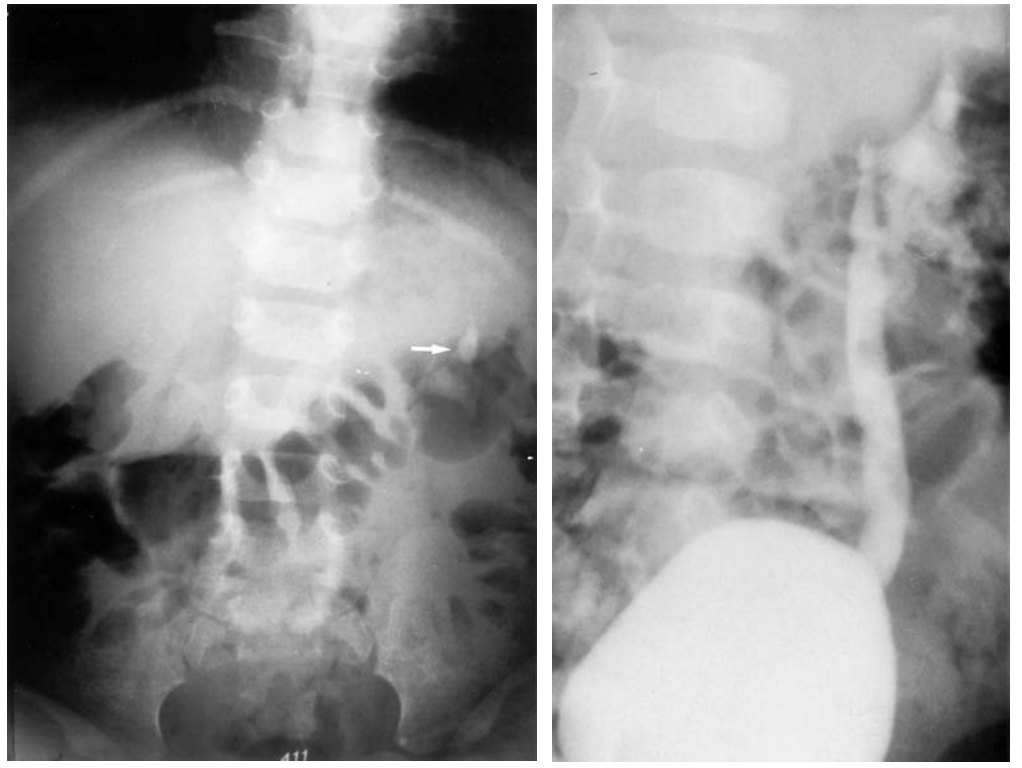
11.4.5 Yo-Yo Reflux

Yo-yo VUR refers to ureteroureteric or pyelopelvic reflux occurring into incomplete duplex kidneys.



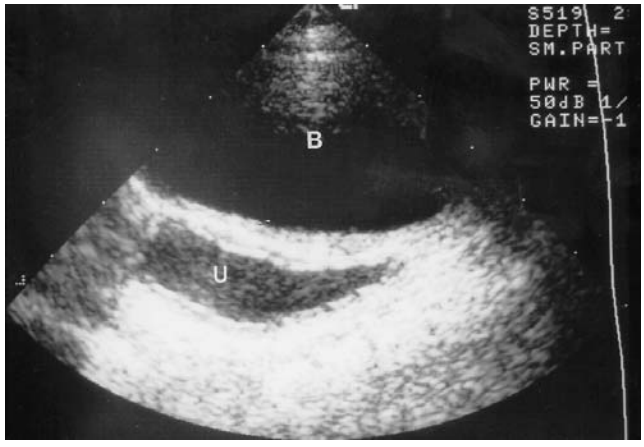
a b

Fig. 11.20a,b. VUR and primary megaureter. **a** VCU: left grade II VUR; the right VUR is very subtle (*arrowheads*) because of the dilatation and obstruction of the ureter. **b** IVU: typical right megaureter



a b

Fig. 11.21a,b. VUR and lithiasis. **a** Plain film of the abdomen showing the lithiasis. **b** VCU: left grade II VUR



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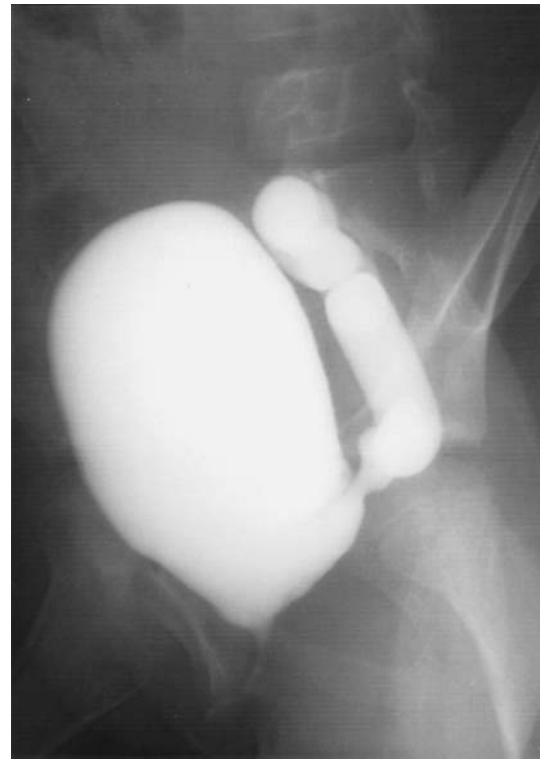


b

Fig. 11.22a,b. VUR in unused ureter after upper pole hemine-phrectomy and partial ureterectomy. **a** On US, a dilated blind ending ureter (*U*) is visualized behind the bladder (*B*). **b** On VCU, VUR into the ureteral stump

The urine refluxes from one collecting system to the other, and surgery must be aimed at preventing this passage (Gonzales 1992).

11.4.6 The So-Called Megacystis-Megaureter Association

In the megacystis-megaureter association, massive bilateral grade IV or V VUR is present. During micturition, the bladder empties normally through the urethra, but also through reflux into the ureters (Fig. 11.23a–d). At the end of micturition, the bladder is completely empty, but only for a very short time. It refills immediately with the refluxed urine; as such, the bladder is never really empty, and the volume of urine within the bladder increases continuously. A vicious circle begins, and the bladder wall thickens progressively because of increasing voiding difficulties (Burbrige et al. 1984; Willi and Lebowitz 1979; Lebowitz and Avni 1980). This diagnosis can be made in utero: a large bladder and bilateral fetal ureterohydronephrosis are present. A bladder outlet obstruction is often suspected. However, in the megacystis-megaureter association, the amount of amniotic fluid is normal, and this helps to differentiate this entity from urinary dilatation secondary to posterior urethral valves in which oligohydramnios is usually present (Mandell et al. 1992; Avni et al. 1985).

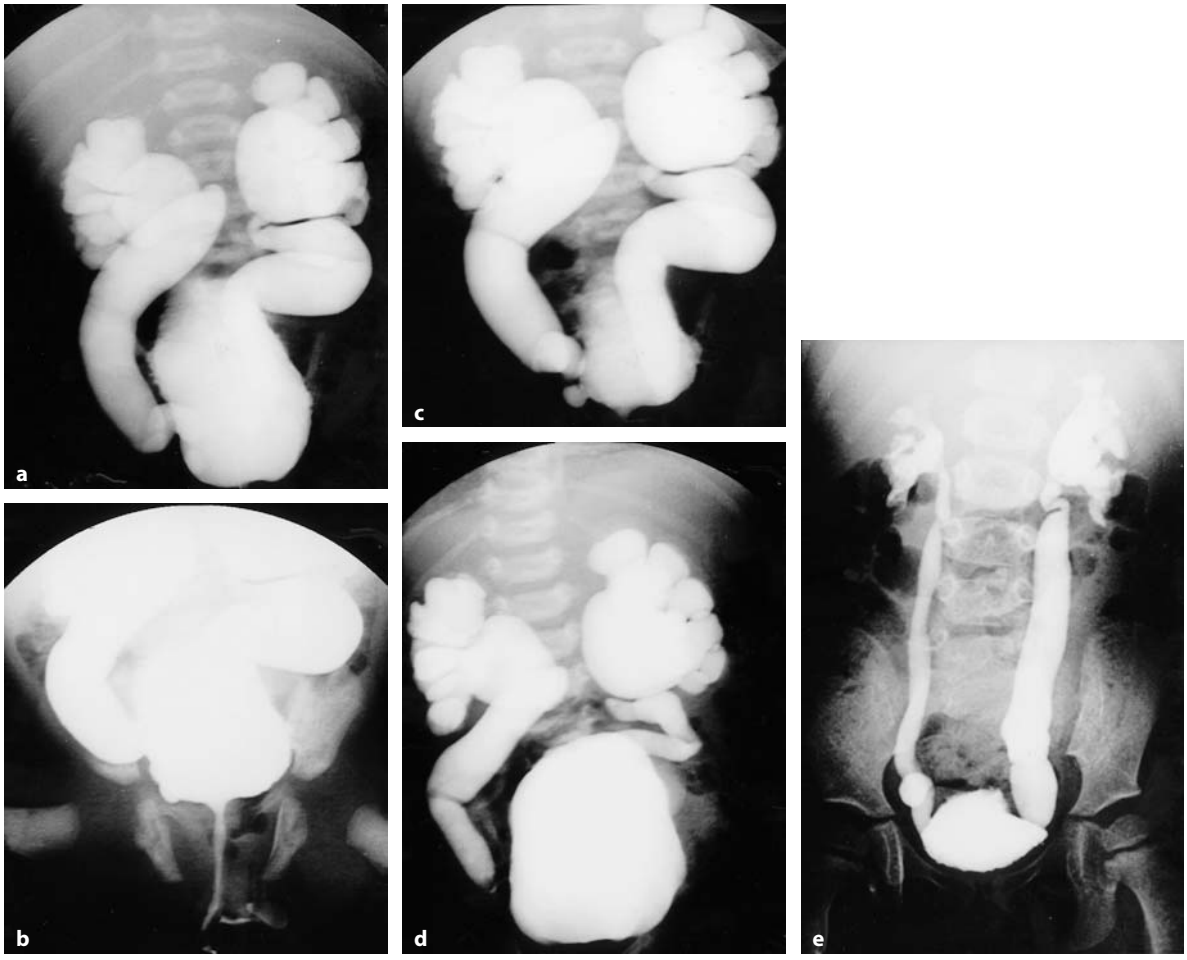


Fig. 11.23a–e. VCU, megacystis-megaureter association in a newborn girl. **a** Prevoiding: bilateral grade IV–V VUR. **b** Voiding: normal urethra. **c** Postvoiding: the bladder is almost empty, but the VUR has increased. **d** A few seconds later the bladder has refilled with the refluxed urine. **e** At age 2, VUR is still present, but has improved

11.4.7 Reflux and Duplex Kidneys

VUR may occur in both moieties of a duplex kidney, but it is much more frequent into the lower pole (Fig. 11.24). This is associated with the more lateral opening of the corresponding ureteral orifice. This type of VUR may be associated with renal damage at the corresponding lower pole (reflux nephropathy; see below). Severe VUR into the lower pole may be associated with significant ureterohydronephrosis, which may obscure the presence of a duplex system. VUR into a lower pole still has a potential of spontaneous resolution just as VUR can spontaneously resolve into a single collecting system (Ben-Ami et al. 1989; Bisset and Strife 1987; Claudon et al. 1999).

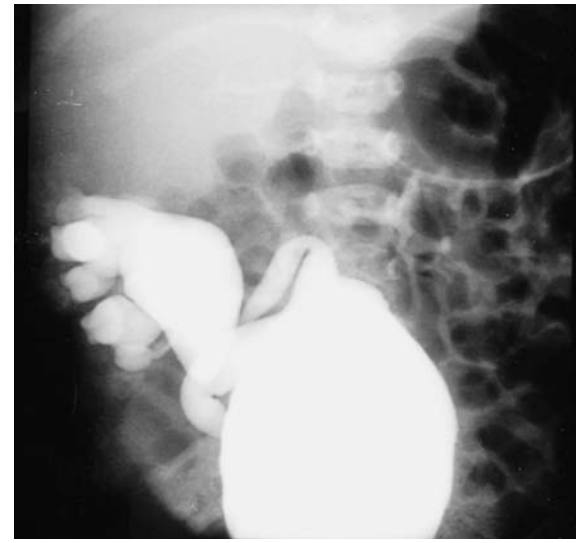


Fig. 11.24. Grade IV VUR into the lower pole of a right duplex system

11.4.8 Reflux into Ectopic Ureter

VUR into an ectopic ureter that opens into the urethra or near the bladder neck may be difficult to visualize during a conventional VCU (Fig. 11.25). Cyclic filling of the bladder helps to demonstrate this condition, which is usually, but not always, associated with a duplex collecting system (Wyly 1984). A single-system ectopic ureter is usually associated with a small dysplastic kidney.

11.4.9 Iatrogenic VUR

Inadvertent catheterization of an ureterocele during a VCU may lead to VUR into an upper pole of a duplex kidney. Reflux into an upper pole also occurs after endoscopic unroofing of an ectopic ureterocele (Fig. 11.26) (Blyth et al. 1993).

11.4.10 Reflux and Bladder Diverticulum

Bladder diverticulum reflects a weakness of the bladder wall. Its presence next to a ureteral orifice may lead to secondary VUR; the ureter is progressively included within the diverticulum (Figs. 11.27, 11.28). In such a case, VUR will not resolve spontaneously and will require surgical correction (Boechat and Lebowitz 1978; Hernanz-schulman and Lebowitz 1985; Blane et al. 1994).

11.4.11 Reflux in Case of Other Uropathies

Contralateral VUR may be present in about 10%–20% of patients with multicystic dysplastic kidney (Fig. 11.29). VUR is also present in a significant number of other uropathies, i.e., horseshoe kidney, crossed fused kidney, UPJ, and UVJ obstruction. Therefore, in any anomaly of this type, a VCU should be advised for a complete workup (Atiyeh et al. 1992; Ring et al. 1993; Song et al. 1995; Avni et al. 1997; Cascio et al. 1999).

11.4.12 Fetal Reflux, Ascites, and Pop-Off Mechanisms

Primary fetal reflux is one of the most common causes of fetal hydronephrosis. As mentioned above, gross dilatation resulting from high-grade reflux occurs essentially in baby boys. In utero VUR may also be associated with bladder outlet obstruction and especially with posterior urethral valves. In such cases, VUR results from high bladder pressure that may lead to fornix rupture, to perirenal urinoma, and even to fetal ascites. This type of secondary VUR associated with retrograde high pressure acts as a pop-off protecting mechanism. The phenomenon seems to protect the bladder wall from the deleterious effects of obstruction. Perirenal urinoma and urinary ascites protect the renal parenchyma in a

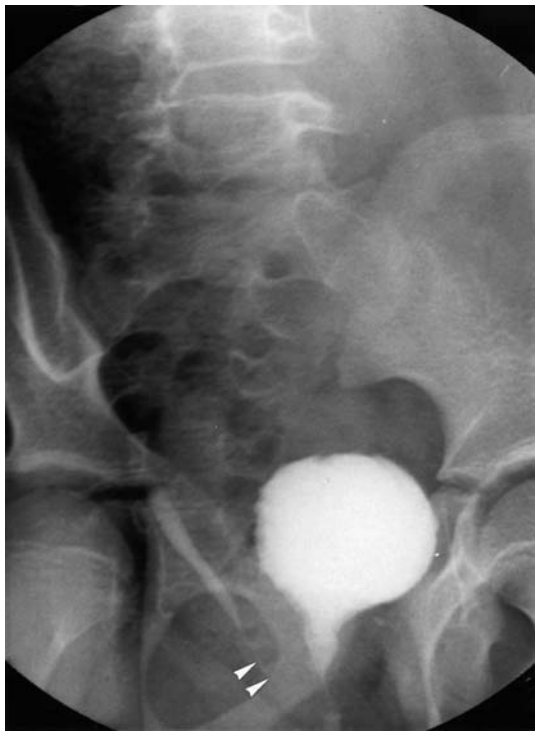


Fig. 11.25. VUR into a ureter that inserts at the level of the bladder neck (*arrowheads*)

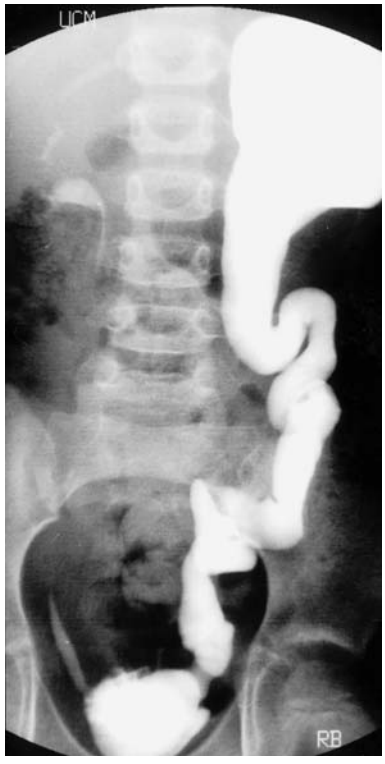


Fig. 11.26. Iatrogenic VUR. VUR into the left upper pole has occurred after endoscopic incision of an ectopic ureterocele

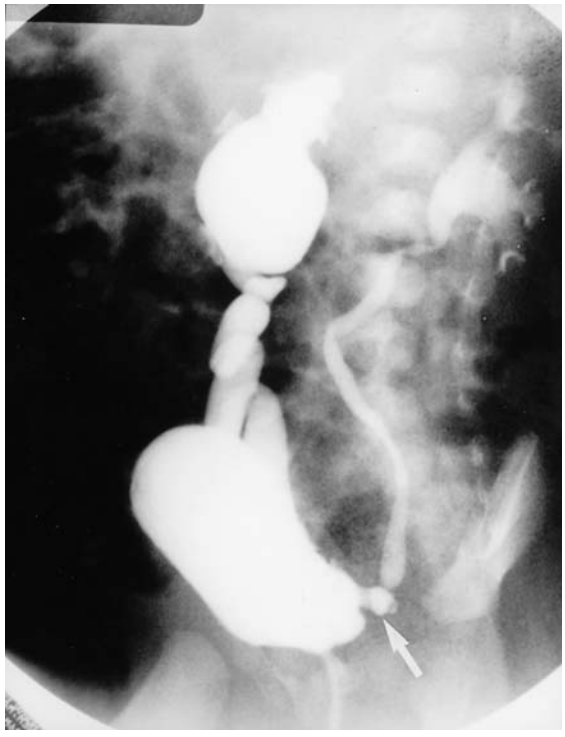


Fig. 11.27. VUR and bladder diverticulum. Bilateral VUR. Left grade II; a small diverticulum is also present (*arrow*)

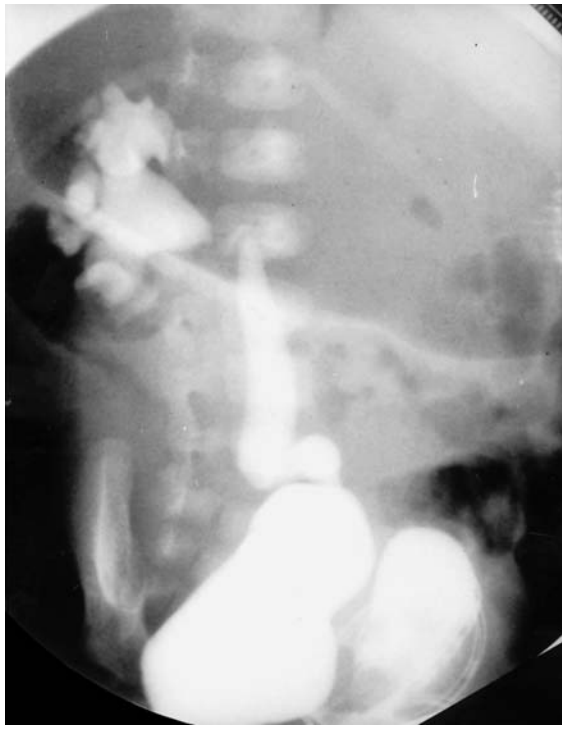


Fig. 11.28. VUR and diverticulum; postvoiding film of a VCU; a large diverticulum is filled along with the right grade III VUR

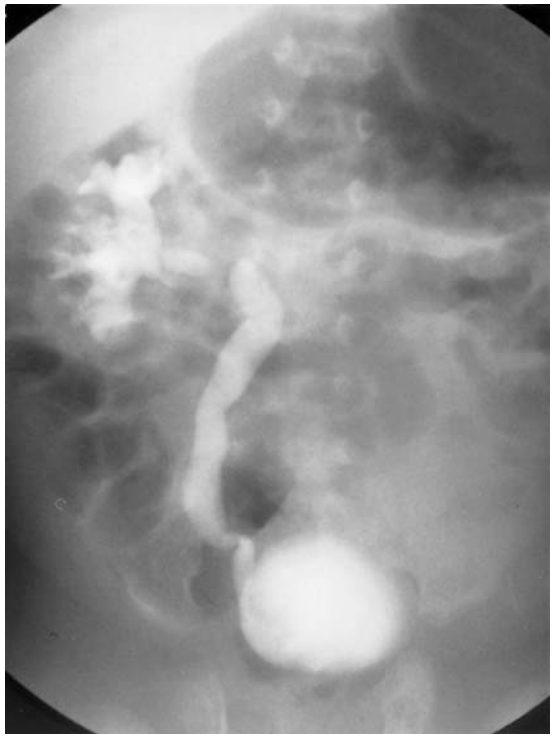


Fig. 11.29. Right grade II VUR in a case of a left multicystic dysplastic kidney

similar way (Rittenberg et al. 1985; Kaefer et al. 1995; Sillen et al. 1992).

Conclusion

VUR may be an isolated finding, but it may also be encountered in many other circumstances. Its management must be adapted to each particular presentation.

11.5 Natural History, Treatment, and Follow-Up of VUR

11.5.1 Conservative Treatment

For years the proper treatment of VUR has been controversial and has lacked a clear-cut attitude (Weiss 1992; Smellie et al. 1992). The contribution of antenatal diagnosis of VUR in asymptomatic patients has brought dramatic modifications in the management of VUR. In infants, several retrospective and prospective studies have shown the spontaneous resolution of a large number of primary VURs (Gordon 1990; Scott 1993; Assael et al. 1998; Yu et al. 1997; Ismaili 2004; Burge 1992). Among infants, VUR tends to resolve or at least to improve markedly in 75% of the patients within 2 to 3 years; higher grades of VUR (grades IV–V) resolve to a lesser extent than VUR of low or moderate grades (I–III) (Fig. 11.23e) (Herndon et al. 1999).

Following all the new data that have now been accumulated, the presently accepted attitude tends much more towards medical than surgical management of VUR. Patients with VUR are placed under prophylactic chemotherapy and followed, clinically and with imaging, for about 2 years: renal growth is monitored by US every 6 months, renal function is followed every year by MAG3-Cr EDTA isotopes, and the resolution of VUR is verified, preferably by a direct isotopic or sonographic cystogram, and if unavailable, by a VCU, reducing the radiation doses as much as possible. The same scheme can be applied to VUR into both moieties of the duplex collecting system or into the lower pole of a duplex system (Ben-Ami 1978; Wennerström et al. 1998; Jodal et al. 1999; Jodal and Lindberg 1999; Bollgren 1999; Ismaili 2006).

In older children, the attitude must be adapted to the previous history of the patient and to the clinical data. Medical treatment should be favored as much as possible. However, recurrent UTI would be an argument towards proposing an alternative treatment. Whenever a voiding dysfunction is also present, resolution of the VUR will be achieved only if the voiding anomaly is managed at the same time (Sillen 1999a).

11.5.2 Surgical Treatment

As mentioned above, surgical treatment of VUR should be considered whenever conservative treatment has not been successful or cannot be conducted satisfactorily. This includes patients with no resolution of the VUR after 2–3 years of proper follow-up, patients in whom decreasing renal function is observed, patients presenting recurrent UTI under correct antibiotic therapy, and patients whose family members are unable to follow the conservative treatment. The presence of bladder diverticula would also require surgical treatment of VUR. In all

patients with secondary VUR, proper management of the anomaly that has resulted in VUR should be considered before treating the VUR (Jodal et al. 1999).

US is usually sufficient for the post-surgical follow-up and demonstrates the ureteral reimplantation well; immediate postoperative dilatation is almost always present, but usually transient. In any abnormal clinical course or if the dilatation increases, contrast-enhanced CT (with urographic post-CT views) may be necessary for the proper management of the patients, showing kidney function and in order to exclude hematoma or urinary leakage (Rypens et al. 1992).

11.5.3 Endoscopic Treatment

The injection under the ureteral orifice of Teflon paste first and collagen and other products thereafter has been proposed as an alternative to surgery. However, the fear of these products migrating has prevented many teams from using this technique routinely. The results in terms of short-term VUR resolution are similar to the success rate of surgery. The resolution of VUR on long-term follow-up has yet to be demonstrated.

The Teflon injected under the ureteral orifice is well demonstrated on US studies (Fig. 11.30). US studies are also helpful in order to demonstrate the rare cases of complications (persisting obstruction). In long-term studies, granuloma-like masses can be found on US studies; they appear as highly dense nodules on CT (Gore et al. 1989; Rypens et al. 1992; Läckgren et al. 1999; Schulman et al. 1990; Yu and Chang 2007).

Conclusion

VUR tends to resolve spontaneously in a large number of patients; therefore, a conservative treatment of VUR is preferable. Follow-up is achieved by US, isotopes, and optimized VCU.

11.6 Complications of VUR

The aim in detecting VUR and initiating rapidly a prophylactic treatment is to prevent long-term complications (Arant 1991, 1992; Olbing et al. 1992; Bailey et al. 1992; Goldraich and Goldraich 1992; Merrick et al. 1995). This topic has been and remains controversial. There is strong evidence that the medical treatment of VUR and the prevention of superimposed UTI reduce the number of late complications (Jacobsson et al. 1999; Elder et al. 1997). The main concern remains understanding the factors that lead to the development of renal scars, the so-called reflux nephropathy (RN), and preventing complications such as renal hypertension, complicated pregnancies, renal failure, and finally end-stage renal disease (Wolfish et al. 1993; Goonasekera and Dillon 1999; Jungers et al. 1996). The role of imaging is first to detect all patients at risk (having

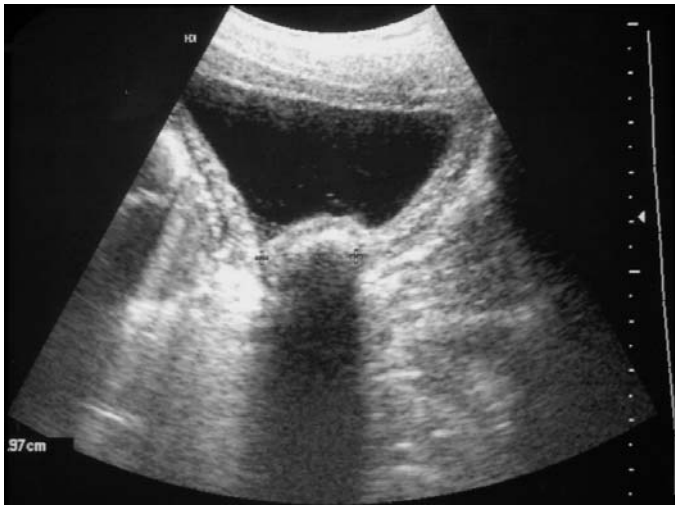


Fig. 11.30. Teflon injection (*between crosses*). Typical sonographic appearance with acoustic shadowing behind the injection

VUR) and then those that have already developed RN (Jakobsson et al. 1999; Gordon 1995; Caione 2004; Mana 2006).

11.6.1 Fetal Reflux Nephropathy

It was long thought that renal scars occur only following a UTI. The antenatal diagnosis of fetal uropathies has revealed that renal damage already exists at birth with no relation to UTI. In utero VUR has deleterious effects on renal parenchyma, probably due to backwards high pressure. This leads to reduced renal growth (Steinhardt et al. 1988; Najmaldin et al. 1990a, 1990b). Many of the kidneys with fetal RN already show reduced function on isotopic studies in the neonatal period (Assael 1998). On imaging, the kidney appears small and irregular with a cortical thinning (Fig. 11.31). The pyelocalyceal system may be dilated and clubbed. The presence of fetal RN may explain why patients with congenital uropathies that are protected by prophylactic antibiotic therapy nevertheless progress towards renal failure (Mana 2004; Caione 2004; Gobet et al. 1999; Stock et al. 1998).

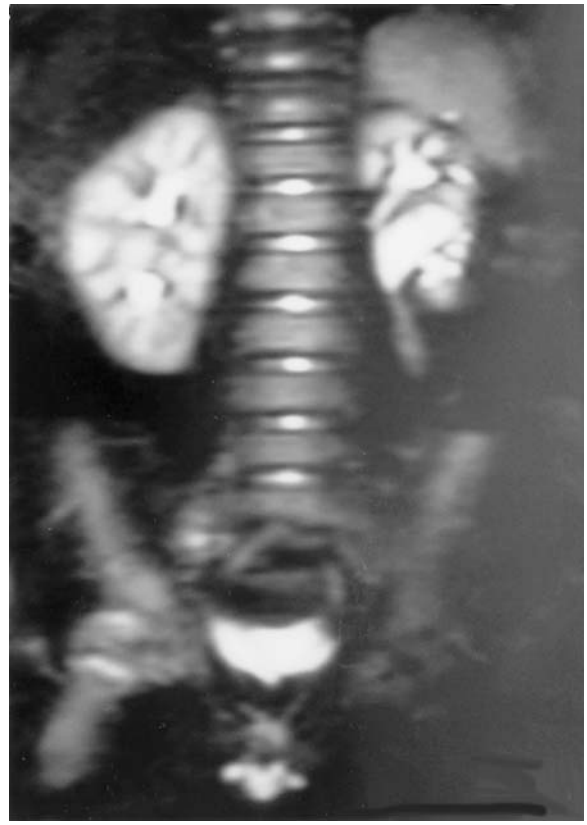


Fig. 11.31. Fetal reflux nephropathy. MR urography shows a small left kidney in a 2-month-old baby boy with VUR (SPIR T2 sequence)

11.6.2 Imaging Reflux Nephropathy and the Progression of Renal Disease

DMSA scanning is considered as the gold standard technique for the demonstration of RN lesions. DMSA has the advantage of being a low-irradiating technique with a good rate of detection of scar lesions (once the acute episode of the UTI has been treated) (Fig. 11.32). However, it brings no information on the pyelocalyceal system or even on the renal parenchyma if there is a tubular dysfunction. IVU provides information on the pyelocalyceal system, and a scoring system has been introduced that facilitates patient follow-up, but it is an irradiating technique and should not be used anymore (Monsour et al. 1987; Stokland et al. 1999; Merguerian et al. 1999; Olbing et al. 1992; Farnsworth et al. 1991). US can demonstrate the typical lesions of RN: cortical thinning and irregularities (Fig. 11.33). However, compared to the two above-mentioned methods, US is not accurate enough for assessing the number and extent of renal scars (Stokland et al. 1994). Another difficulty for US is to differentiate scars from fetal lobulation and interrenicular fat deposition (Fig. 11.34).The role of US is mainly to monitor renal growth. CT can also demonstrate the parenchymal lesions, but it is an irradiating technique, and contrast injection is mandatory (Fig. 11.35).

More recently, MRI has been shown to demonstrate RN. The technique appears accurate for demonstrating both the scars and the pyelocalyceal system (Figs. 11.36, 11.37a). The technique could develop as the gold standard once it becomes more accessible (Chan et al. 1999).

Some patients with RN may progress towards renal failure, as progressive glomerulosclerosis and fibrosis develop in the damaged kidney (Cotran 1982; Matsuoka et al. 1994; Walker 1990; Berstein and Arant 1992). Compensatory hyperfiltration may occur in less damaged areas, detectable on US studies as diffuse or localized cortical hyperechogenicity (Figs. 11.37b, 11.38) (Damry et al. 2005). These areas should not be misinterpreted as renal tumors.

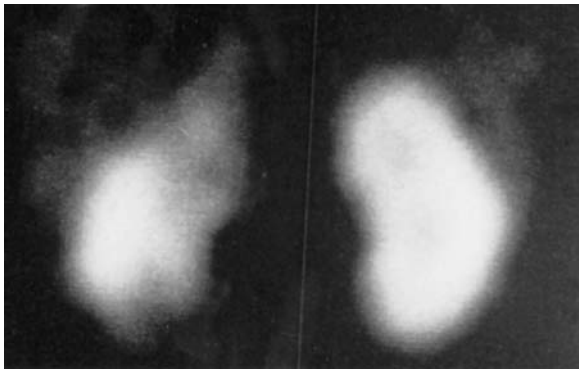


Fig. 11.32. DMSA scan: scars at the level of the upper and lower poles of the left kidney (PA view)

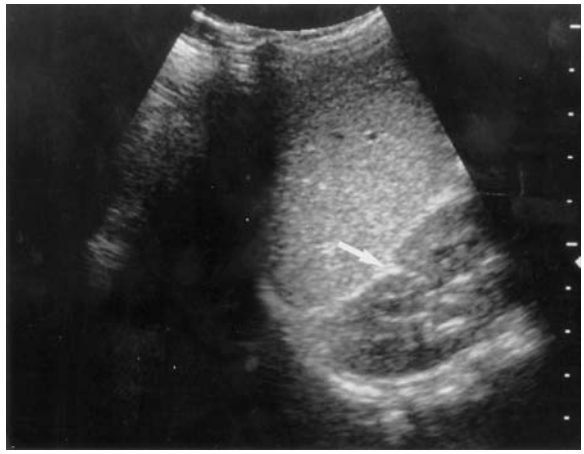
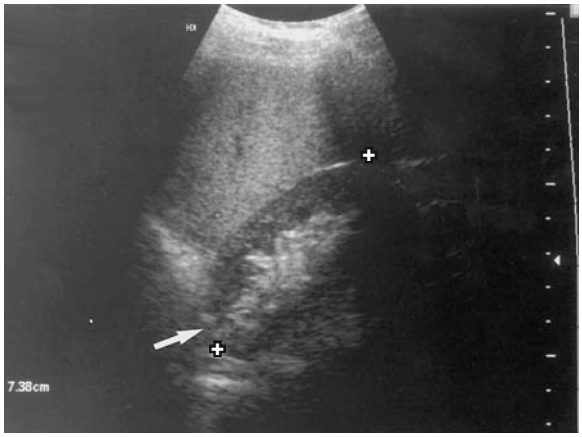
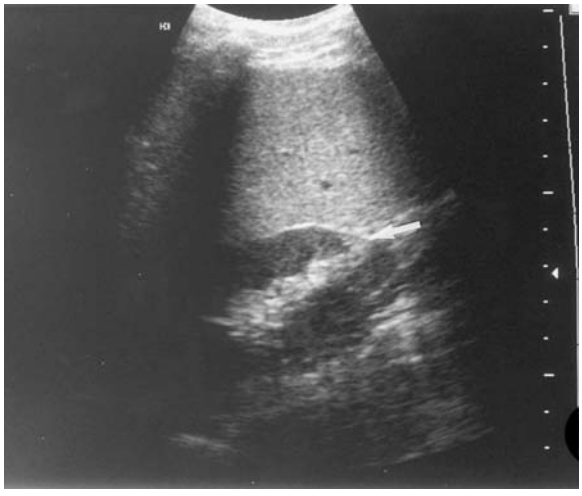


Fig. 11.34. Pseudo-scar corresponding to the interrenicular fat deposition (*arrow*). Sagittal scan of the right kidney



a



b

Fig. 11.33a,b. RN lesions at US. Sagittal scan of the right kidney (*between crosses*). Thinning of the renal parenchyma at the upper (**a**) and lower (**b**) poles of the kidney (*arrows*)

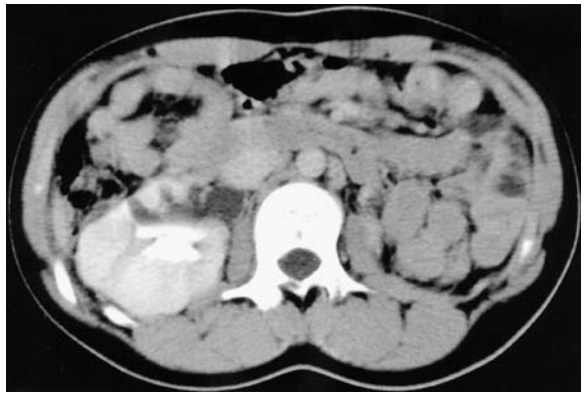
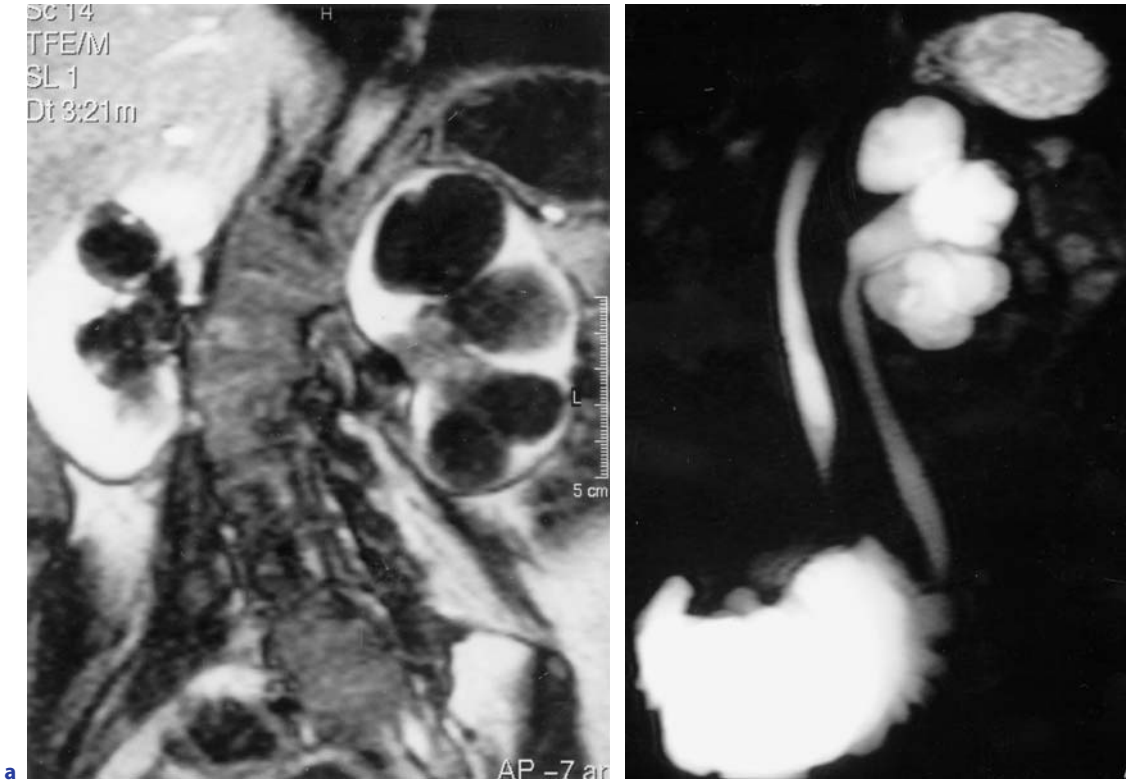


Fig. 11.35. RN at contrast-enhanced CT. Solitary right kidney with clubbed renal cavities and thinning of the parenchyma

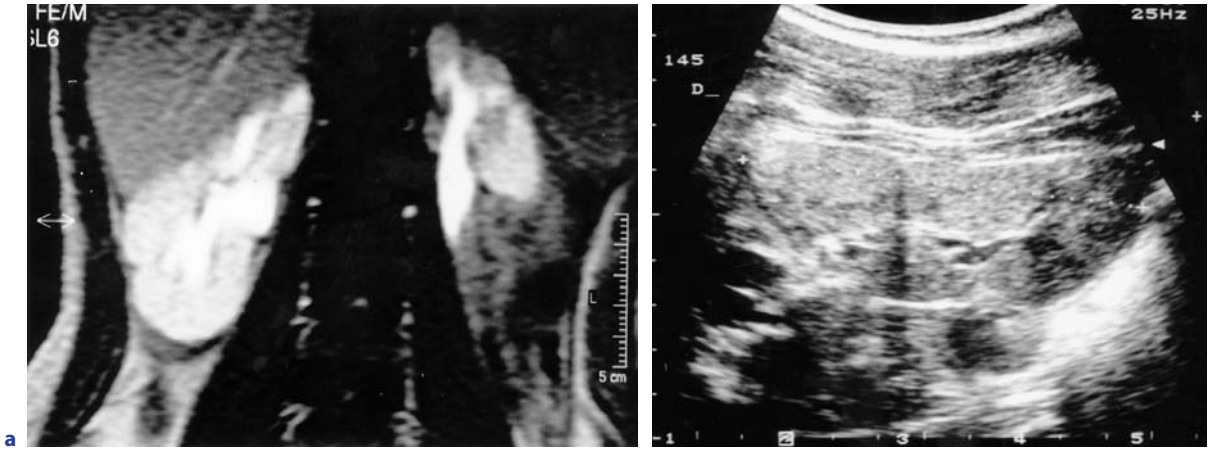
Conclusion

The role of imaging is to detect not only VUR, but also its complications: reflux nephropathy. Presently, DMSA scanning and IVU are the best techniques available for this purpose.



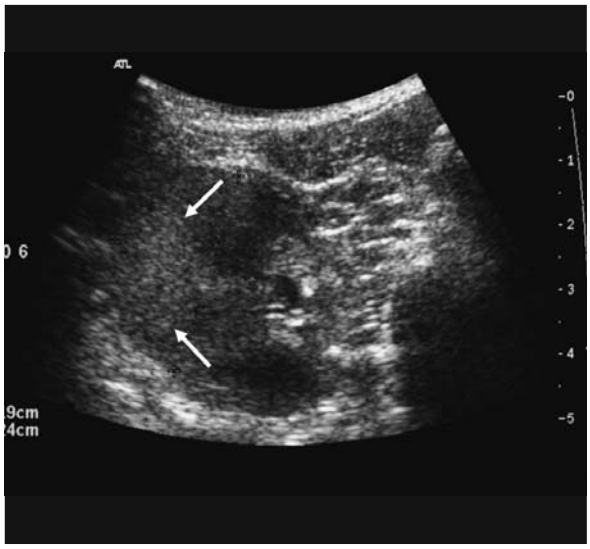
a b

Fig. 11.36a,b. RN associated to neurogenic bladder as demonstrated on MR. **a** Turbo field echo T1 coronal sequence after gadolinium enhancement showing typical thinning of the renal parenchyma. **b** T2-weighted oblique coronal sequence displaying the left dilated collecting system and the neurogenic bladder

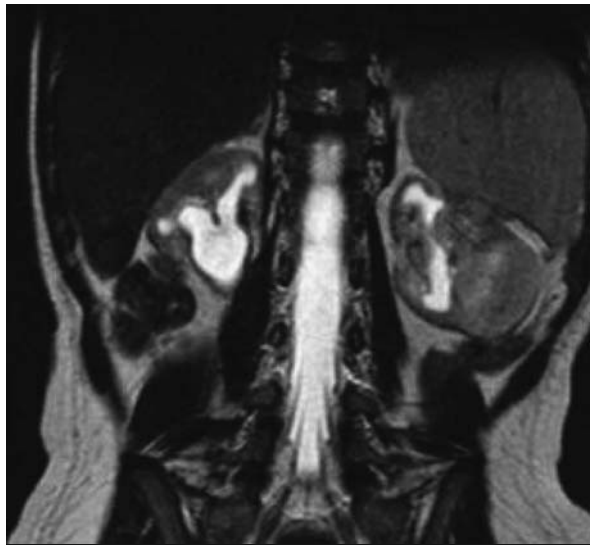


a b

Fig. 11.37a,b. Reflux nephropathy in a 9-year-old girl with known VUR and hypertension. **a** MR urography: typical scarred kidney and clubbed pyelocalyceal system (TFE T1 sequence with gadolinium). **b** US: sagittal scan of the right kidney; diffuse hyperechogenicity of the renal cortex in association with glomerular hyperfiltration



a



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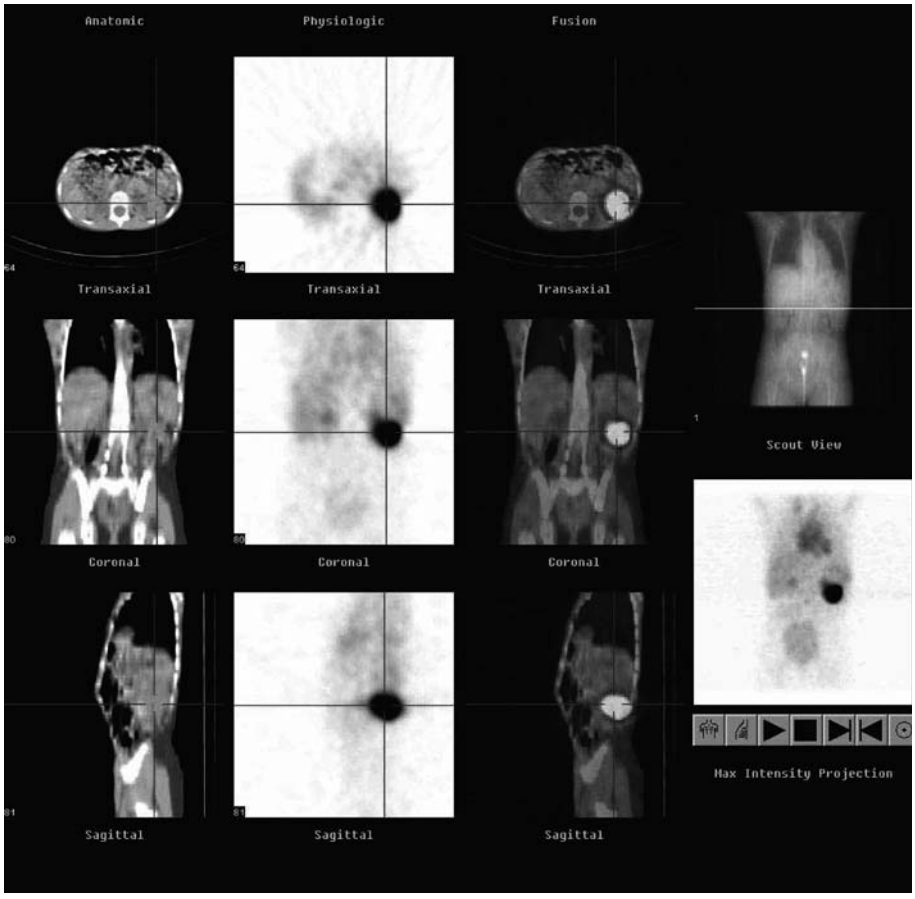

c

Fig. 11.38a–c. Localized pseudotumoral pattern of glomerular hyperfiltration in a case of reflux nephropathy. **a** US: transverse scan of the left kidney; hyperechoic ill-defined area in the external part of the kidney (marked by *arrows*). **b** MR imaging; T2 weighted sequence displays bilateral small irregular kidneys with distorted pelvi-calyceal systems and a "tumoral" appearance of the left kidney. **c** Tc 99 DMSA–SPECT-CT: the outer part of the left kidney highlights suggesting hyperfunction

11.7 Conclusion

VCU is the main investigation that can be used in order to detect VUR. DMSA scan at present, and MRI probably in the future, will be used as complementary examinations in order to detect the patients at risk for further complications

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Upper Urinary Tract Dilatation in Newborns and Infants

12

Melanie P. Hiorns and Isky Gordon

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12.1 Introduction

The main dilemma in the investigation of upper urinary tract dilatation is to distinguish between dilatation with obstruction, dilatation with no obstruction and dilatation associated with vesicoureteric reflux (VUR). At times the obstructive cause is obvious, e.g., duplex kidney with upper moiety dilatation due to a ureterocele or upper tract dilatation due to posterior urethral valves. However, the commonest abnormality found is unilateral renal pelvic dilatation (RPD), commonly termed ureteropelvic junction obstruction (UPJ). There is controversy concerning the investigations and the treatment of RPD in certain clinical situations. Renal cysts are uncommon in children, and a dilated upper pole calyx of a duplex kidney is an important differential diagnosis to be excluded. Causes of upper urinary tract dilatation are listed in Table 12.1.

Table 12.1. Differential diagnosis of hydronephrosis

- RPD with obstruction
- RPD with no obstruction
- Megaureter (with or without reflux)
- Multicystic dysplastic kidney
- VUR with upper-tract dilatation
- Bladder outlet obstruction (commonly posterior urethral valve)
- Complicated duplex kidney
- Upper moiety dilatation, due to either a ureterocele or ectopic drainage of the ureter
- Lower moiety dilatation, due to either VUR or less commonly RPD

RPD, renal pelvic dilatation

12.2 Renal Pelvic Dilatation

Renal pelvic dilatation can be defined as a kidney that on US examination has calyceal dilatation plus a dilated renal pelvis that measures greater than 10–15 mm in its AP diameter, and there is no associated US evidence of a dilated ureter. This is synonymous with pelvi-ureteric junction dilatation (PUJ), ureteropelvic dilatation (UPJ) and 'pelvicaly-

M. P. Hiorns, MBBS, MRCP, FRCR
Consultant Paediatric Radiologist, Great Ormond Street Hospital, London, WC1N 3JH, UK
I. Gordon, FRCP, FRCR, FRCPaed
Professor of Paediatric Imaging, Institute of Child Health, 30 Guilford Street, London, WC1N 1EH, UK
and
Honorary Consultant Radiologist, Great Ormond Street Hospital, London, WC1N 3JH, UK

ceal dilatation'. The calyces must be carefully evaluated since a renal pelvis measuring 10–15 mm in AP diameter with no evidence of calyceal dilatation may represent an extrarenal pelvis, which may be a normal variant. The reverse is also important, i.e., when there are dilated calyces and only minimal dilatation of the renal pelvis (AP diameter 10 mm or less), one must be careful to recognise this as a truly intrarenal pelvis which may proceed to obstruction. This RPD has been termed UPJ obstruction or UPJ stenosis in the past. Clinical presentation varies: the commonest presentation now is that of a prenatal diagnosis of RPD. However there are still young children who present with a UTI, intermittent loin pain or haematuria, or are being examined for another reason, and RPD is discovered. The implication of RPD in terms of investigation and management will vary with the clinical presentation. In the young child who presents with intermittent loin pain and is found to have RPD, surgery is indicated for the symptoms since, frequently when the child comes to the radiology department and is asymptomatic, the US and diuretic renogram may both be normal or simply show dilatation with good washout (see Fig. 12.1). Only when these examinations are done during an episode of pain will the true pathophysiological state of the kidney become clear.

In the antenatal period, the identification of RPD on US is that of an AP renal pelvis which is greater than 50% of the longitudinal length of the kidney. This equates to approximately a 5-mm pelvis at 20 weeks gestation and a 10-mm pelvis in the third trimester or at full term. RPD is most commonly unilateral, but may be bilateral; the importance of this

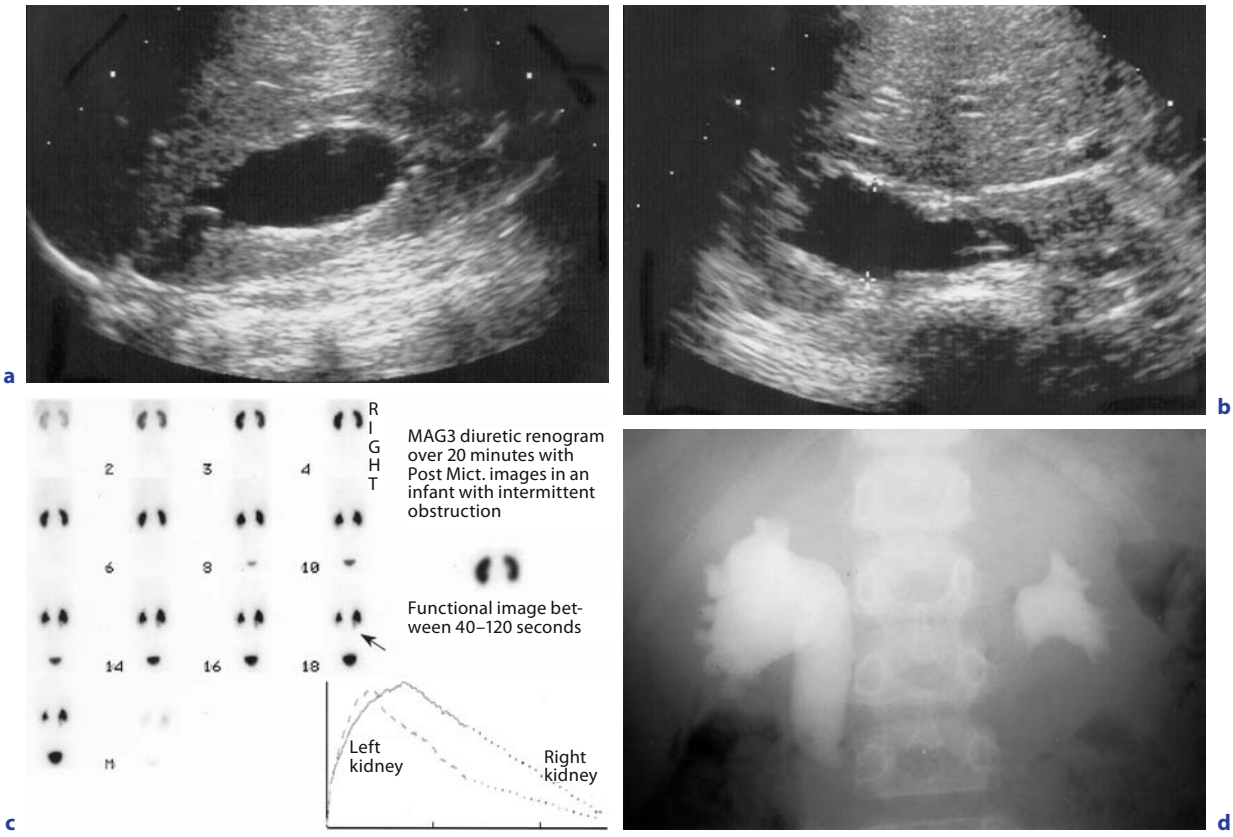


Fig. 12.1a–d. An 18-month-old child with an intermittent right UPJ obstruction. **a** The ultrasound scan shows a dilated renal pelvis with good renal parenchyma. **b** The oblique ultrasound shows that there is dilatation of the upper ureter as well. No ureter was seen behind the bladder. **c** Tc99m MAG3 diuretic renogram shows good function of both kidneys (DRF right = 45%) with good drainage bilaterally. The images towards the end of the study show a dilated upper right ureter (*arrow*). This study was undertaken when the child was asymptomatic. **d** An emergency IVU during a screaming attack shows full renal pelvis bilaterally with clubbing of all the calyces on the right and a dilated upper ureter. At surgery this was found to be an intermittent obstruction due to a retrocaval ureter

distinction is that if unilateral there is no urgency in terms of investigating the newborn. Bilateral dilatation should be investigated promptly, especially in boys in whom there may be a distal obstructing lesion such as posterior urethral valves which may be correctable. The discussion which follows relates to unilateral or isolated RPD.

There is controversy concerning a diagnosis based on prenatal ultrasound since the infants and children are asymptomatic and no natural history studies have been undertaken. In the few formal conservative studies that have been undertaken, the children have been given antibiotic prophylaxis for varying periods of time (Ransley et al 1990; Koff 1998). All these infants are asymptomatic during the first period of life. In the 1980s, many centres operated early on most of these asymptomatic infants with UPJ obstruction, (RPD), but now only about 25% undergo surgery in some teaching institutions. Many centres are attempting to develop indications for surgery, but these indications are still debated. There are more children who are currently being followed expectantly so that a body of experience is building up, suggesting both how to investigate and when to operate on these children. The problem arises from the fact that the mere presence of isolated calyceal dilatation and RPD in this clinical setting does not necessarily imply an obstruction that requires surgery (Kass 1985).

Definition of Obstruction. Obstruction is not easily defined physiologically, but the best definition may be a restriction to urine flow that, left untreated, will cause progressive renal deterioration. The effects of obstruction are recognised as hydronephrosis, parenchymal atrophy and impaired renal function. These changes are the results of obstruction, but do not define or predict the potential for progressive renal deterioration. What finally matters most is the effect of obstruction on the kidney. The clinical definition of obstruction has been based solely on the washout curve of the diuretic renogram using a T-half value greater than 20 min; for values that fall between 10 and 20 min the result is considered indeterminate. This clinical definition is not universally accepted. The reason for this is that in children with prenatal ultrasound detection of RPD, two observations have been made: the first is the variable drainage on diuretic renograms (Koff 1988), and the second is the controversy among paediatric urologists and nuclear medicine physicians regarding the interpretation of the results of impaired drainage on diuretic renography in this group of patients (Gordon 1991). As more children are followed up conservatively, the observation has been made that on sequential diuretic renograms there are both stable differential renal function (DRF) and stable size of the renal pelvis, yet the drainage is often impaired to varying degrees. The only fully accepted diagnosis of obstruction is that if nothing is done and either function deteriorates or renal pelvic dilatation increases, then an obstruction was present. Similarly, if surgery was carried out and there is an improvement in function, then there was obstruction. However, if functional evaluation has taken place in the neonatal period, then postoperative improvement of renal function may simply be due to the renal maturation that occurs during the first 2 years of life. The converse of these statements is also accepted, i.e., if the function and dilatation remain unchanged, then that kidney is in equilibrium. This includes a kidney that may have reduced, but stable, renal function from birth.

Indications for surgery must be divided up according to the clinical presentation. In a child with intermittent loin pain and a dilated renal pelvis, surgery is indicated for the symptoms, and the US and diuretic renogram may appear normal or near normal if done in a nonacute state (Fig. 12.1). In the asymptomatic newborn or infant with a prenatal diagnosis of RPD, the indications are controversial; some institutions will operate based on a renal pelvis greater than a certain arbitrary size, renal function below an arbitrary level on the initial radionuclide study, and results of pressure perfusion studies, although these are rarely performed nowadays. Examples of arbitrary threshold levels for surgery are: dilatation of a renal pelvis in an AP diameter of over 50 mm, DRF less than 30% and a diuretic response where there is more than 50% of the isotope remaining in the renal pelvis 20 min after the diuretic challenge (i.e., T-half > 20 min) (O'Reilly et al. 1996). The validity of these indications on early single measurements is strongly debated because of observations made in a few institutions which have not operated. Follow-up studies in asymptomatic children with prenatal diagnosis of RPD treated conservatively suggest that only a small proportion of kidneys will deteriorate. Ransley et al. (1990) suggested a figure of 25%, while Koff et al. (1988) suggested 7% and concluded that RPD is a relatively benign condition. This latter work also

showed the inaccuracy of the drainage curve on the diuretic renogram in the diagnosis of obstruction, an observation also made by other workers. Koff further observed that the renal pelvis enlarges during diuresis in children with hydronephrosis and that this enlargement causes dilution of isotope within the renal pelvis during DR, which prolongs the isotope washout rate sufficiently to produce an obstructed washout pattern in more than 40% of hydronephrotic kidneys that are ultimately proven to be nonobstructed. This misdiagnosis of obstruction is particularly likely to occur in children younger than 2 years because pelvic volume expansion is so exaggerated. Consequently, poor drainage appears to be particularly vulnerable to inaccuracy in diagnosing obstruction in this age group, and, therefore, it should not be relied on as an operative determinant (Koff et al. 2005). The patho-physiology of the immature kidney and the volume of the dilated renal pelvis are further reasons why poor drainage may be seen when no obstruction is present (Gordon 2001). Dhillon (personal communication) also showed that surgery in the first 3–6 months of life had no beneficial results in an age-matched control group when all the infants started with a differential renal function of 40% or more. Ulman et al. (2000) found that a significant number of infants with reduced function of the affected kidney at the onset had the same renal function as those who started off with no impairment, when they were treated conservatively. All agreed that sequential ultrasound and diuretic renogram studies that show either an increase in dilatation or a decrease in function will require surgery (Fig. 12.2); what remains controversial, however, is the interpretation of the poor drainage on the diuretic renogram and when to operate in infants with reduced function.

Conclusion

The only unequivocal diagnosis is that if nothing is done and either the dilatation increases or the function falls, then the kidney is obstructed.

The main imaging techniques used are ultrasound (US) and diuretic renography; MRI is starting to be used as a practical tool, although much work is still research based. The advantage of MRI is that it can potentially be a 'one-stop-shop' when imaging dilatation of the upper renal tract, by giving both anatomical and functional information and the absolute differential function of each kidney (Riccabona 2004)

US and diuretic renography should be carried out in a uniform manner especially as many of these newborns or infants will undergo sequential examinations. The infant or child should be well hydrated and the examinations should include the status of the upper tracts with both a full and an empty bladder. Two results have caused debate: one is the variable RPD size on US and the other is the impaired drainage on diuretic renography. The variable RPD size may be ascribed to two possible causes: firstly, the variable state of hydration of the child, and secondly, how the measurement of the RPD was made. Children should be encouraged to drink before the ultrasound to stimulate a physiologic diuresis thereby allowing a representative measurement of the AP renal pelvis to be obtained. Secondly, the measurement of the RPD should always be made in the same manner: the RPD should be examined in the transverse plane and the AP diameter measured. The explanation for the apparent variable drainage on diuretic renography in the infant with prenatal US diagnosis of RPD may be related to three factors: the acquisition and analysis of the data and the interpretation of the results. The drainage is assessed with an empty bladder as in US (Conway 1992). This does not require a bladder catheter, since the diuretic will cause almost all children, including infants, to void spontaneously. In addition, since the examination is carried out in the supine position, gravity should be allowed to have its full effect (see Chap. 1.3, Nuclear Medicine: Postmicturition Images). Renal function must be taken into account when assessing drainage since with a well functioning kidney one would expect a better response than with a poorly functioning kidney (see Chap. 1.3 Nuclear Medicine: PEE). Yet there may be clear evidence of impaired drainage, as shown in Table 12.2 and Fig. 12.3.

Conclusion

Poor drainage is not the same as obstruction. Poor drainage not due to obstruction may be caused by: (1) inadequate data acquisition; (2) inadequate analysis of the data; (3) renal pathophysiology in infancy.

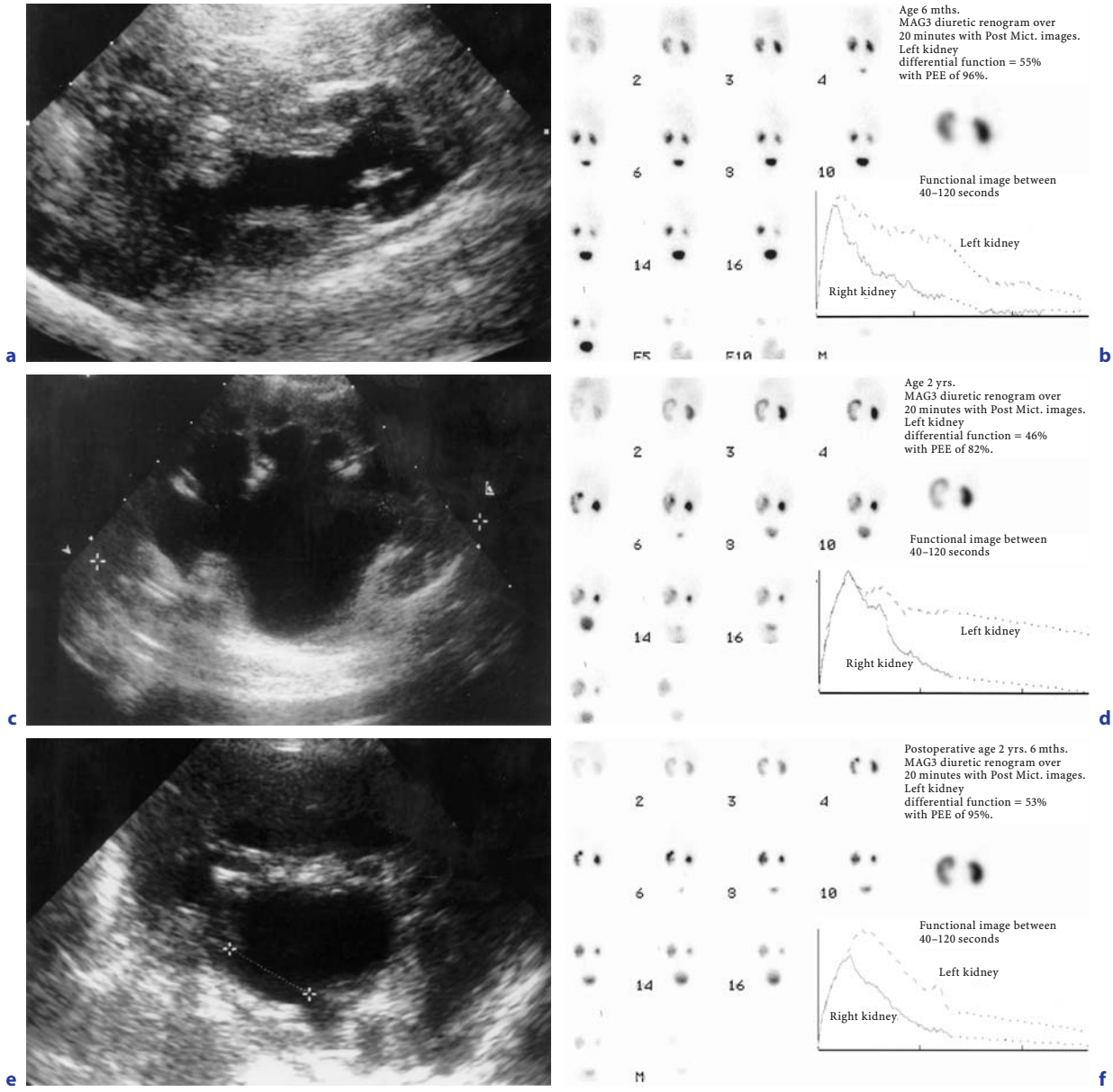
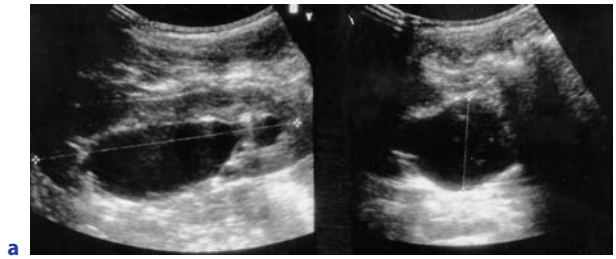


Fig. 12.2a–f. Antenatal diagnosis of renal pelvic dilatation of left kidney with obstruction and postsurgical follow-up. **a** The postnatal US during the first 6 months of life showed a renal pelvis of 18 mm with calyceal dilatation. **b** MAG3 diuretic renogram at 6 months of age shows equal function of both kidneys with good drainage following the diuretic. **c** The US at 2 years of age showed increase in the dilatation with a renal pelvis of 35 mm and marked calyceal dilatation. **d** MAG3 diuretic renogram at 2 years of age shows that the left kidney has enlarged on the functional image and the DRF has fallen from 55% to 46%. Drainage, however, is good following the diuretic. **e** Following surgery the US 3 months later showed some reduction in the pelvic dilatation. **f** Postoperative MAG3 diuretic renogram at 2 years 6 months of age shows better function of the left kidney with even better drainage following the diuretic. The changes in both dilatation and function strongly suggest that this kidney was obstructed and that surgery has returned the kidney to a nonobstructed state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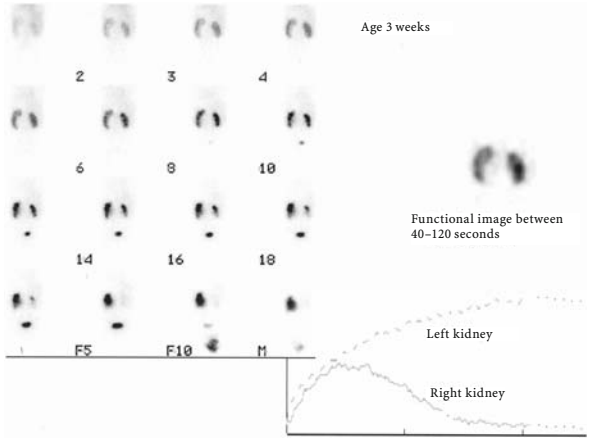

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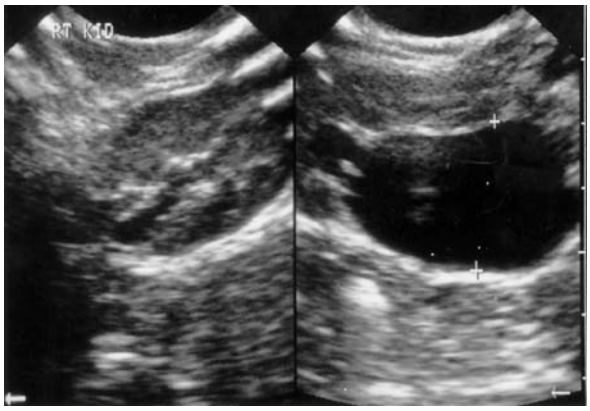

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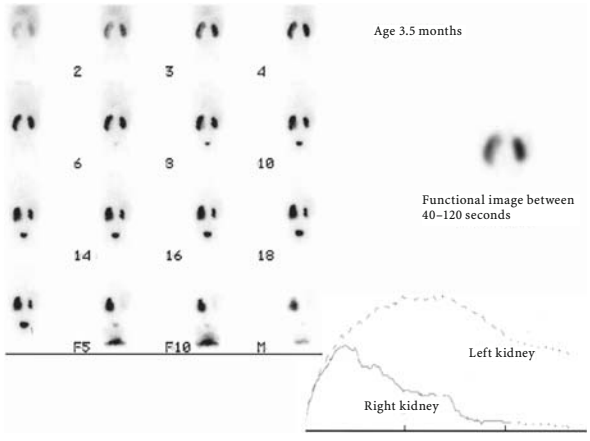

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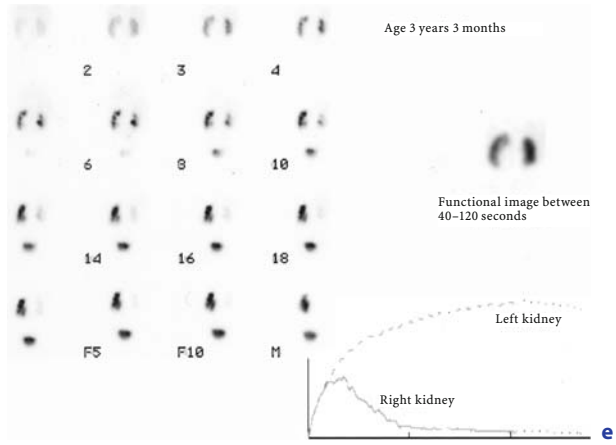

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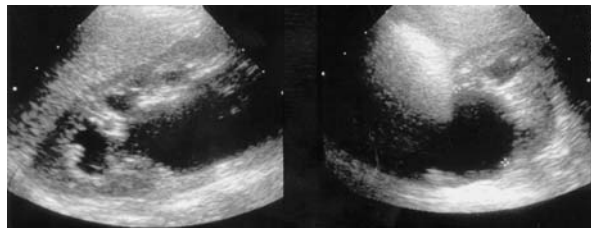
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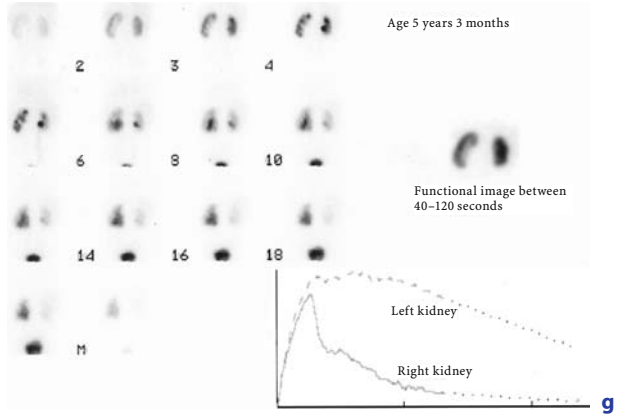

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Fig. 12.3a–g. Antenatal diagnosis of renal pelvic dilatation of left kidney with conservative follow-up. No obstruction present (see also Table 12.2). **a** Longitudinal and transverse US of the left kidney showing the pelvic and calyceal dilatation at 1 week of age. **b** MAG3 diuretic renogram at 3 weeks of age shows equal function of both kidneys with poor drainage following the diuretic on the left. **c** Transverse US of the left kidney showing the pelvic and calyceal dilatation at 3 months of age. The right kidney is normal. **d** MAG3 diuretic renogram at 3.5 months of age shows that the left kidney remains enlarged on the functional image; the DRF has not changed. Drainage, however, is impaired, but better following the diuretic. **e** MAG3 diuretic renogram at 3 years 3 months of age shows no change in function of the left kidney with worse drainage following the diuretic. **f** Longitudinal and transverse US of the left kidney showing the pelvic and calyceal dilatation at 5 years of age. **g** MAG3 diuretic renogram at 5 years 3 months of age shows no change in function of the left kidney with very good drainage following the diuretic, a change in posture and micturition

Table 12.2. Sequential imaging results on a boy with prenatal unilateral renal pelvic dilatation diagnosed at 20 weeks' gestation

Age	Tc99m MAG3 diuretic renogram		Ultrasound results		
	Diff funct	Drainage (PEE)	Renal pelvis	US renal	US renal
	Left kidney		AP diameter	Length left	Length right
3 weeks	51%	71%–impaired	26 mm	66 mm	49 mm
3.5 months	50%	71%–impaired	30 mm	69 mm	55 mm
15 months	53%	56%–impaired	25 mm	76 mm	63 mm
2 y 3 months	49%	43%–impaired	30 mm	88 mm	66 mm
3 y 3 months	50%	62%–impaired	26 mm	85 mm	77 mm
5 y 3 months	55%	85%–good	33 mm	96 mm	83 mm

Diff funct, differential renal function of affected kidney; PEE, pelvic excretion efficiency of affected kidney (see Chap. 1.1, Nuclear Medicine, for details of PEE)

12.3 Imaging Protocol

The protocol must vary depending on the clinical presentation. Children with asymptomatic RPD have to be managed differently from those with intermittent loin pain and a dilated renal pelvis in whom symptoms may be relieved by surgery. With intermittent loin pain, intermittent hematuria or urinary tract infection, a full abdominal US examination is required. The discovery of RPD requires a diuretic Tc99m MAG3 renogram to assess function and drainage. If there is uncertainty about the relation between the intermittent loin pain and the RPD, then imaging during an episode of pain is essential. This could simply be by US, which, if it showed a marked increase in RPD size compared with the baseline study, would prove the intermittent nature of the obstruction. Alternatively, emergency IVU or MRI during the acute painful episode may show evidence of obstruction. Although renal calculi are uncommon in young children, the discovery of a calculus on US in a child with acute loin pain and yet no dilatation does not exclude a calculus obstruction, and emergency IVU/Tc99m MAG3 renography or MRI (gadolinium-enhanced) is required.

With a prenatal diagnosis of unilateral RPD, US examination should be undertaken about 48–72 h after birth to assess pelvic and calyceal dilatation, to both confirm the RPD and measure the transverse diameter of the pelvis, and to confirm that there is no dilated ureter and that the bladder and opposite kidney are structurally normal. If the US examination is undertaken earlier, then dilatation may be absent due to the normal physiological dehydration and subsequent reduced urine output in the neonate over the first 24–48 h, and it is for this reason that many centres routinely repeat the US studies in these patients at 6 weeks of age. With a secure diagnosis of unilateral calyceal and RPD dilatation, the child requires assessment of renal function and drainage. With severe dilatation, the assessments should start earlier and be more frequent, while with moderate dilatation there is little urgency. With an AP renal diameter greater than 30 mm on US in the first week of life, a diuretic Tc99m MAG3 should be undertaken early (2–4 weeks of age), followed by both US and repeat diuretic Tc99m MAG3 renography at 4–8 weeks of age. This also applies to the child with reduced DRF on the early Tc99m MAG3 scan. With moderate dilatation, or with function that is within the normal range, less frequent follow-up is suggested; this could be undertaken at about 8–12 weeks of age (this allowing for some renal maturation to occur and thus providing a more stable renal function assessment). Long-term follow-up should be with US and diuretic Tc99m MAG3-at 6 months and at 12 months for moderate dilatation/normal function, while for severe dilatation/reduced function repeat examinations at 3-month intervals are recommended. If the situation is stable, US at 2 years and US plus diuretic Tc99m MAG3 at 5 years could be undertaken (Fig. 12.3). Long-term follow-up is strongly recommended until at least 15–20 years of age. There is no role for voiding cystourethrography (VCU) in those children who have calyceal dilata-

tion plus a dilated renal pelvis that measures more than 10–15 mm in its AP diameter and who have no evidence of a dilated ureter. There is no test available at the moment that will predict which kidney with a prenatal diagnosis of RPD, if left alone, will deteriorate. The parameters which are currently being evaluated are the AP renal pelvis measurement on US, the DRF and drainage on diuretic Tc99m MAG3 scans. Many paediatric urologists believe that recovery of renal function is not the aim of reconstructive surgery; rather, the aim is prevention of further deterioration. All, however, will agree that progressive dilatation on US or a fall in DRF of more than 5%–10% on Tc99m MAG3 requires surgery.

Special mention of the duplex kidney should be made. The second commonest abnormality of the lower moiety is that of RPD (Fig. 12.4).

Conclusion

1. With prenatal diagnosis treatment remains controversial.
2. When the patient has intermittent pain, surgery is for the pain, not the result of imaging.

12.4 Bilateral Renal Pelvic Dilatation

This is an unusual finding in the symptomatic child and is most commonly seen in the asymptomatic newborn, infant or child with a prenatal diagnosis from US. There is debate about the investigation and management of these children. Should surgery be undertaken, and if so when and on which side? Some surgeons will opt for a nonsurgical approach as long as the degree of dilatation and differential function are stable, while others prefer to operate on the better functioning kidney, and yet others will operate on the worse kidney or the one with the greater dilatation. Judging the results of US and/or diuretic Tc99m MAG3 is very difficult. The investigative protocol in this situation should include both US and diuretic Tc99m MAG3 renography; the DRF must be interpreted with caution, and an early functional image is invaluable (see Chap. 1.3, Nuclear Medicine). These investigations should be coupled with a formal measurement of the glomerular filtration rate (GFR). All these examinations should be repeated at regular intervals; the frequency cannot be rigidly laid down, but will depend on the findings of the examinations. Until more information becomes available no rigid approach can be recommended. The role of MRI is not fully established in this clinical situation, but may become important in the future.

12.5 Multicystic Dysplastic Kidney

Multicystic kidney or multicystic dysplastic kidney (MCDK) (Fig. 12.5) may occasionally cause confusion with severe unilateral RPD. In MCDK there is no

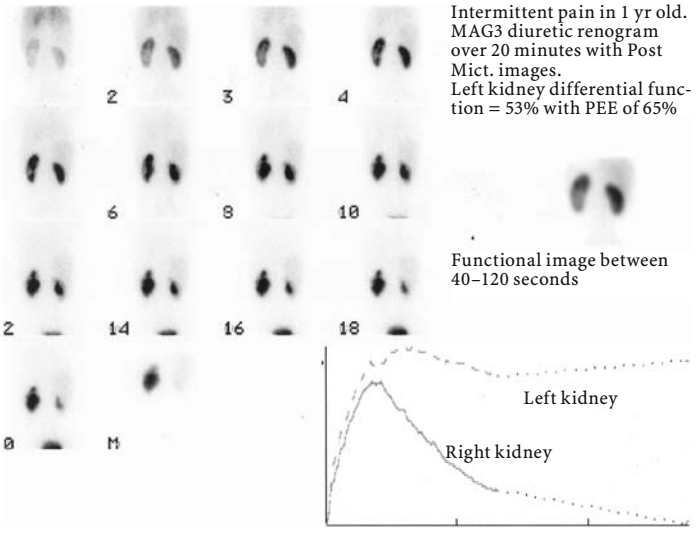


Fig. 12.4. UPJ in lower moiety of duplex left kidney. Antenatal diagnosis of left renal pelvic dilatation found to be renal pelvic dilatation in a duplex kidney. Tc99m MAG3 diuretic renogram shows good function of the left kidney (DRF= 53%). The early functional image shows that there is very good function in the upper portion of the left kidney with reduced function in the lower two-thirds, features strongly suggesting a duplex kidney. There is impaired drainage from the dilated renal pelvis despite a change of posture and an empty bladder. Follow-up showed no change over a period of years in either dilation or function

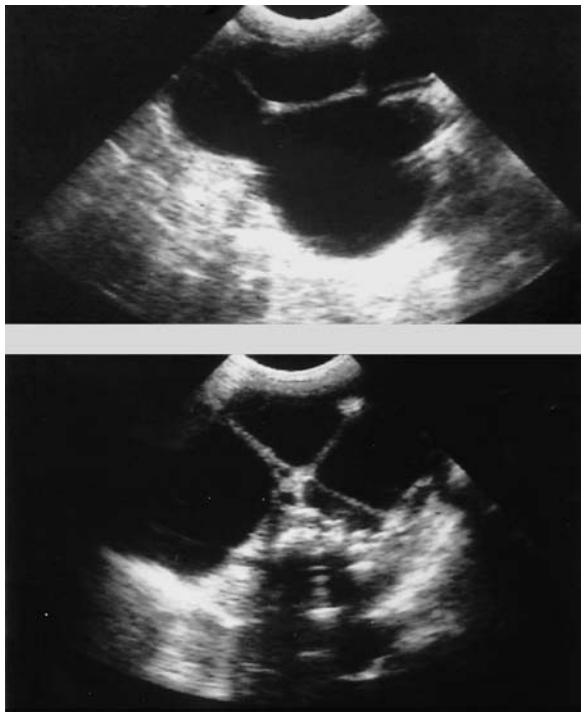


Fig. 12.5. Multicystic dysplastic kidney, US. Antenatal diagnosis of hydronephrosis. On the lower image there is a clear multicystic kidney, but the upper image shows how one may experience difficulty in distinguishing between a large renal pelvic dilatation and a multicystic kidney

normal overall structural pattern to the kidney, with loss of lobular organisation, although small islands of renal tissue are occasionally identified microscopically. An MCDK is characterised on ultrasound by a reniform structure in the renal fossa of variable size appearing to comprise almost entirely of 'cysts' with little if any intervening renal parenchyma. That which may be delineated is likely to be echo-bright. It is essential that the sonographer establishes whether these 'cysts' are discrete or whether they are connected. If connected the diagnosis is likely to be severe hydronephrosis rather than an MCDK, in which case a nephrostomy can be considered and function evaluated 3–4 weeks later.

In MCDK there is always an atretic ureter and the kidney is nonfunctioning. However, in severe RPD and MCKD, it may be difficult to clearly distinguish cysts from calyceal dilatation; in this context a Tc99m MAG3 renogram may be useful, since if any function at all is noted then this is a RPD and requires drainage. If there is absolutely no function, then this is likely to be a MCKD. A totally nonfunctioning RPD never recovers function following a drainage procedure, so the management of the "cystic" mass is the same.

The commonest presentation of MCDK is at antenatal US. MCDK is more common in males, and the natural history is that of involution over time, although some persist unchanged for years. There have been a few case reports of the development of either hypertension or malignancy, but this is not yet accepted as a true association. Indications for surgery include a mass so large as to impede breathing or feeding in early infancy, a mass which is enlarging, or one which by the age of 1 year remains over 5 cm in size, although approaches differ in different centres. The prognosis depends on the function of the contralateral kidney, in which there is a high rate of associated abnormalities (30%), usually UPJ obstruction or ureteric stenosis.

Imaging. On ultrasound, there is a spectrum of appearances from a small single cyst to a large mass containing multiple, usually anechoic, cysts of varying sizes, often with a dominant large cyst situated peripherally. There is either no, or very little, identifiable renal parenchyma. On radioisotope studies there is no function in the MCDK. The opposite kidney requires Tc99m MAG3 renography to assess drainage, especially if the US has detected a dilated renal pelvis. VCU is not routinely required unless the US examination reveals a dilated ureter or an abnormal bladder.

12.6 Dilatation of Renal Pelvis and Ureter

The dilated ureter includes both the classical definition of a megaureter, i.e., ureteric dilatation with an abnormality of the circular muscles of the distal ureter resulting in abnormal peristalsis as well a dilated ureter in which there may be reflux; the function of the kidney is often preserved. In addition, the upper moiety of the duplex kidney may be dilated due to obstruction by a ureterocele. The management of most of these infants is problematic during the first year of life, since there is a growing impression from the urologists that surgery undertaken on the immature bladder (< 1 year of age) may lead to abnormal bladder function and reimplantation should be avoided in the first year of life. This attitude has coloured the investigations which these

children may undergo. The presence of urosepsis often forces intervention. The management of the ureterocele with an obstructed upper moiety is less controversial, with surgery being undertaken early.

These children may present either with a UTI or, more commonly, as asymptomatic infants following a prenatal ultrasound diagnosis of hydronephrosis. In this latter clinical setting, the investigative protocol is similar to that of RPD as recommended above, with the addition of VCU to document or exclude VUR rather than a megaureter. In the absence of reflux, a diuretic Tc99m MAG3 study should be undertaken at 4–8 weeks of age with follow-up studies of both diuretic Tc99m MAG3 renography and US at 6 and 12 months. The ultrasound must in addition focus on the bladder and vesicoureteric junction since it is imperative to exclude a small ureterocele or other bladder abnormalities. Usually the bladder appears normal on both US and VCU, in which case there may be a functional abnormality. If urodynamics are planned the difficulty comes in interpreting the results in the first year of life and does not make the handling of these children any easier. With a suspected nonneurogenic bladder-sphincter dysfunction, consideration should be given to spinal US in early infancy, preferably in the first few weeks of life, as it can be useful in excluding obvious spinal cord pathology.

With increasing dilatation on sequential US, fall in DRF on sequential diuretic Tc99m MAG3 studies or the presence of urosepsis, there is an increasing tendency to insert a double J stent from the ureter into the bladder to relieve a presumed obstruction. This will require an antegrade study at the time of double J insertion. Such intervention requires follow-up imaging with US and diuretic Tc99m MAG3 studies 3 and 12 months after stent insertion as well as after stent removal. With bilateral megaureter, the imaging protocol is the same as for unilateral megaureter with the addition of GFR estimation. Careful evaluation of the bladder should be undertaken with US for ureteroceles, bladder wall thickness and of the posterior urethra in males for urethral dilatation due to posterior urethral valves.

Conclusion

One must exclude VUR, and VCU is required. If VUR is found a Tc99m DMSA scan is required.
If there is no VUR then diuretic Tc99m MAG3 renography is required.

12.7 Vesicoureteric Reflux with Upper Tract Dilatation

The common clinical presentation of these newborns, infants or children is either a prenatal ultrasound diagnosis of hydronephrosis or a UTI. It is important to ensure that there is no pathology at the vesicoureteric junction, the bladder itself or bladder outflow and that the dilatation observed is related solely to the presence of VUR. Important causes to exclude are posterior urethral valves in boys, a neuropathic bladder, or an obstructed megaureter as defined in the preceding section. Pathology in the spine should not be overlooked. The importance of VUR in the clinical context of a child with a UTI has fluctuated over the years. Some time ago, VUR was considered the prime cause of renal damage in the setting of UTI, but data over the past 10 years suggest that VUR, especially in the older child, may be of little consequence unless there are recurrent UTIs. A recent review of the world literature suggested that in children with UTI, VUR on its own was neither sufficient nor necessary for renal damage to occur (Tables 12.3, 12.4).

However, in the context of an US finding of a dilated upper urinary tract including the ureter, the most logical imaging protocol to follow is cystography and a functional study (Fig. 12.6). VCU and spinal ultrasound will exclude those pathologies mentioned above. This should then be followed by a Tc99m DMSA scan to assess whether any focal renal damage has occurred as well as establish the differential function of the affected kidney(s). In the context of an asymptomatic infant with a prenatal diagnosis of hydronephrosis, an abnormal Tc99m DMSA scan does not imply renal scarring, but rather suggests the maldevelopment of both the kidney and its collecting system, possibly renal dysplasia. Follow-up cystograms of these children should use radioisotopes: direct catheter cystography if the child is under 3 years of age and indirect cystography if the child is toilet-trained.

Conclusion

VUR on its own is neither sufficient nor necessary to cause renal damage in the context of UTI.
When hydronephrosis is associated with a dilated ureter, VUR must be excluded.

Table 12.3. The results of a world literature search showing the relationship between renal damage on a Tc99m DMSA scan and VUR in kidneys in children with UTI, at different times after the UTI. Results from 5,460 kidneys

	Early DMSA n = 3,251	DMSA 6 wk–6 mths n = 883	Late DMSA n = 800	Not stated n = 526
VUR+/DMSA+	570 (18%)	142 (16%)	96 (12%)	94 (13%)
VUR+/DMSA–	462 (14%)	276 (31%)	116 (15%)	118 (22%)
VUR–/DMSA+	666 (20%)	99 (11%)	123 (15%)	66 (13%)
VUR–/DMSA–	1553 (48%)	366 (41%)	465 (58%)	248 (47%)

For all kidneys the risk difference is 0.28 (CI 0.24, 0.32), the relative risk is 1.78 (CI 1.63, 1.94). VUR+, VUR present; VUR–, VUR absent; DMSA+, DMSA abnormal; DMSA–, DMSA normal; early DMSA, DMSA scan <6 weeks after UTI; DMSA 6 wk–6 mths, DMSA scan between 6 weeks and 6 months after UTI; late DMSA, DMSA scan >6 months after UTI

Table 12.4. The results of the world literature search showing the relationship between renal damage on Tc99m DMSA scan and VUR in children with UTI, at different times after the UTI. Results from 2,323 children

	Early DMSA n = 1,142	DMSA 6 wk–6 mths n = 560	Late DMSA n = 527	Not stated n = 94
VUR+/DMSA+	335 (29%)	142 (25%)	105 (20%)	23 (24%)
VUR+/DMSA–	202 (18%)	81 (14%)	77 (15%)	15 (16%)
VUR–/DMSA+	263 (26%)	117 (21%)	112 (21%)	33 (35%)
VUR–/DMSA–	342 (30%)	220 (39%)	233 (44%)	23 (24%)

For all children the risk difference is 0.27 (CI 0.24, 0.29); the relative risk is 2.10 (CI 1.95, 2.26). VUR+, VUR present; VUR–, VUR absent; DMSA+, DMSA abnormal; DMSA–, DMSA normal; early DMSA, DMSA scan <6 weeks after UTI; DMSA 6 wk–6 mths, DMSA scan between 6 weeks and 6 months after UTI; late DMSA, DMSA scan >6 months after UTI

12.8 Complicated Duplex Kidney

Either moiety may be suspected as being abnormal following an US finding of upper tract dilatation. The duplex kidney should always be considered since even experienced radiologists and urologists make the mistake of forgetting to look for the duplex kidney. The commonest pathology causing upper moiety dilatation is obstruction due to either a ureterocele or ectopic drainage of the ureter (Fig. 12.7). The function of the upper moiety varies from very good and worth preserving to virtually nonfunctioning. Either Tc99m DMSA or Tc99m MAG3 renography may be undertaken to assess function; the advantage of the Tc99m MAG3 study is that it gives information about drainage and involves a lower radiation burden. Rarely the dilatation in the upper pole is due to an isolated dilated calyx (Fig. 12.8), and renal cysts are seen, but are exceptionally uncommon. Lower moiety dilatation is most commonly due to VUR, but RPD is well recognised (Fig. 12.4).

Conclusion

Duplex kidney should always be borne in mind when one finds an abnormal kidney.
"You only find what you look for, and you only look for what you know".

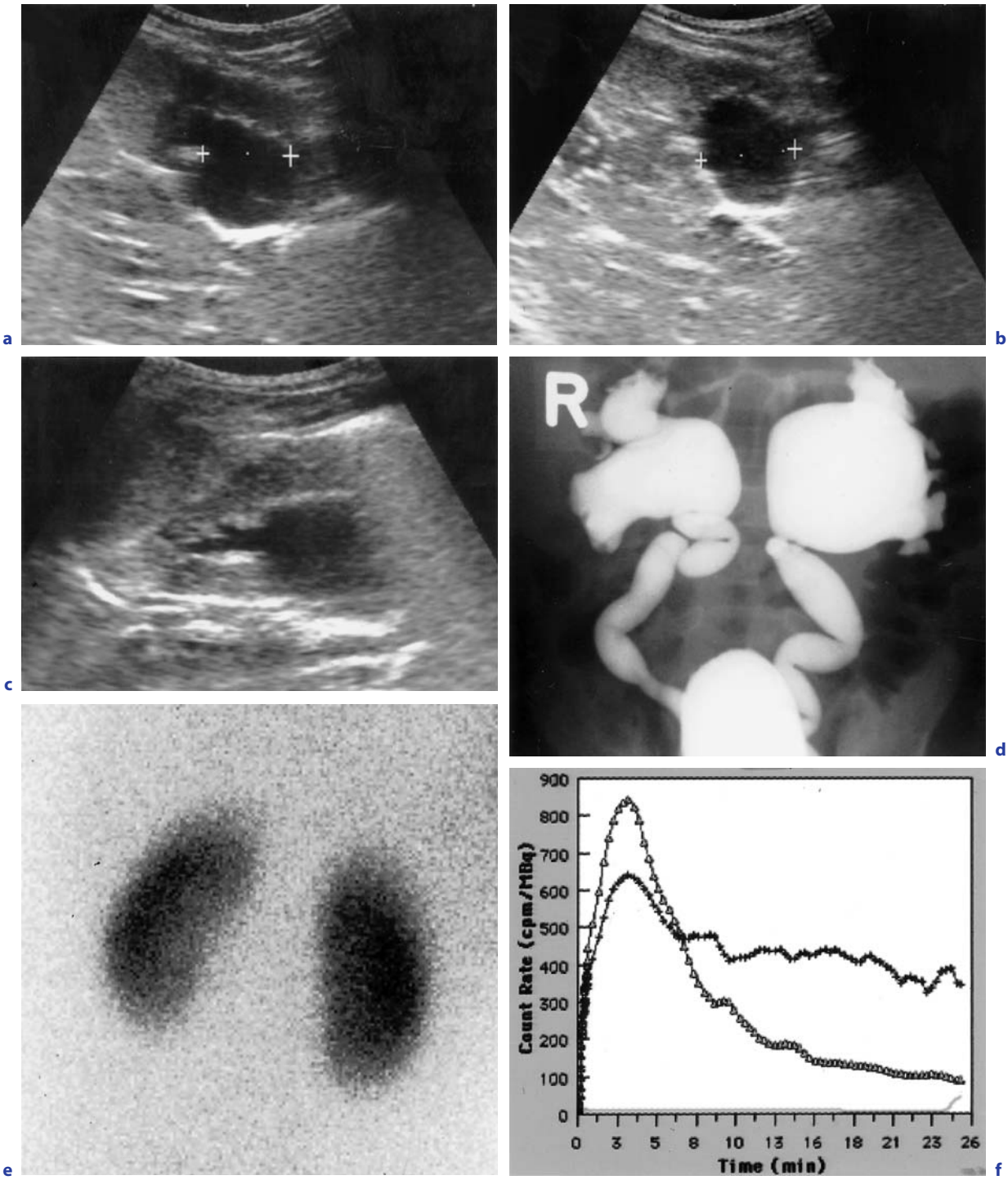
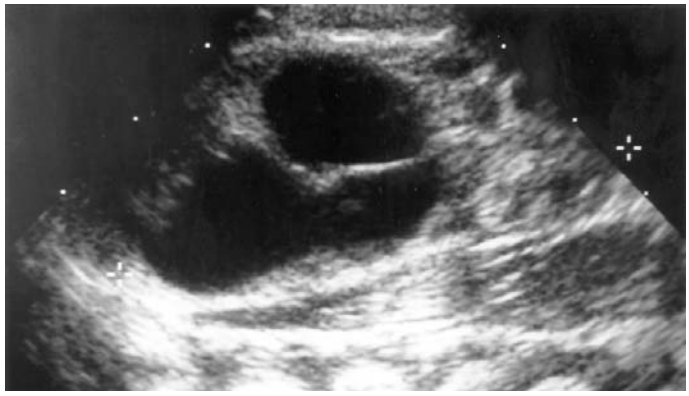


Fig. 12.6a–f. Antenatal diagnosis of hydronephrosis found to be due to bilateral VUR with upper-tract dilatation and a normal bladder outflow. **a** Postnatal ultrasound at 1 week of age shows a dilated renal pelvis of the left kidney with calyceal dilatation on the longitudinal cuts. **b** Transverse scan of the left kidney on the same examination also shows a dilated renal pelvis. **c** The longitudinal scan of the right kidney shows a similar dilatation. There were dilated ureters seen behind the bladder which was not thick-walled (not shown). **d** The VCU shows bilateral reflux into both pelvicalyceal systems which are dilated. The bladder is smooth walled. The urethra was normal (not shown). **e** Tc99m DMSA scan at 3 months of age fails to show any focal abnormality, there is slightly reduced function in the left kidney compared to the right. **f** The curves of the dynamic Tc99m MAG3 scan show the right kidney functions slightly better and drains more promptly than the left kidney



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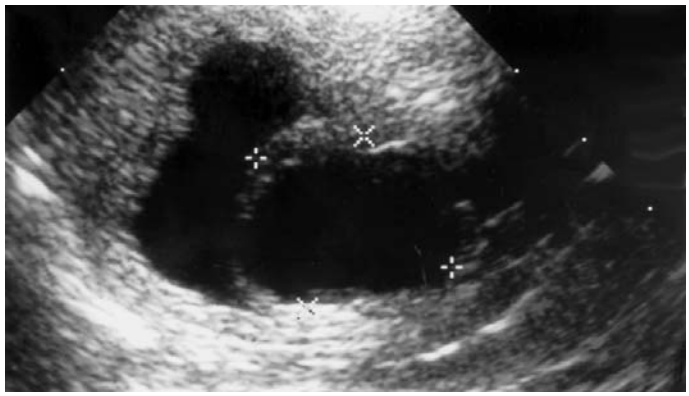

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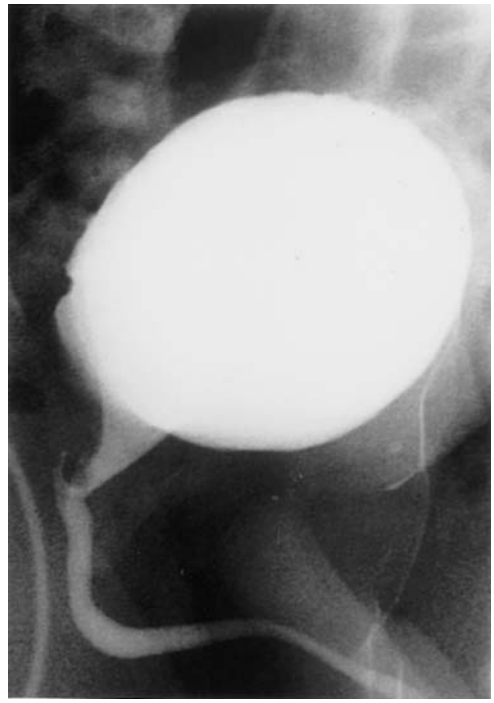

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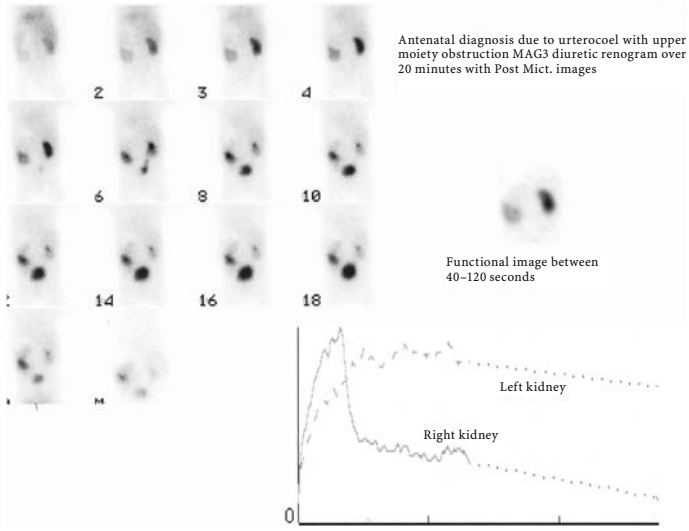

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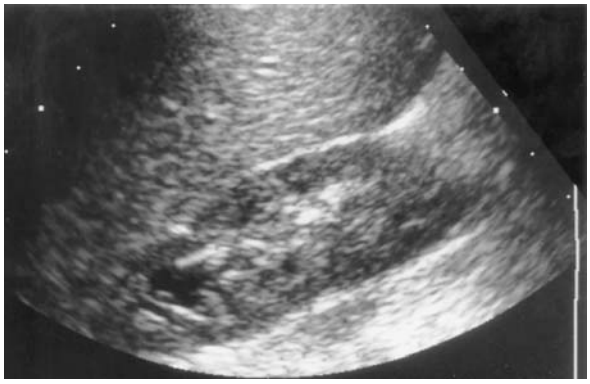
Fig. 12.7a–d. Obstructed upper moiety due to a ureterocele. **a** Longitudinal US section of the left kidney shows dilatation of the upper moiety with no dilatation of the lower moiety. **b** Longitudinal US section of the bladder showing the ureterocele with a little urine above. **c** The micturating view of the VCU shows an impression on the bladder base and posterior urethra of the ureterocele. No reflux is seen. **d** MAG3 diuretic renogram showing only moderate function in the displaced lower left moiety, but with good drainage. The upper moiety functions very poorly with poor drainage



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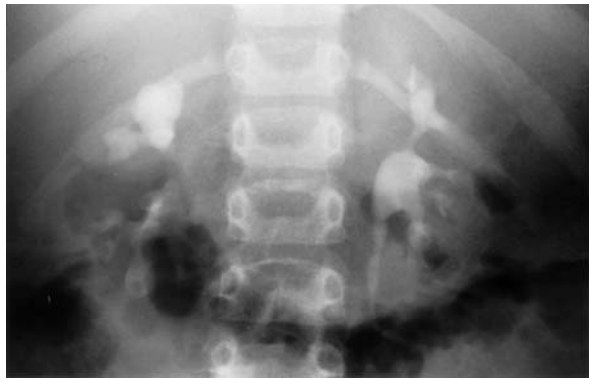

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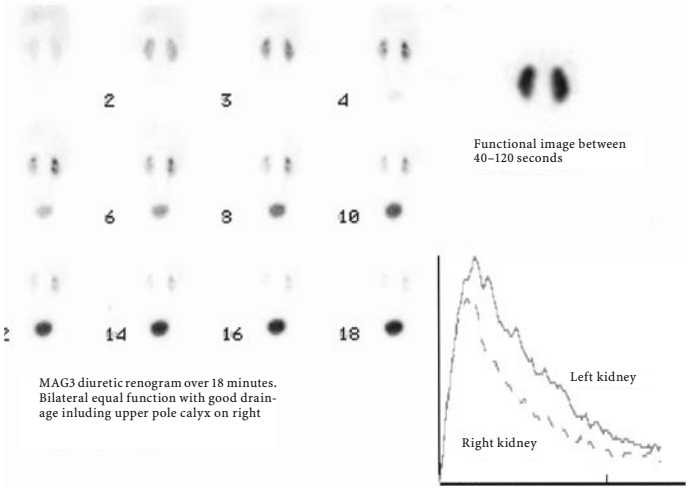

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Fig. 12.8a–c. Upper pole calyceal dilatation due to partial hold-up of the minor pelvis. Fraley's syndrome (original diagnosis: calyceal cyst). **a** Longitudinal US scan of the right kidney showing a transonic lesion in the upper pole of the kidney. **b** Coned 10 min image following 30 cc of nonionic contrast. The right kidney shows blunting of the compound calyx. Despite changes in posture and compression the minor pelvis, draining the upper pole calyces, could not be demonstrated. A repeat US of this area failed to demonstrate an anatomical abnormality. **c** The MAG3 renogram shows good equal function of both kidneys with no hold-up in the upper-pole collecting system of the right kidney

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The Postnatal Workup of Congenital Uronephropathies

13

Fred E. Avni, Michelle Hall, Marie Cassart, and Khalid Ismaïli

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F. E. Avni, MD, PhD
M. Cassart, MD, PhD
Department of Medical Imaging, Erasme Hospital, 808 Route de Lennik, 1070 Brussels, Belgium
M. Hall, MD
K. Ismaïli, MD, PhD
Department of Pediatric Nephrology, Children's Hospital Queen Fabiola, Avenue JJ Crocq 15, 1020 Brussels, Belgium

13.1 Introduction

In many European countries, obstetric ultrasound (US) is performed routinely during normal pregnancies. (In Belgium, three sonographic examinations are performed, one in each trimester.) This leads to the discovery of many fetal anomalies, and among them, uronephropathies represent one of the largest groups amenable to neonatal management. Furthermore, dramatic changes have occurred in this management since nowadays the uropathies are detected in mostly asymptomatic patients, and the treatment is mainly preventive. Also, antenatal detection and postnatal follow-up have yielded new data on the natural history of many pathologies (Levi et al. 1991; Thomas 1990; Scott and Renwick 1999; Rosendahl 1990; Livera et al. 1989; Preston and Lebowitz 1989).

13.2 Normal Sonographic Appearance of the Fetal Urinary Tract

Urine production starts during the 9th week of fetal life. The first US landmark of the normally functioning urinary tract is the bladder, which is visualized as a cystic structure in the fetal pelvis around the 11th week (Fig. 13.1a, Fig. 13.2). The kidneys themselves are visible as oval echogenic structures in the two lumbar areas around 13th week (Fig. 13.2b). During the rest of the pregnancy, their aspect will change and their size will increase progressively (Rosati and Guariglia 1996; Zalel 2002). The size measured during an examination can be plotted against the nomograms of renal growth (Cohen et al. 1991; Scott et al. 1995; Chitty and Altman

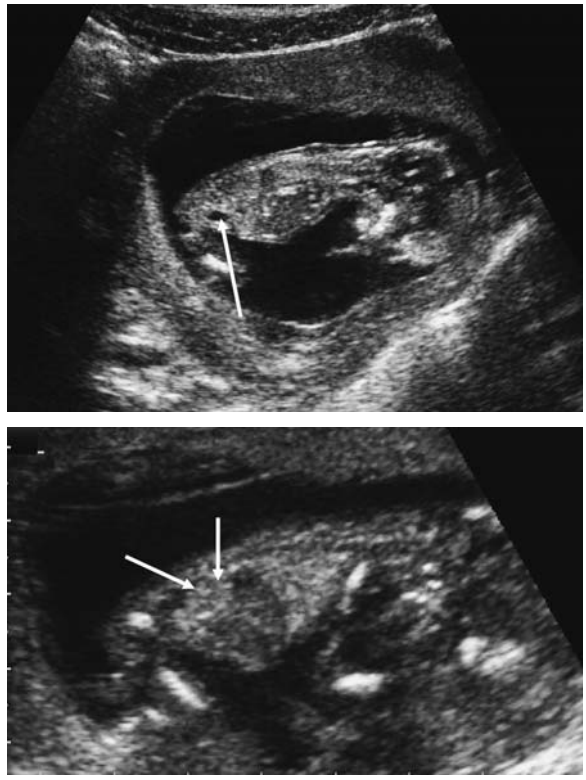


Fig. 13.1a–b. Normal urinary tract first trimester. **a** Fetal bladder 12 weeks' gestation. Mid-sagittal scan of the fetus. A small bladder (*arrow*) is visible. **b** Fetal kidney 12 weeks' gestation. Latero-sagittal scan of the fetus; the kidney appears as an ovoid echogenic mass (*arrows*)

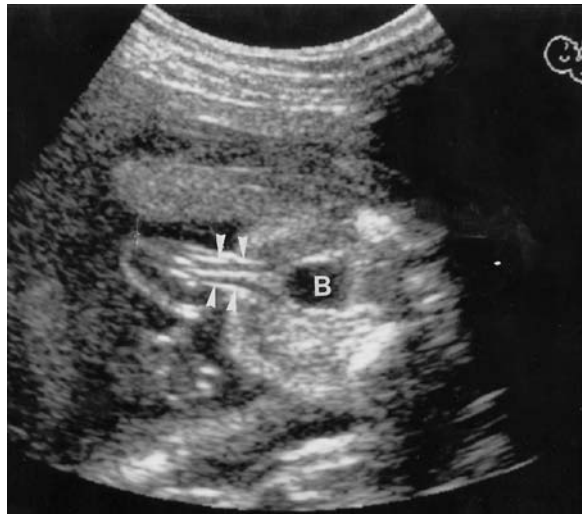


Fig. 13.2. Fetal bladder at 18 weeks after the last menstrual period (*LMP*). Transverse scan of fetal pelvis. The bladder (*B*) appears as a cystic structure limited by the two umbilical arteries (*arrowheads*)

2003). The echogenicity of the kidneys decreases with time and simultaneously the corticomedullary differentiation appears. The final sonographic appearance is demonstrated around the 26th week (Fig. 13.3). The fetal bladder fills and empties continuously, and this can be monitored during the US examinations (Chamberlain et al. 1984). These cycles become slower during the third trimester, particularly in female fetuses. Under normal conditions, the fetal ureters are not visible.

Besides the visualization of a normal-appearing urinary tract, other indirect evidence of a normally functioning urinary tract is a normal amount of amniotic fluid (two-thirds of which is produced

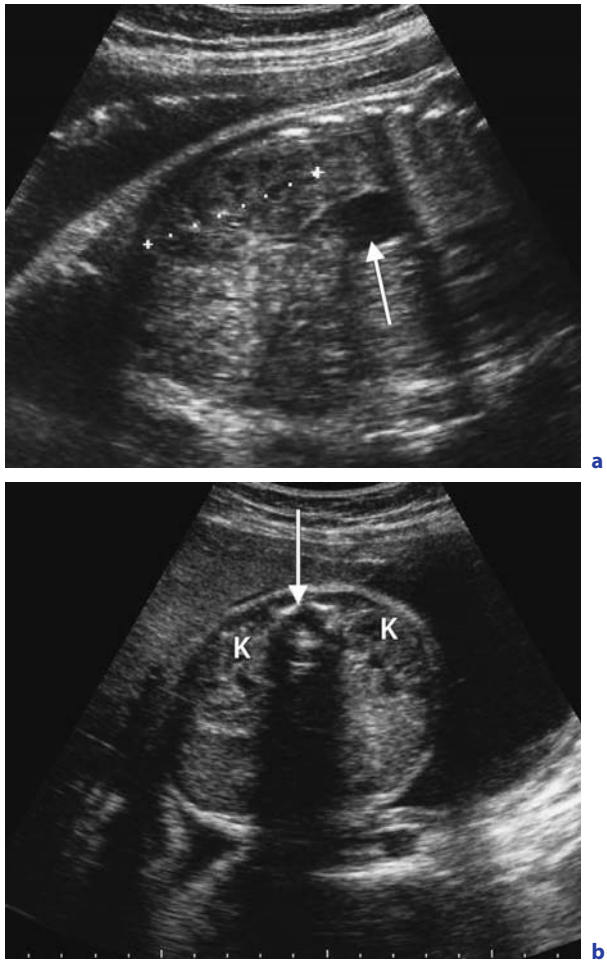


Fig. 13.3a,b. Normal kidney third trimester. **a** Sagittal scan of the left kidney; limited by the "+." It displays a normal cortico-medullary differentiation. The *arrow* points to the stomach. **b** Transverse scan of the fetal abdomen (the fetus is prone). Both kidneys (*K*) are visualized on each side of a vertebra (*arrow*)

by the fetal kidneys) after 15 weeks of pregnancy and normal development of the lungs (Rosati and Guariglia 1996; Thomas 1990; Hill et al. 1983).

13.3 Abnormal Urinary Tract in Utero

Anomalies that can and have been detected in utero are numerous; they include anomalies of the kidney itself, the collecting system, the bladder, and the urethra (Gunn and Dermot Mora 1995; Fine 1992; Rosendahl 1990; Gloor et al. 1995; Barakat and Drougas 1991; Weisel et al. 2005).

13.3.1 Abnormal Renal Number

Bilateral renal agenesis is part of Potter syndrome and is incompatible with extra-uterine life. At obstetrical US, no recognizable renal parenchyma is visible. At no time a bladder is demonstrated. Anamnios is the rule.

Unilateral renal agenesis is more common (1/500 pregnancies) and usually without consequence on postnatal life. On US examination, no renal structure can be found in one of the lumbar areas. When the left kidney is missing, the space is occupied by the splenic flexure of the colon (Fig. 13.4a,b). The adrenal may look hypertrophied and can be mistaken for a kidney. Renal agenesis is part of the dif-

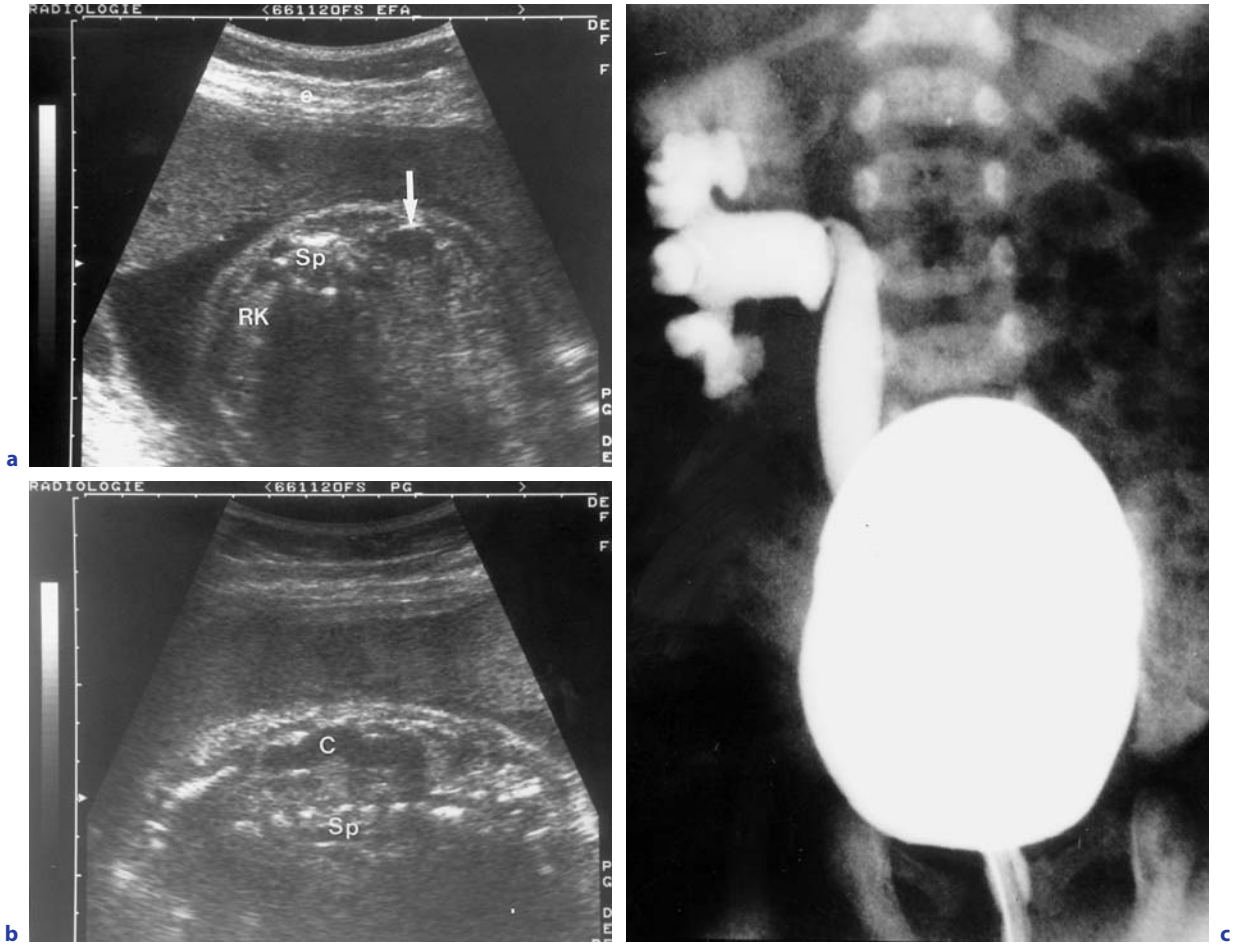


Fig. 13.4a–c. Unilateral renal agenesis. **a** Transverse scan of the fetal abdomen. A cystic structure (*arrow*) occupies the renal fossa, corresponding to the left colon. *RK*, right kidney; *Sp*, fetal spine. **b** Sagittal scan of the fetal trunk through the left lumbar fossa visualizing the colon (*c*). *Sp*, spine. **c** VCU at birth shows a grade III VUR with intrarenal VUR at the upper pole of the right solitary kidney

ferential diagnosis of the empty renal fossa in the fetus (see below) (Jeanty et al. 1990; Mandell et al. 1994). A workup will still be necessary after birth in order to confirm the status of the normal kidney and to look for associated vesicoureteric reflux (VUR) (Fig. 13.4c).

13.3.2 Abnormal Renal Location

When only one kidney is found, the second one must be searched in all the other potential locations, especially in the pelvis. Other ectopic locations such as crossed fused or horseshoe kidney (Fig. 13.5) can be detected, and the diagnosis is confirmed by the presence of the typical corticomedullary differentiation (Jeanty et al. 1990; Meizner and Bernhard 1995).

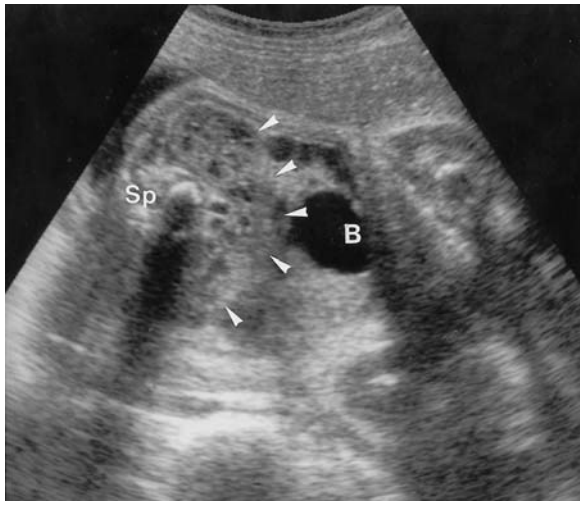


Fig. 13.5. Horseshoe kidney. Transverse scan of the low fetal abdomen. The horseshoe kidney (*arrowheads*) is identified thanks to the corticomedullary differentiation. *B*, bladder; *Sp*, spine

13.3.3 Abnormal Renal Echogenicity

Abnormal echogenicity results either from the presence of cysts (micro- or macroscopic) or from dysplasia (or both: cystic obstructive dysplasia) (Fig. 13.6) and from vascular insults. Corticomedullary differentiation is no longer visible; the thickness of the renal parenchyma may be reduced or increased (Kaefer et al. 1997; Blane et al. 1991; Avni et al. 2006; Chaumoitre et al. 2006).

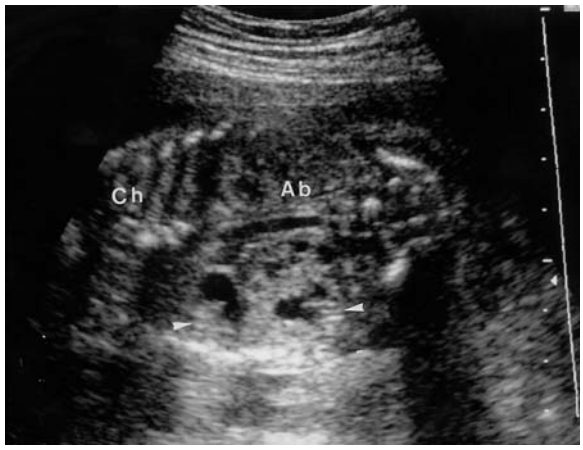


Fig. 13.6. Hyperechoic dysplastic cystic kidney (25 weeks LMP). Coronal view of the fetus. The left kidney (*between arrowheads*) appears hyperechoic and contains cysts of variable size (this kidney did not function and shrank after birth). *Ch*, fetal chest; *Ab*, fetal abdomen

13.3.4 Abnormal Renal Size

Small renal size most often corresponds to hypodysplastic kidneys. The etiology may be primitive or secondary to growth impairment due to VUR or obstruction (Avni et al. 1987b). The prognosis is related to the remaining renal function, which may be difficult to assess in utero. Cases with oligohydramnios have the poorest prognosis (Oliveira et al. 1999).

13.3.5 Urinary Tract Dilatation

Urinary tract dilatation is the most common anomaly detected in utero (Zerin et al. 1993; Tripp and Homsy 1995; Homsy et al. 1990; Mouriquand et al. 1999). The most common causes are obstruction at the ureteropelvic junction (UPJ) and fetal VUR. On the basis of the neonatal findings, several authors tend to differentiate between obstructive and nonobstructive UPJ. The other causes of urinary tract dilatation are listed in Table 13.1. The US approach to a dilatation of the fetal urinary tract is similar to that after birth. The aim of US is to

Table 13.1. Etiologies of dilatation of the fetal urinary tract

UPJ obstruction	45%
VUR	30%
Non obstructive UPJ	10%
UVJ obstruction	10%
Duplex kidneys	7%
PUV	4%
MDK	4%

differentiate upper from lower urinary tract dilatation. The basis for the diagnosis of a UPJ obstruction is the demonstration of a dilated renal pelvis as measured on a transverse scan (Figs. 13.7, 13.8). Various cut-off diameters have been proposed as abnormal. Most authors accept the limit of 4 mm at 4 months of pregnancy and 7 mm at 7 months. It is worth noting that most cases amenable to treatment are detected during the third trimester. Once a dilatation is detected, the next step is to try to quantify or to grade the "obstruction", and various classi-

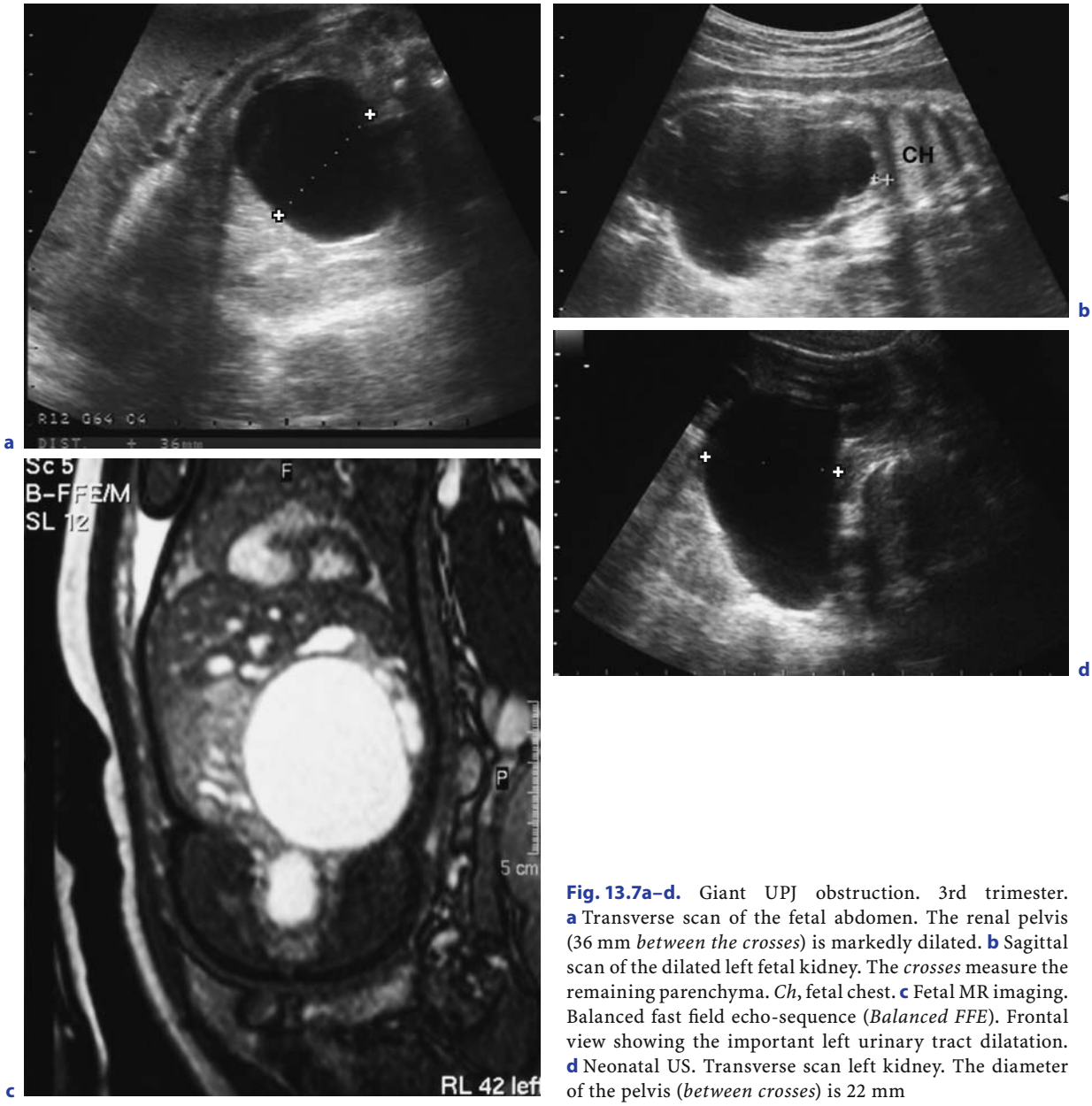


Fig. 13.7a–d. Giant UPJ obstruction. 3rd trimester. **a** Transverse scan of the fetal abdomen. The renal pelvis (36 mm *between the crosses*) is markedly dilated. **b** Sagittal scan of the dilated left fetal kidney. The *crosses* measure the remaining parenchyma. *Ch*, fetal chest. **c** Fetal MR imaging. Balanced fast field echo-sequence (*Balanced FFE*). Frontal view showing the important left urinary tract dilatation. **d** Neonatal US. Transverse scan left kidney. The diameter of the pelvis (*between crosses*) is 22 mm

fications have been proposed based on the degree of dilatation, the thickness, and the echogenicity of the renal parenchyma (Table 13.2) (Anderson et al. 1995; Maizels et al. 1992; Dremsek et al. 1997; Pates et al. 2006; Gramellini et al. 2006; Cohen-Overbeek et al. 2005; Ismaïli et al. 2003; John et al. 2004; Wollenberg et al. 2005; Riccabona et al. 2006). The more dilated the collecting system is, the more probable a decrease in renal function at birth.

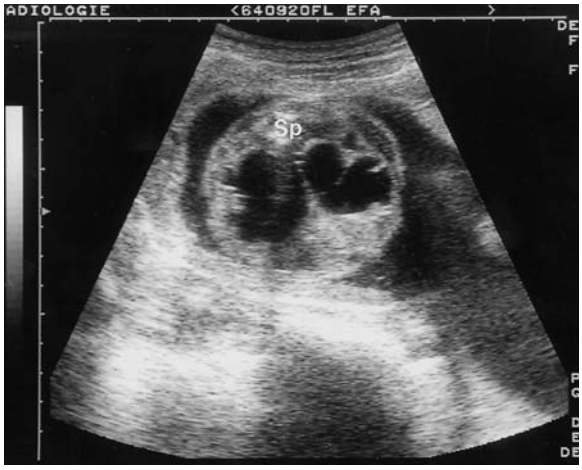


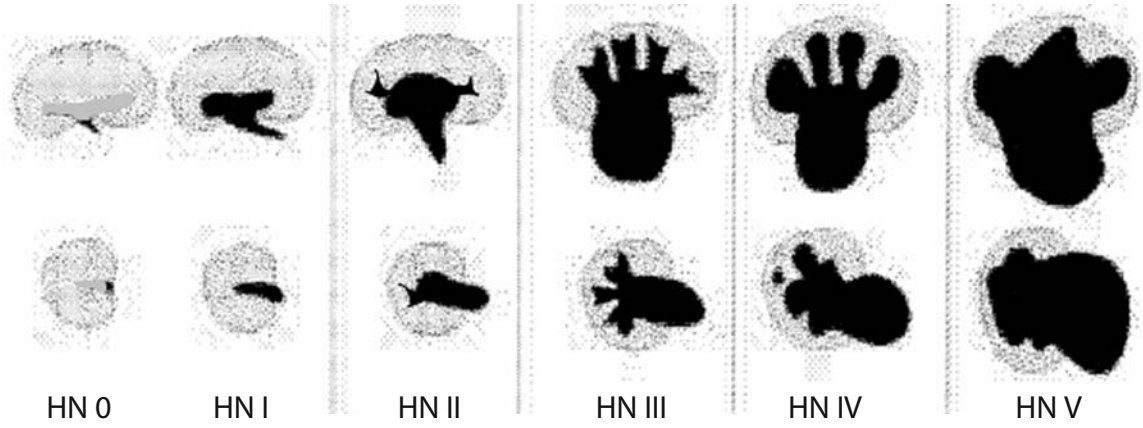
Fig. 13.8. Bilateral UPJ obstruction at 32 weeks. Transverse scan of fetal abdomen showing bilateral dilatation. *Sp*, fetal spine

Yet, there is no direct correlation between the degree of dilatation and renal function. The best marker of renal obstructive dysplasia and probable poor renal function is probably hyperechoic parenchyma with macrocysts within it (Blane et al. 1991).

The main differential diagnosis of UPJ obstruction is ureterovesical junction (UVJ) obstruction and VUR (Pates et al. 2006). The presence of a dilated ureter tips the balance towards a UVJ (Fig. 13.9) obstruction or VUR (Fig. 13.10a) (Weinberg et al. 1998). Variability of the pelvic dilatation during the examination seems more specific for VUR (Fig. 13.10b,c). When there is a large bladder, bladder outlet obstruction should also be considered (Fig. 13.11). Furthermore, bilateral ureterohydronephrosis and a thickened bladder wall in a male fetus suggest posterior ureteral valves. Megacystis-megaureter associated with VUR and megacystis-microcolon-hypoperistalsis syndrome are the potential differential diagnoses (Mandell et al. 1992; McHugo and Whittle 2001).

Other etiologies for urinary tract dilatation include duplex kidneys complicated by a dilatation of the upper or the lower pole (Abuhamad et al. 1996; Vergani et al. 1999). Such anomalies can be associated with an ectopic extravesical ureter (Fig. 13.12) or an ectopic ureterocele (Fig. 13.13), which can be demonstrated in utero.

Table 13.2. Classification of fetal dilatation (Riccabona et al. 2006)



HN 0 = no or minimal collecting system visible, considered normal
HN I = just the renal pelvis visible with an axial diameter less than 5–7 mm, usually considered normal
HN II = axial renal pelvis diameter less than 5/7–10 mm; some calices with normal foniceal shape visible
HN III = marked dilatation of the renal calices and pelvis larger than 10 mm with reduced forniceal and papillar differentiation without parenchymal narrowing
HN IV = gross dilatation of the collecting system with narrowing of the parenchyma
HN V = used in some places additionally to communicate an extreme HN with only a thin, membrane-like residual renal parenchymal rim

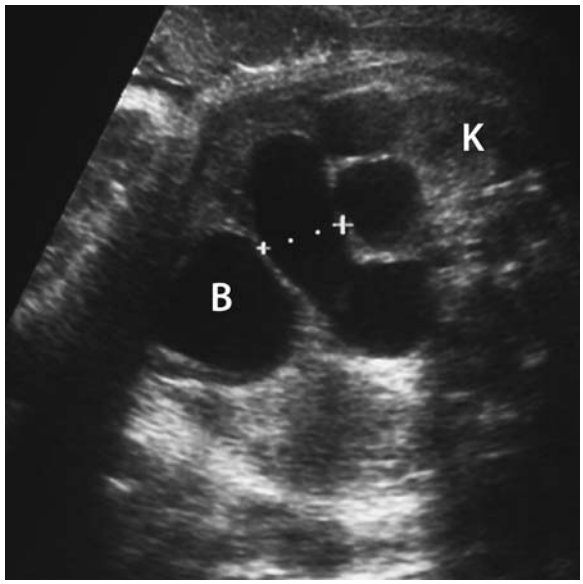


Fig. 13.9. Right UVJ obstruction. 3rd trimester. Transverse scan of the fetal abdomen. A circonvoluted dilated ureter (12 mm *between the crosses*) is visible. *K*, kidney; *B*, bladder

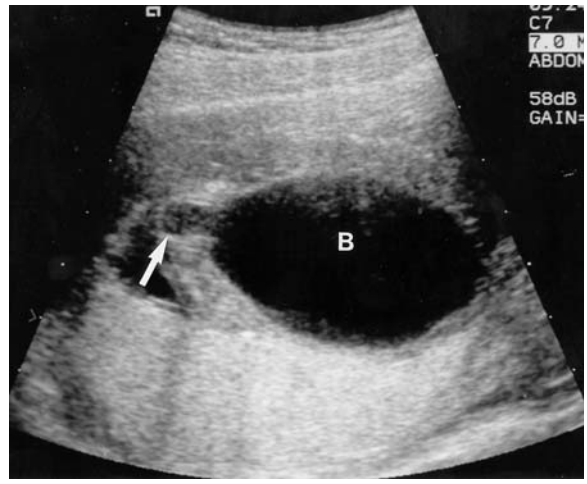
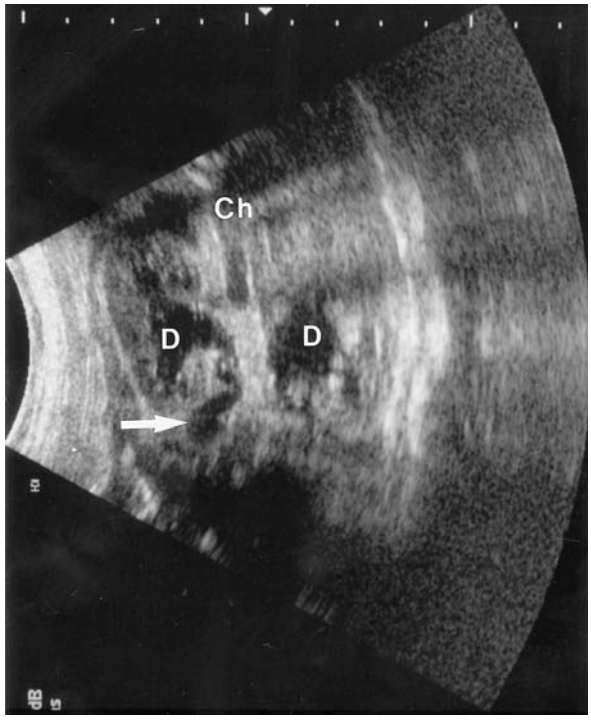
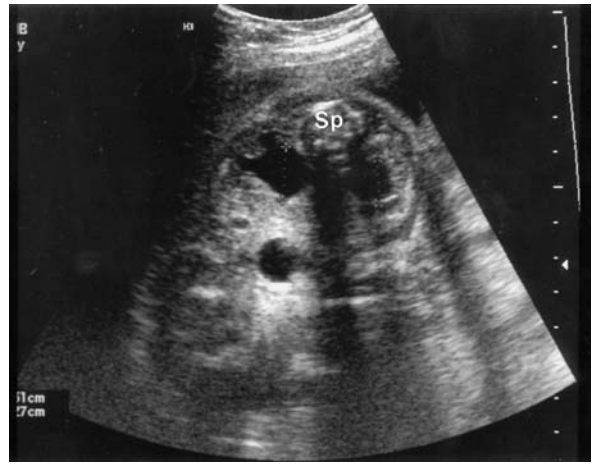


Fig. 13.11. Urethral atresia at 15 weeks' LMP. Huge fetal bladder (*B*) that occupies the entire fetal abdomen. The proximal urethra is dilated (*arrow*)



a



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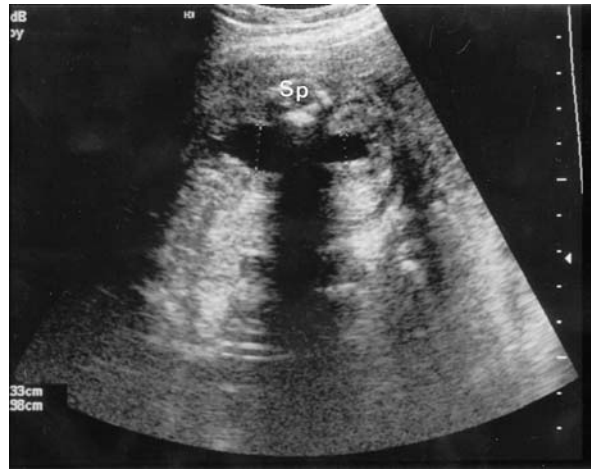
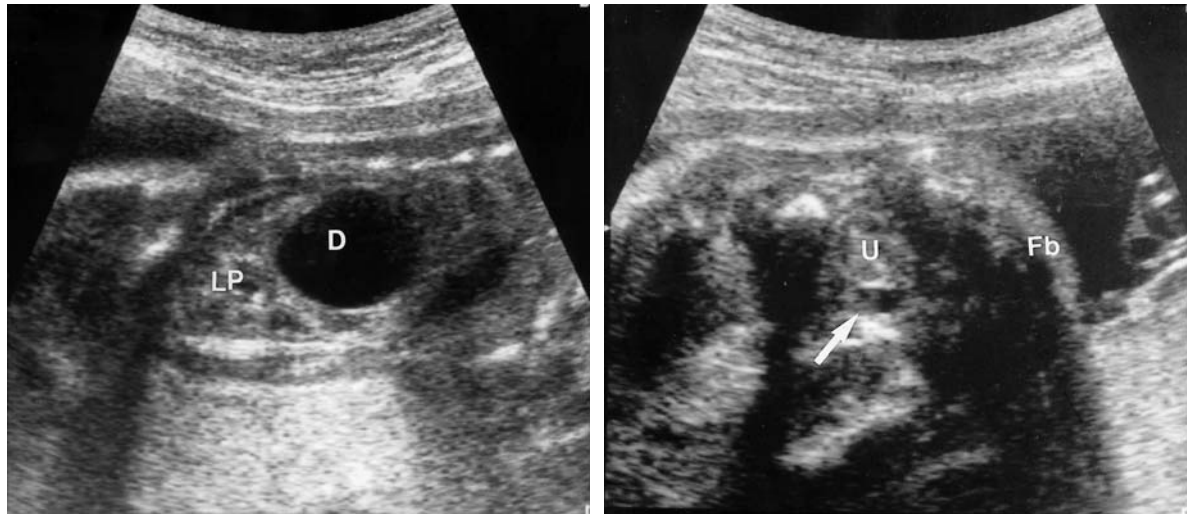


c

Fig. 13.10a–c. VUR in utero. **a** Coronal view of the fetal trunk showing bilateral hydronephrosis (*D*) and unilateral ureteral dilatation (*arrow*). *Ch*, fetal chest. **b,c** Transverse scans of the fetal abdomen a few seconds apart showing variable dilatation of the renal pelvic dilatation, highly suggestive of VUR. *Sp*, spine



a b

Fig. 13.12a,b. Duplex kidney with dilated upper pole and ectopic extravesical ureteral insertion. **a** Sagittal scan of the kidney with dilatation (*D*) of the upper pole and nondilated lower pole (*LP*). **b** Transverse scan of the fetal pelvis; the dilated ureter (*arrow*) is visualized lateral the fetal uterus (*U*). *Fb*, fetal back

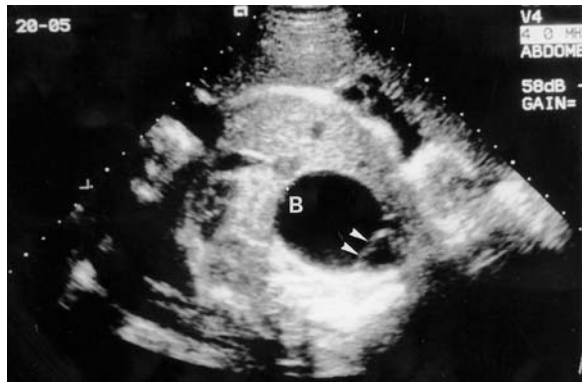


Fig. 13.13. Ectopic ureterocele associated with a duplex kidney. Transverse scan through fetal bladder (*B*) showing a septum (*arrowheads*) that limits the ureterocele

In selected cases, where US is unable to determine a precise diagnosis, fetal MR imaging may provide additional information that will help counsel pediatricians and parents (Fig. 13.7c) (Cassart et al. 2004).

13.3.6 Cystic Renal Diseases

Multicystic dysplastic kidney disease is by far the most common cystic renal disease that can be detected in utero. The condition is usually unilateral. Bilateral cases are incompatible with extrauterine life. Sonographically, the typical pattern includes a mass with multiple cysts of varying sizes with no connections between them and without normal renal parenchyma (Fig. 13.14). The main differential diagnosis is UPJ obstruction (Aslam et al. 2004; Avni et al. 1987).

Polycystic kidney diseases can also be detected in utero. In the typical presentation of the recessive type, the kidneys are very large (+4 – +8 SD) with increased echogenicity and lack of cortico-medullary differentiation; more unusual presentations include the presence of medullary cysts or reversed cortico-medullary differentiation (Fig. 13.15); oligohydramnios and lung hypoplasia indicate a poor prognosis. In the dominant type, the renal cortex appears hyperechoic, increasing the cortico-medullay differentiation. Cysts may be detected in utero. Other cystic diseases are usually related to syndromes (i.e., Meckel-Gruber syndrome and Bardet-Biedl syndrome) (Avni et al. 2006).

13.3.7 Tumors

Renal tumors are rare. They can be cystic, solid or of mixed type. Multiple cystic masses are more likely to correspond to a multicystic dysplastic kidney that can affect only part of a duplex kidney. Differential

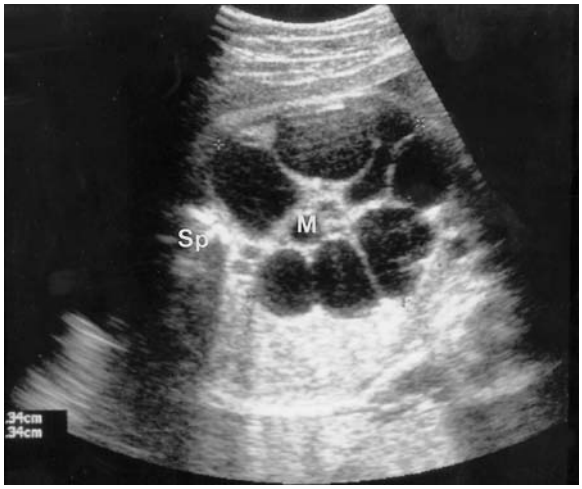


Fig. 13.14. Multicystic dysplastic kidney in utero at 30 weeks. Transverse scan of the fetal abdomen showing the large typical multicystic mass (*M*). *Sp*, spine

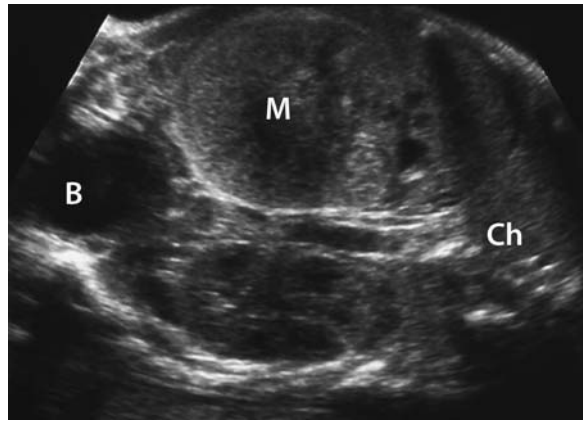


Fig. 13.16. Right mesoblastic nephroma. 3rd trimester. Frontal view of the fetus. A huge solid mass (*M*) has developed in the lower pole of the right kidney. It was removed by surgery postnatally. *B*, bladder; *Ch*, chest

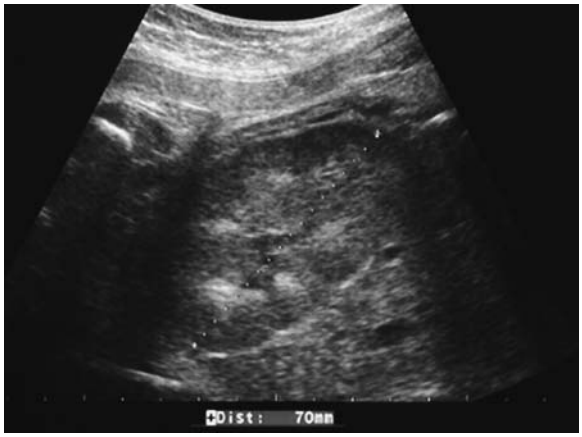


Fig. 13.15. Autosomal recessive polycystic kidney. 3rd trimester. Sagittal scan of a kidney (the contra-lateral kidney had the same appearance). Massively enlarged left kidney (7 cm) with increased ehcogenicity and reversed corticomedullary differentiation. Oligohydramnios was obvious

diagnoses include mesoblastic nephroma (Fig. 13.16) and Wilms' tumor (Bove 1999; Shibahara et al. 1999; Applegate et al. 1998; Irsutti et al. 2000).

13.3.8 Prognosis – In Utero Therapy?

The prognosis in utero is based on the time of diagnosis, the degree of urinary tract dilatation, the presence of an uni- or bilateral dilatation, the amount of amniotic fluid, signs of renal dysplasia, and pulmonary development. Factors of poor prognosis are listed in Table 13.3. The lethal uropathies are mainly detected during the first half of pregnancy (Fig. 13.11) (Blachar et al. 1994). Nonlethal renal anomalies are mainly diagnosed during the second half of pregnancy (Economou et al. 1994; Oliveira et al. 1999). Chromosomal analysis is indicated mainly in bilateral obstructive anomalies and when anomalies of other systems are demonstrated. Analysis of fetal urine is possible and has led several teams to obtain fetal urine (Spitzer 1996; Elder et al. 1990; Muller et al. 1993). To date there is no convincing evidence that such measures have had beneficial consequences on fetal outcome (Freedman et al. 1996). It should be noted that unless there is evidence of fetal distress, no uropathy justifies advancing the date of delivery.

Table 13.3. Factors of poor prognosis for uropathies detected in utero

• Early diagnosis (< 20 weeks)
• Oligohydramnios
• Bilateral ureterohydronephrosis
• Bilateral cystic dysplasia
• Associated anomalies in other systems
• Chromosomal anomalies

The main advantage of an in utero diagnosis is to induce an optimized neonatal workup of the uropathy so that no supplementary damage will occur to the kidney (Elder 1992; Skari et al. 1998; Wooddard 1993).

Conclusion

A wide spectrum of uropathies can be detected in utero with more and more diagnostic accuracy. UPJ obstruction and VUR are the two most common causes of fetal urinary tract dilatation.

13.4 Postnatal WorkUp

After birth, severe bilateral renal disease can be associated with pneumothorax, lung hypoplasia, and life-threatening respiratory distress (Fig. 13.17) (Perlman et al. 1973). This respiratory failure is an emergency situation, and mechanical respiratory assistance is mandatory even before any treatment can be considered for the urinary tract anomaly. Conversely, whenever a neonate presents seemingly spontaneous pneumothorax, an US examination should be performed in order to verify the status of the urinary tract.

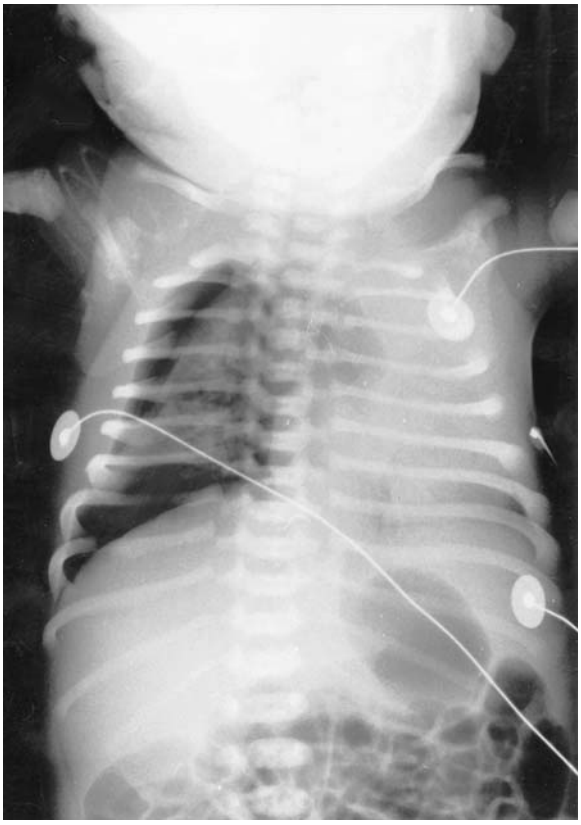
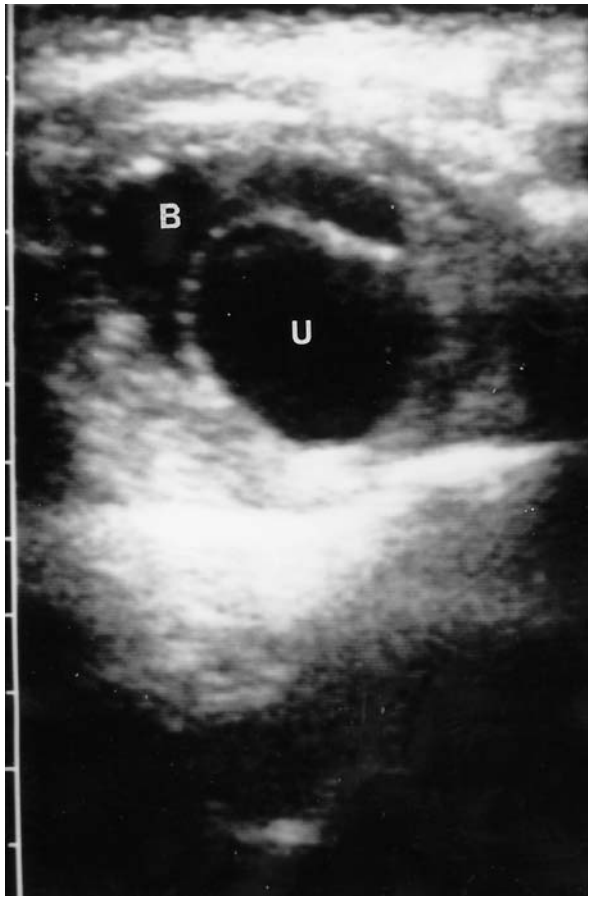


Fig. 13.17. Right pneumothorax and bilateral lung hypoplasia in a neonate with recessive type polycystic kidney disease

No other uropathy amounts to a real emergency. Yet, several conditions could necessitate early management and workup in the immediate neonatal period. For instance, in case of posterior urethral valves, the rapid placement of a cystocatheter is preferable in order to derive the urine and to reduce the dilatation (Nakayama et al. 1986). Ectopic ureterocele associated with an obstructed upper pole of a duplex kidney is prone to prolapse into the urethra during micturition and to provoke acute bladder outlet obstruction and obstructive anuria (Figs. 13.18a,b; Fig. 13.19) (Avni et al. 1991; Austin et al. 1998). Unroofing the ureterocele under cystoscopy is therefore advocated by several teams as the first step in managing this type of duplex kidneys (Fig. 13.18c,d) (Van Savage and Mesrobian 1995; Hagg et al. 2000).

For all uropathies, the workup has been markedly standardized. Nowadays, the major workload of an imaging department dealing with neonatal pathology is related to the management of antenatal diagnosis of a urinary tract dilatation and its significance (Owen et al. 1996; Devaussuzenet et al. 1997). The extensive neonatal workup performed in recent years by many teams has increased mainly the detection of neonatal VUR (Zerin et al. 1993; Van Eeide 2007; Ismaïli et al. 2006).

Two approaches have been proposed. For some authors, whatever the result of a neonatal US, a VCU should be performed in case of any antenatal diagnosis of a urinary tract dilatation. For them, US is a poor predictor of VUR (Tibbals and De Bruyn 1996; Walsh and Dubbins 1996; Scott et al. 1991; Blane 1991). For others, a VCU should not be performed in all neonates; there will be too many false-negative studies, partly because spontaneous resolution of VUR is frequent. Also, complications of VCU may occur (Vates et al. 1999). A VCU should be performed only in those patients in whom the anomaly had been confirmed after birth (Yerkes et al. 1999). Therefore, US is performed first in order to confirm the anomaly (Fig. 13.7d) (Marra et al. 1994; Avni et al. 1997; Hulbert et al. 1992). In an urgent case, it can be performed as soon as the clinical condition



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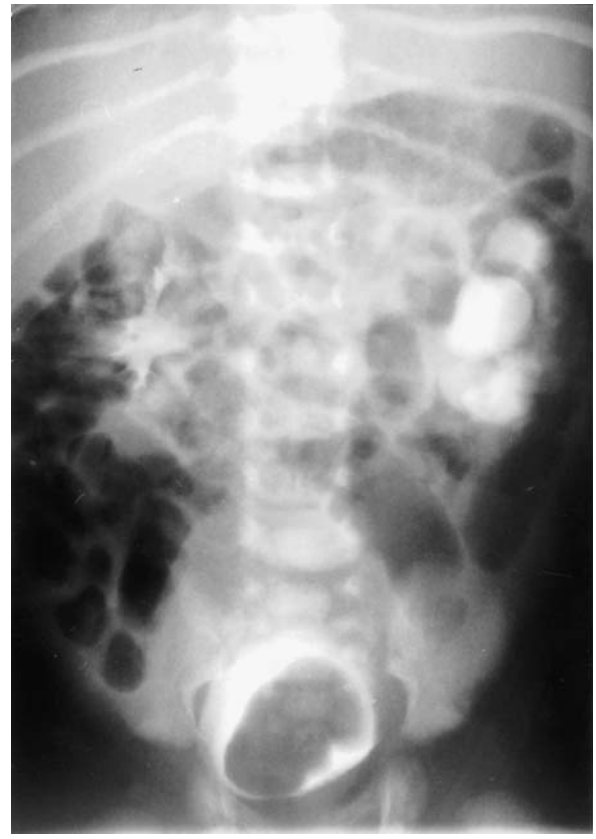

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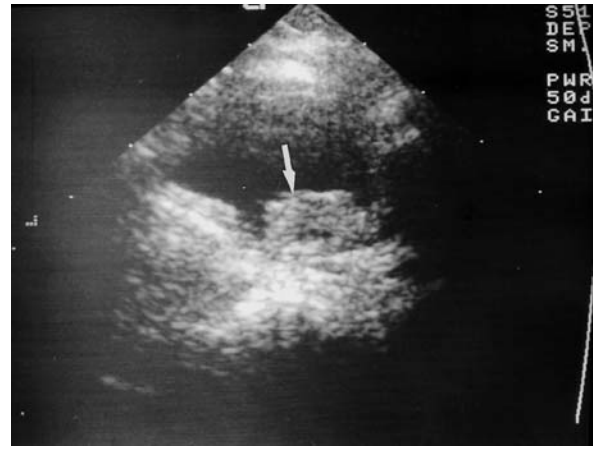

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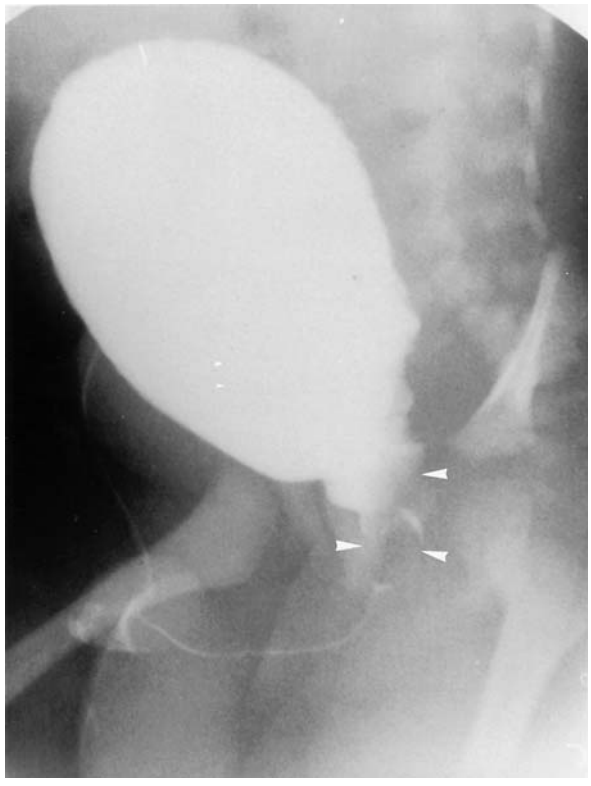
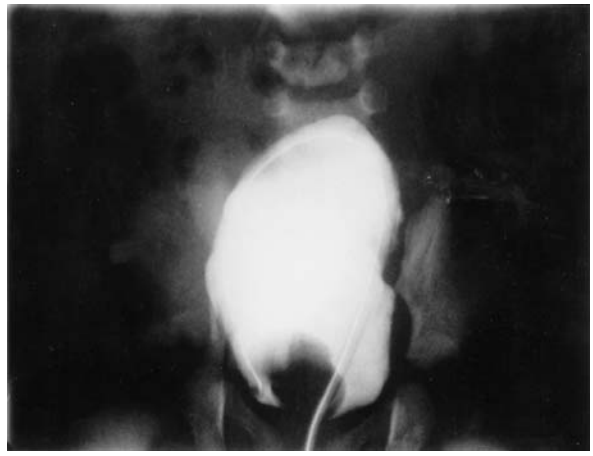


c

Fig. 13.18a–d. Duplex kidney with ectopic ureterocele in a baby boy. **a** Transverse scan of the bladder (*B*) showing a typical ureterocele (*U*). **b** IVU showing a left duplex system with a non fuctioning upper pole displacing the lower moiety laterally. The upper pole is associated to an ectopic intravesical ureterocele that appears as a filling defect. **c** VCU (micturition phase); the ureterocele (*arrowheads*) has prolapsed into the urethra and prevents voiding. **d** Transverse scan of the bladder after endoscopic incision of the ureterocele that determines a pseudo-mass (*arrow*).



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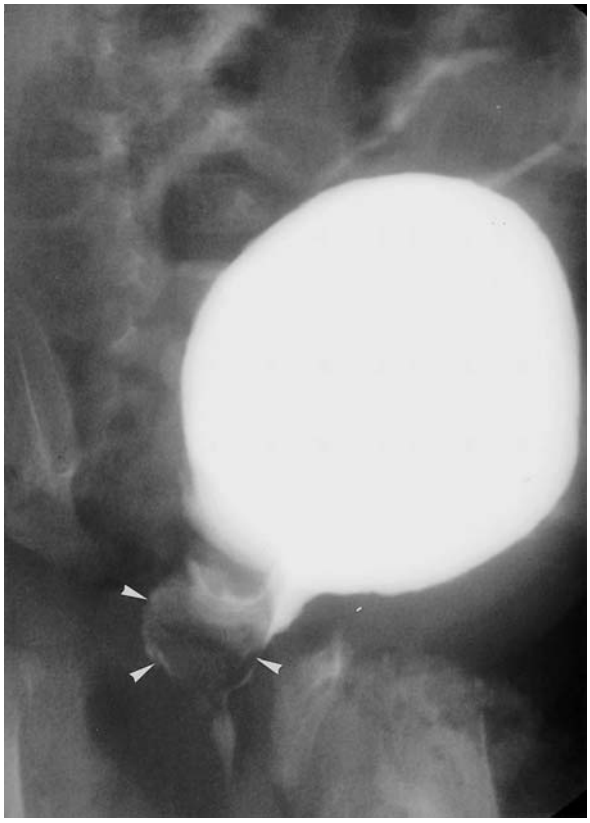


b

Fig. 13.19a,b. Duplex kidney with an ectopic ureterocele in a baby girl. **a** VCU: filling phase with the ureterocele in the bladder. **b** VCU: voiding phase. The ureterocele prolapses into the urethra (*arrowheads*)

permits. For all other cases, it should be delayed to the postphysiological dehydration period, namely after the 5th day. At that time, the US examination should be as detailed as possible in order to detect every anomaly that would justify continuing the workup. The presence of a urinary tract dilatation is the most important landmark; 7 mm is the most widely accepted upper limit of normal (some prefer 5 mm, others 10 mm). Dilatation of the pelvis is not the only anomaly that should be looked for. Other anomalies can be associated with VUR (Table 13.4). Loss of corticomedullary differentiation is a good predictor of high-grade VUR. One should not forget to examine the bladder; a large thickened bladder could be a sign of VUR. With a meticulous US examination, one should be able to detect over 85% of cases of VUR. Those that are missed are nondilating or grade I–II VUR (Marra et al. 1994; Avni et al. 1997; Weinberg and Yeung 1998; Ismaïli et al. 2004; Bouzada et al. 2004).

We favor the second approach and a decision tree based on the neonatal US (Table 13.5a,b) based on the neonatal and follow-up sonographic findings. If the US examination is entirely normal, it seams reasonable to perfom a follow-up examination at 1 or 3 months in order to detect cases that would have escaped the neonatal screening (Dejter and Gibbons 1989; Clautice-Engle et al. 1995; Riccabona et al. 2006).

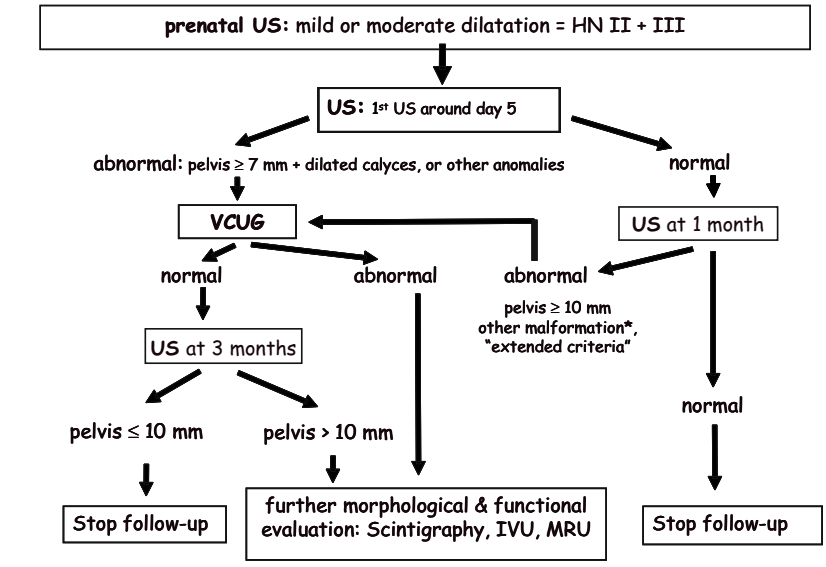
Table 13.4. US findings that may be associated with VUR

- Pelvic dilatation more than 7 mm
- Variable dilatation
- Calyceal dilatation
- Ureteral dilatation more than 3 mm
- Pelvic wall thickening
- Loss of CM differentiation
- Small kidney
- Signs of dysplasia
- Enlarged bladder

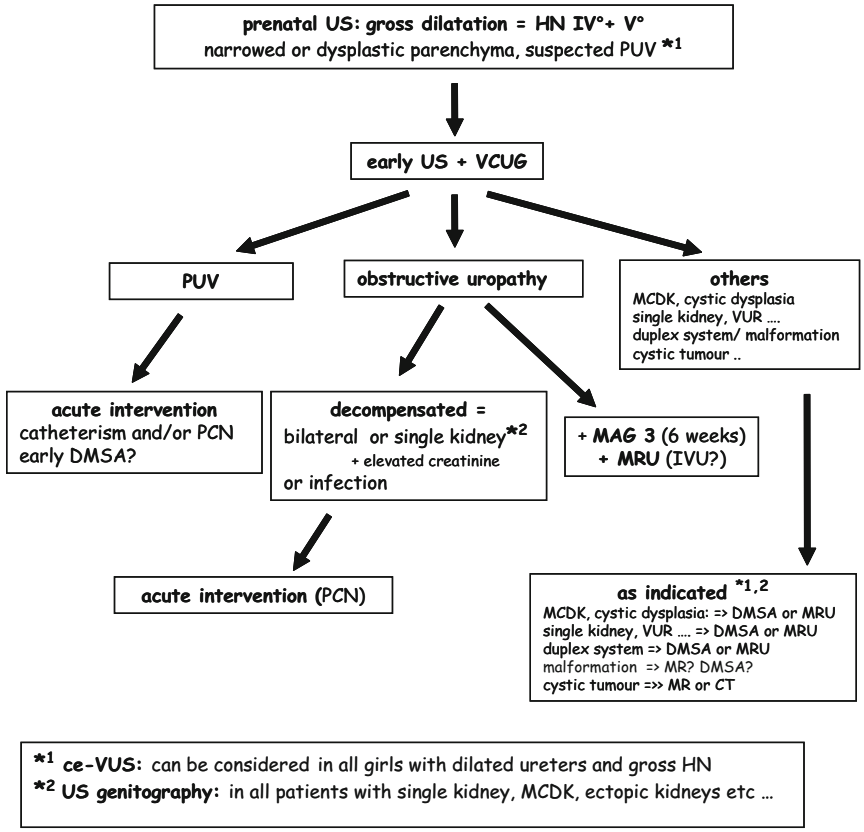
In case of abnormal US, a VCU should be performed, preferably during the first 2 weeks of life. The examination should be performed under antiseptic chemotherapy. The aim of the examination is to detect VUR and bladder or urethral anomalies.

Table 13.5. a (mild to moderate dilatation) and **b** (severe dilatation). Proposed neonatal workup of fetal uropathies:

a Postnatal imaging algorithm in mild or moderate foetal hydronephrosis (Riccabona et al. 2006)



b Postnatal imaging algorithm in severe foetal hydronephrosis



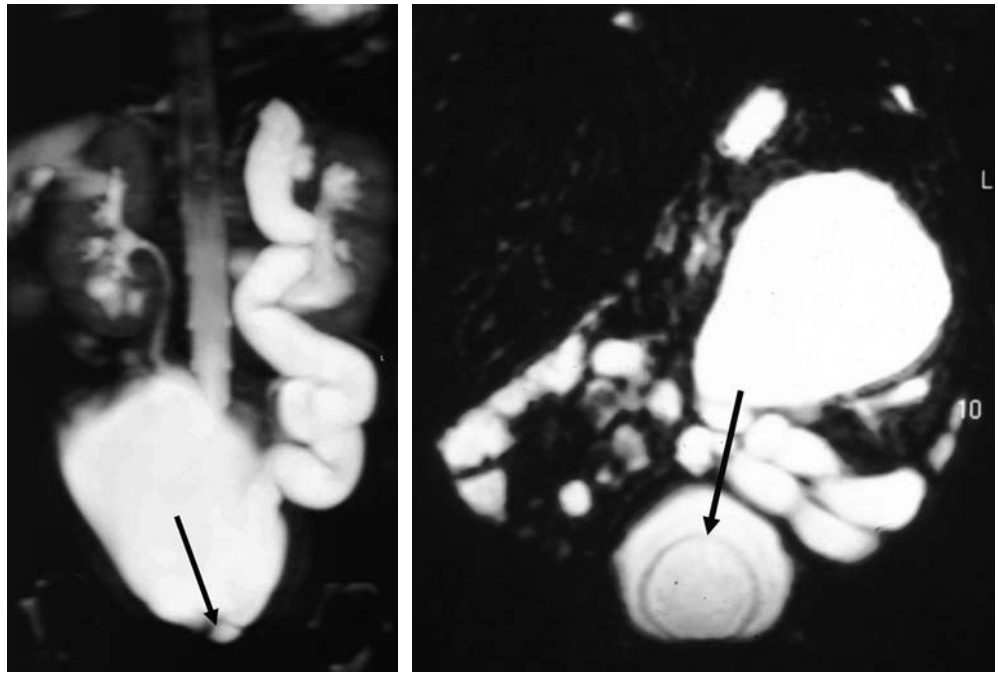
If VUR is demonstrated, the patient is given prophylactic antibiotic therapy and followed up clinically and by imaging for 2 years with the hope that the VUR will resolve spontaneously. During this period of time, renal growth is monitored every 2–3 months using US and renal function every 6 months with isotope studies. The resolution of VUR is verified every year on isotopic or radiological VCU.

If no VUR is present, the dilatation is probably related to obstruction and the workup must be completed by isotopic studies, including a furosemide nephrogram especially in cases with severe dilatation.

If surgery is chosen, the morphology of the urinary tract must be assessed. Intravenous urography (IVU) used to be performed for this purpose. However, it is an irradiating technique that requires injection of contrast material. Also, the poorer the function, the poorer the opacification of the dilated urinary tract will be. Therefore, nowadays more and more authors advocate the use of MR urography for the assessment of a dilated urinary tract (Fig. 13.20) (Nolte et al. 1992; Borthne 1999). Furosemide is usually injected in order to increase the diuresis and to optimize the visualization of the urinary tract. T2 sequences, inversion recovery sequences, and post-gadolinium enhancement 3D-T1 sequences allow a good evaluation of the urinary tract (see Chap. 1.2). The drawback of the method is that it requires sedation and that it is not widely available.

In case of a duplex collecting system, the workup is similar to that for obstruction, except that the morphological assessment must be more rapid since a therapeutic decision might have to be made early. Again US, VCU, and MR urography will optimally evaluate the morphology (Figs. 13.18–13.20). MR urography is the best method to visualize an ectopic extravesical ureter. An isotope study using Tc-99m DTPA or MAG3 is also mandatory in order to evaluate the remaining function of the two poles (Avni et al. 2000; Piez 2006).

For all other anomalies, especially multicystic dysplastic kidney, renal ectopia, or unilateral agenesis, the workup should also include US and eventually a VCU in order to detect ipsi- or contralateral VUR, which would require prophylactic chemotherapy (Atiyeh et al. 1993; Flack and Bellinger 1993; Selzman and Elder 1995; Ismaïli et al. 2005). Also of interest is to search for associated genital anomalies on pelvic ultrasound (Table 13.5) (Riccabona et al. 2006).



a b

Fig. 13.20a,b. MR imaging in complicated duplex kidney. **a** Left duplex with obstructed upper pole and ectopic infravesical insertion of the dilated ureter (*arrow*). **b** Left duplex with obstructed upper pole and ectopic ureterocele (*arrow*)

In the case of hereditary renal cystic disease, the workup will depend upon the type of cystic disease and the clinical condition (Avni et al. 2006). In the case of renal tumor, a classical workup will determine the type of tumor and its extension. A nephrectomy will usually be required.

Conclusion

An US examination has to be performed at birth in all patients with an antenatal diagnosis. A VCU should follow in the case of an US abnormality. The presence or absence of VUR will determine the rest of the neonatal workup.

13.5 Treatment in Light of the Natural History of Uronephropathies

As mentioned above, antenatal diagnosis has led to dramatic changes in the management of uropathies. First, the patients are mostly asymptomatic; second, the medical follow-up of many pathologies has shown their potential to resolve spontaneously. Consequently, surgery has been less and less advocated. The main goal of the prophylactic treatment is presently to prevent further renal damage during the period when spontaneous resolution is expected. It should be noted that infection does occur in some cases despite the prophylactic antibiotic therapy; these cases make alternative treatment necessary (Dacher et al. 1992; Jaswon et al. 1999; Morin et al. 1996; Ismaïli et al. 2006; Lee et al. 2006).

13.5.1 Vesicoureteric Reflux

Many series have shown that 2/3 of neonatal VUR (yet, mainly grades I-III) are likely to resolve or at least to improve during an observation period of 2 years. Therefore, once the anomaly is detected the patient is given prophylactic antibiotic therapy and followed clinically and by imaging as described above. In some circumstances another therapeutic approach (surgery or endoscopic injection of collagen) should be proposed: in the case of infection despite therapy, if there is failure to thrive, or if continuing the treatment is problematic for the family (Herndon et al. 1999; Burge et al. 1992; Bouachrine et al. 1996; Dudley et al. 1997; Assael et al. 1998; Ismaïli et al. 2006).

13.5.2 UPJ Obstruction

The therapeutic management of UPJ obstruction has been much more controversial than for VUR. Advocates and opponents of neonatal surgery have published large amounts of scientific material that shows opposite or contradictory results. For some, early surgery is safe and improves renal function notably. For others, the UPJ obstruction has been present for a long time, and there is only a faint chance of improving the condition by surgery. This does not justify operating on a neonate. Furthermore, the dilatation may resolve spontaneously (Fig. 13.21). Yet others suggest following up renal function and operating on only those patients who

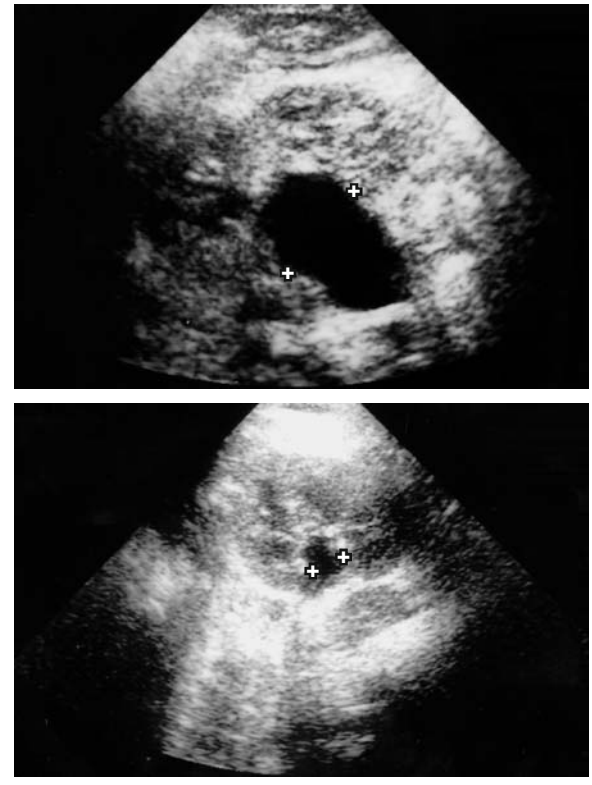


Fig. 13.21a,b. Resolution of a right UPJ "obstruction." **a** At birth the renal pelvis is dilated and measures 15 mm (*between the crosses*) on the transverse scan of the kidney. **b** At the age of 6 months, the remaining dilatation measures 5 mm

show functional deterioration. Finally some suggest following renal growth on US and operating when the contralateral kidney displays compensatory growth. Also, the criteria used to diagnose obstruction are not clear-cut, either on US or on many isotopic studies.

On the basis of all the data accumulated, conservative management seems the most adequate in mild or moderate cases. Clinical status and renal function must be monitored closely. In most cases the dilatation will be stable or even resolve. Surgery must be proposed if clinical symptoms appear or if renal function deteriorates. In the more severe cases, spontaneous resolution is less likely and symptoms related to abdominal discomfort are more frequent. For such patients, surgery may be beneficial (Koff and Campbell 1994; Docimo and Silver 1997; Blachar et al. 1994; Duckett 1993; Arnold and Rickwood 1990; Koff and Campbell 1992; Dowling et al. 1988; Capolicchio et al. 1999; McAlleer and Kaplan 1999; Chertin et al. 1999; Tapia and Gonzalez 1995; Salem et al. 1995).

13.5.3 Ureterovesical Junction Obstruction

Like VUR, UVJ obstruction has shown great potential for spontaneous resolution, probably because of the maturation of the UVJ (Fig. 13.22). Therefore, after completion of the workup a prophylactic antibiotic therapy should be started and the urinary tract monitored by US and eventually isotopes. US may underestimate the dilatation, especially since the renal pelvis may not be dilated. Therefore, before confirming complete resolution, morphological assessment of the urinary tract may be necessary (best by MR urography) (Baskin et al. 1994; Liu et al. 1994; Avni et al. 1992; Avni et al. 2000).

13.5.4 Multicystic Dysplastic Kidney

Once the diagnosis of multicystic dysplastic kidney (MDK) appears highly probable (on the basis of the neonatal US examination and on the lack of

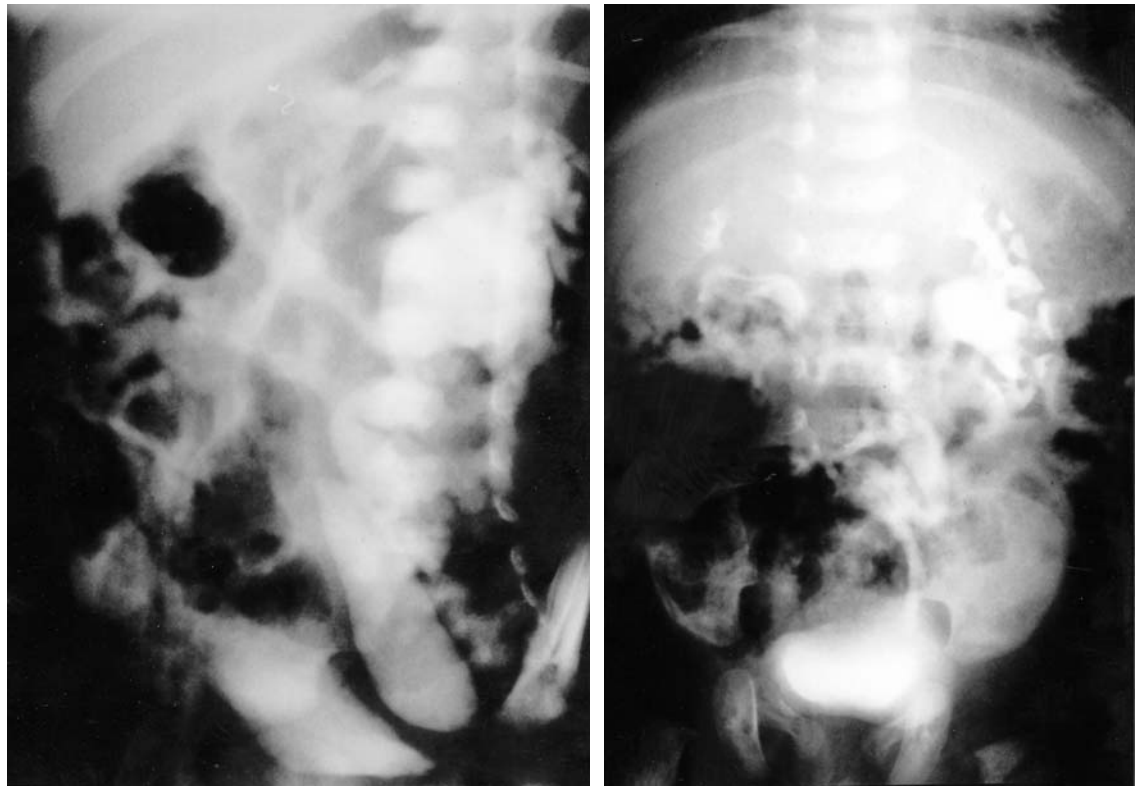


Fig. 13.22a,b. Spontaneous resolution of a primary megaureter. **a** Intravenous urography at the age of 2 months showing a typical left megaureter. **b** Intravenous urography at 8 months showing the resolution of the ureteral dilatation

function demonstrated by isotopes), a clinical and imaging (US) follow-up is the most widely accepted approach. In two-thirds of cases, MDK diagnosed in utero will involute spontaneously within the first 2 years of life; the involution may start in utero (Fig. 13.23). Complications are very unusual. Only very large MDK causing abdominal discomfort and without resolution on follow-up examinations will require surgical removal (Strife et al. 1993; Hrair-Georges et al. 1993; Avni et al. 1987; Rabelo et al. 2004; Aslam et al. 2006, Vinocur et al. 1988).

13.5.4 Duplex Kidneys

In case of duplex collecting systems, one of the aims of imaging will be to differentiate between ectopic ureteral insertion and ectopic ureterocele. In case of an extravesical ectopic ureter without residual function, an upper-pole heminephrectomy is proposed; ureteral reimplantation and modeling are performed if some renal function is preserved. In the case of ectopic ureterocele determining a large obstruction, incision of the ureterocele is performed under cystoscopy in order to relieve the high pressure obstruction (Fig. 13.18a,c). Resection of the ureterocele with heminephrectomy is performed secondarily according to the degree of remaining renal function (Husman et al. 1999; Blyth et al. 1993).

Conclusion

Apart from acute conditions requiring immediate treatment, the therapeutic approach to congenital uropathies is less and less surgical as time goes on. Prophylactic antibiotic therapy is usually started in the direct neonatal period.

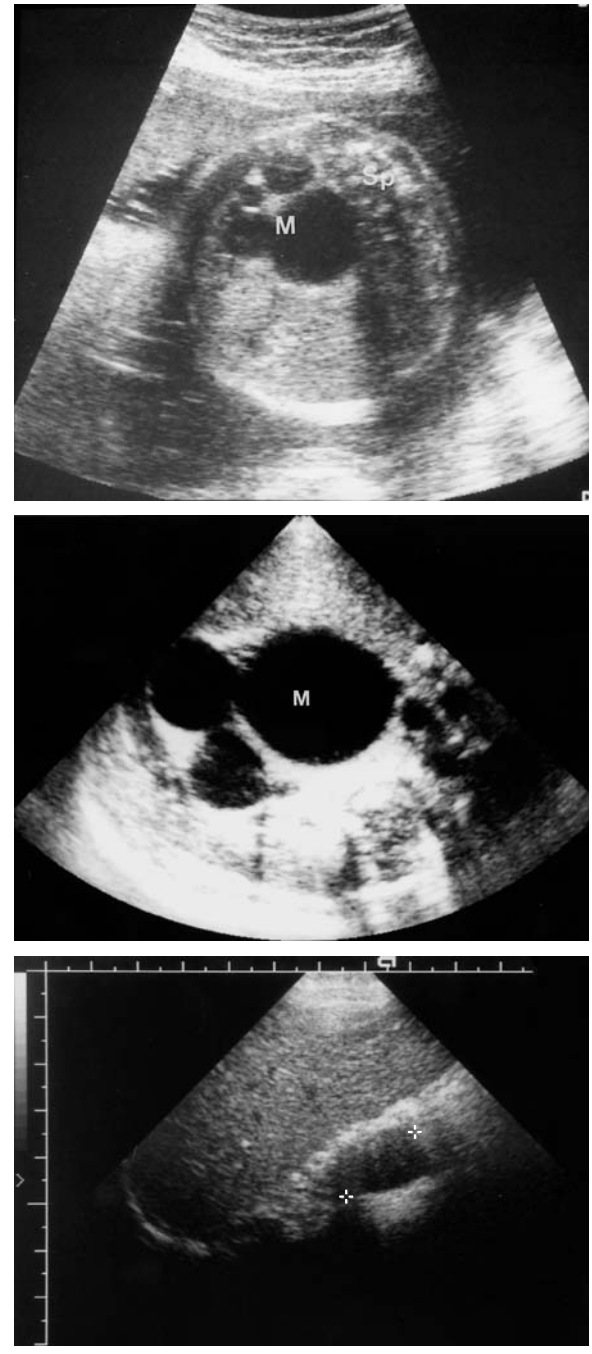


Fig. 13.23a–c. Spontaneous involution of a multicystic dysplastic kidney. **a** In utero at 34 weeks, transverse scan of fetal abdomen. Typical right multicystic kidney (*M*); *Sp*, spine. **b** At birth transverse scan of the right kidney: same appearance of the mass (*M*) as in utero. **c** At the age of 2 years sagittal scan of the right kidney: only one small cyst remains (*between the crosses*)

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Nonneurogenic Bladder-Sphincter Dysfunction ("Voiding Dysfunction")

14

Richard Fotter

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R. Fotter, MD
Professor and Chairman, Department of Radiology, Head Division of Pediatric Radiology, University Hospital, Medical University Graz, Auenbruggerplatz 34, 8036 Graz, Austria

14.1 Introduction

Nonneurogenic bladder-sphincter dysfunction ("voiding dysfunction") is a very common childhood disorder that all pediatric urologists, pediatricians and (pediatric) radiologists encounter in their daily practice. The most common clinical presentations are recurrent urinary tract infections (UTI), vesicoureteral reflux (VUR) and daytime and nighttime wetting. If constipation and/or encopresis are associated with nonneurogenic bladder-sphincter dysfunction ("voiding dysfunction"), it is called dysfunctional elimination syndrome (Koff et al. 1998).

One or more of the clinical symptoms of nonneurogenic bladder-sphincter dysfunction were reported in 26% of 7-year-old Swedish children; most had moderate urgency as a sign of incomplete voluntary bladder control (Hellström et al. 1990).

The prevalence of daytime wetting has been reported to be 0.2% to 9% in children aged 6–12 years, with daytime wetting more common in girls than in boys (Bakker et al. 2002; Lee et al. 2000; Swithinbank et al. 1994). Combined daytime and nighttime wetting occurred in 1.5% to 2.8% (Lee et al. 2000; Gür et al. 2004; Järvelin et al. 1988).

Therefore, nonneurogenic bladder-sphincter dysfunction ("voiding dysfunction") in children should not be seen as an isolated phenomenon. It should always be seen in the context of the pertinent clinical symptoms, in particular frequency, urge and (urge) incontinence, and it should be seen as one among other risk or predisposing factors such as VUR of the disease complex urinary tract infection-permanent renal damage (Yeung et al. 2006; Batisky 1996), which in addition are very closely associated (Chen et al. 2004). Furthermore, "voiding dysfunction" probably is also a causal factor for the development of VUR (Barroso et al. 2001; Koff

et al. 1979; Nasrallah and Simon 1984; Homsy et al. 1985; Scholtmeijer and Nijman 1994; Koff 1992).

However, in textbooks and scientific publications VUR and nonneurogenic bladder-sphincter dysfunction ("voiding dysfunction") are commonly dealt with separately. As a clinical consequence regular management often consists of ad hoc treatment for every UTI with only minor attention to an underlying nonneurogenic bladder-sphincter dysfunction. This monosymptomatic approach may cause undue morbidity from nonneurogenic bladder-sphincter dysfunction and urinary tract infections in a group of patients with a prevalence as high as 40% for VUR and 30% for refluxnephropathy (Van Gool 1995; Koff et al. 1979; Griffiths and Scholtmeijer 1987; Van Gool et al. 1992a). This problem is further enhanced by a mislabeling: The nighttime component of wetting is often misinterpreted as enuresis nocturna, although the wetting is not exclusively at nighttime (Van Gool 1995).

In addition, numerous definitions and categories are in use for nonneurogenic bladder-sphincter dysfunction, blaming either the bladder or the urethral sphincter for the various clinical expressions of nonneurogenic bladder sphincter-dysfunction. In this chapter not only the whole spectrum of nonneurogenic bladder-sphincter dysfunction will be described, but how dysfunction is embedded into the disease complex UTI-renal damage will be shown. Furthermore, the associations and the causal relationship to VUR, UTI, renal damage and constipation will be discussed and the various clinical manifestations will be elucidated.

In the past imaging and corresponding research predominantly were focused on VUR, and pediatric radiologists mostly were not adequately aware of the important role that nonneurogenic bladder-sphincter dysfunction plays in this common nephrourologic disease complex. Nonneurogenic bladder-sphincter dysfunction is one of the most underestimated topics in pediatric uroradiological daily work, education and research, but on the other hand pediatric radiologists are often the first and only urological experts who get in touch with those children. Missing dysfunction may lead to treatment delay or failure; it may increase treatment costs (Benoit et al. 2002); it may lead to reimplantation surgery failure, and last but not least may lead to kidney damage. With this article we will try to bring this important topic to the awareness of the reader.

14.2 Terminology–Categorization

Different terminologies and categorizations have been used for children who present with varying degrees of "functional" urinary symptoms. Some are based on the urodynamic pattern (reflecting the underlying pathophysiology and the diagnosis), others on clinical presentation. The term "urge syndrome" has been used to describe both the clinical symptoms and the overactivity of the detrusor muscle (unstable bladder). The problem is that uninhibited detrusor contractions as the underlying pathology of unstable bladder cannot be demonstrated in all children during an urodynamic study, although the symptoms are indicative of overactivity of the detrusor. It would be better to use the term unstable bladder or overactive bladder for these patients presenting with frequency and urgency, with or without incontinence.

Over the last years numerous articles dealing with all aspects of nonneurogenic bladder-sphincter dysfunction in infants and children have been published.

A broad spectrum of terms such as nonneuropathic vesicourethral dysfunction (Koff 1984), overactivity of the bladder and striated urethral muscle (Van Gool et al. 1984), nonneuropathic or nonneurogenic bladder-sphincter dysfunction (Hoebeke et al. 1999), dysfunctional bladder (Hinman 1986), unstable bladder (Koff 1982), nonneurogenic neurogenic bladder (Allen 1977) and Hinman syndrome (Hinman 1986) is still in use for sometimes overlapping patterns of nonneurogenic bladder-sphincter dysfunction.

Nonneurogenic neurogenic bladder or the so-called Hinman syndrome is at the extreme end of the spectrum of nonneurogenic bladder-sphincter dysfunction. This syndrome shows severe clinical manifestations including urinary retention, severe bladder-sphincter dysfunction, VUR, hydronephrosis and hydroureter and renal scarring.

"Voiding dysfunction" is a rather vague, today often used overall term in the literature for urinary symptoms resulting from nonneurogenic bladder-sphincter dysfunction. It presents with a mixture of lower urinary tract symptoms in particular urge, urge incontinence, frequency, infrequency and urinary tract infection. Furthermore, voiding dysfunction is used as a misnomer for dysfunctional voiding.

This term describes a sign and is now used in an imprecise way as well, because it is indiscriminately applied to two different pathophysiological disturbances that may overlap and coincide, but may require different treatment. One is overactivity of the detrusor during bladder filling, which is represented by uninhibited detrusor contractions (unstable bladder or overactive bladder), the other is overactivity of the external urethral sphincter during voiding (dysfunctional voiding in particular) (Koff 1982). These children may also demonstrate uninhibited detrusor contractions indicative for unstable bladder on urodynamic studies and present clinically often with urge and frequency, with or without incontinence.

There are at least three theories on how those two patterns of dysfunction are seen in terms of categorization and treatment. In the first, there are two distinct entities that can manifest in isolation or in combination. The second theory states that there is a spectrum ranging from minor unstable detrusor contractions during higher filling volumes of the bladder to the full-blown type of nonneurogenic neurogenic bladder or the so-called Hinman syndrome at the far end of the spectrum. The third theory claims that the two entities are closely related and are two components of the dysfunctional voiding complex with different expression. Referring to the latter theory, there is disagreement about whether the primary abnormality is overactivity of the detrusor during bladder filling or overactivity of the external urethral sphincter during voiding.

Bauer (1992) grouped into primarily unstable bladder (small capacity, hypertonic bladders and detrusor hyperreflexia), infrequent voiding associated with large-capacity bladders (lazy bladder syndrome) and psychogenic nonneuropathic bladder (Hinman syndrome).

Others such as van Gool et al. (1992a,b) and Hjälmas (1992) published other urodynamic classifications. Hjälmas (1992) described unstable bladder, sphincter dyscoordination, lazy bladder and occult neurogenic bladder. Van Gool et al. (1992a) divided conditions into two main groups, urge syndrome and dysfunctional voiding; the latter is subdivided into staccato voiding, fractionated voiding and lazy bladder syndrome.

Mayo and Burns (1990) confirmed the hypothesis that children with bladder instability and dysfunctional voiding represent two separate groups. They described one group with instability alone and a second group with dysfunctional voiding with or without instability. They found infection and/or reflux to be common in the former, the more devastating urinary tract changes, particularly heavy trabeculation of the bladder, to occur in the latter group.

This confusing use of different terms in original articles, editorials and review articles makes it not only difficult for the reader to understand this important topic in general, but inhibits comparative research on diagnosis, treatment, outcome and costs. Therefore, a standardization of lower urinary-tract dysfunction in children has been published by the International Children's Continence Society (Nørgaard et al. 1998). Two main dysfunctions are classified: unstable bladder (urge syndrome) and dysfunctional voiding. The authors state that those disorders might not be the separate entities they seem, as transitional phases between urge syndrome and dysfunctional voiding do occur. Also, the associated complex of functional incontinence and recurrent urinary tract infection (UTI) may start with detrusor overactivity and hold maneuvers with a gradual progression to fractionated and incomplete voiding (dysfunctional voiding).

All these rather divergent discussions on terminology and categories can be reduced to one common pathophysiological denominator: impaired coordination between the smooth muscle of the urinary bladder (the detrusor muscle) and the striated muscle of the external urethral sphincter (pelvic floor muscles), which leads to repeated pathologically high intravesical pressure during bladder filling and/or voiding with all its negative consequences for the bladder, the ureterovesical junction, the ureteric orifices, the ureters and the kidneys.

Conclusion

The classification of the International Children's Continence Society should be used to eliminate confusion, to facilitate and enable comparative research and metaanalyses. This classification recognizes two main dysfunctions: overactive bladder or unstable bladder (urge syndrome) and dysfunctional voiding. The common denominator of lower urinary tract dysfunction is bladder sphincter discoordination leading to chronic high intravesical pressure with resulting negative consequences for the urinary tract.

14.3 Incidence

Bauer et al. (1980) found that the majority of children with urinary tract dysfunction had unstable bladder and only a small number had the severest type of dysfunction, which is called nonneurogenic neurogenic bladder (Allen 1977).

Schulman et al. (1999) described unstable bladder or urge syndrome in 52% of cases of nonneurogenic bladder-sphincter dysfunction followed by dysfunctional voiding in 25%. Himsl and Hurwitz (1991) state as well that the underlying problem in the great majority of children with functional disorders of the lower urinary tract is unstable bladder.

The study by Mayo and Burns (1990) and the publication of Hoebeke et al. (1999) show that the number of cases with unstable bladder is around 60%. Passerini-Glazel et al. (1992) describe a rate of unstable bladder of 90% in children with nonneurogenic bladder-sphincter dysfunction. In 156 children with daytime incontinence, Van Gool (1992a) found unstable bladder in 53% and dysfunctional voiding in 59%. Weerasinghe and Malone (1993) reported unstable bladder in 54% and dysfunctional voiding in 3.5%.

In a study on the utility of video-urodynamics in children with UTI and nonneurogenic bladder sphincter-dysfunction, Glazier et al. (1997) also found a majority of cases with unstable bladder and only 30% of patients with dysfunctional voiding.

Hoebeke et al. (2001) in a publication about 1,000 videourodynamic studies in children with nonneurogenic bladder dysfunction found urge syndrome (overactive bladder or unstable bladder) in 58% (male:female ratio 58:42), dysfunctional voiding (overactivity of the external urethral sphincter) in 32% (male:female ratio 49:51) and lazy bladder in 4% (male:female ratio 20:80). Furthermore, he found that the age distribution provided evidence against a dysfunction sequence as mentioned above.

Conclusion

The prevalence of nonneurogenic bladder-sphincter dysfunction ("voiding dysfunction") in children is high. One or more symptoms of disturbed bladder function were reported in up to 26% of children. Overactive bladder (unstable bladder) turned out to be the most common dysfunction.

14.4 Physiology

For many years uninhibited detrusor contractions have been considered a normal phenomenon in neonates. In several publications a normal functioning infant bladder has been described as unstable (Hjälmas 1988; Lapides and Diokno 1970; Couillard and Webster 1995). A possible explanation was a lack of cortical inhibition of the micturition reflex (Muellner 1960; de Groat 1993). But recently, the hypothesis that uninhibited detrusor contractions are physiological in neonates was challenged by Yeung et al. (1995), who observed detrusor instability in only 1 out of 21 normal infants using natural filling cystometry. Therefore, it was concluded that the function of the infant bladder is under control of higher centers, and uninhibited detrusor contractions are an abnormal phenomenon resulting from a lack of inhibition through the central nervous system.

Yeung et al. (1995) suggested that "incomplete coordination between detrusor contraction and urinary sphincter relaxation could be normal." In a further study by Yeung et al. (1998) two separate patterns of micturition could be distinguished: a normal pattern typified by a continuous urinary stream coordinating with a detrusor contraction and an immature pattern typified by an interrupted stream and apparently discoordinated micturition. This is in agreement with our own observations.

By the age of 4–5 years many children have been toilet-trained successfully and have adopted an adult pattern of urinary control. This is also characterized by the absence of involuntary or uninhibited detrusor contractions during bladder filling. Even if the bladder is full and there is a strong desire to void, no bladder contractions will occur. With micturition, coordinated relaxation of the external urethral sphincter takes place. Therefore, bladder emptying is under low intravesical pressure in children and adults.

14.5 Toilet Training (Bladder Control)

Toilet training is a highly complex process that is normally completed during the first 4 to 6 years of life; much of it is not completely understood. In addition to a normal anatomy of the lower urinary tract, a diffuse neuronal network must be present, centrally connected and controlled. Bladder emptying of the young infant is reflexive; it undergoes a gradual change to the voluntary control of micturition as the central nervous system gains control of the micturition process during the first 4 to 5 years of life. Daytime control mostly precedes nighttime continence. The development of continence and voluntary micturition needs maturation of the nervous system and behavioral learning. Cognitive perception of the maturing urinary tract is a prerequisite for toilet training. This implies a high susceptibility to the development of nonneurogenic bladder-sphincter dysfunctions.

Feeding typically stimulates micturition in infants, which is under control of the pontine mesencephalic micturition center in the brain stem with only minimal cortical influence. To gain normal bladder function there are specific developments while the child is maturing. The bladder capacity has to increase, which takes place by about 30 ml per year until puberty.

The cortical inhibitory pathways to and from the pontine micturition center develop between 1 and 3 years of age, allowing the child to gain voluntary control over the reflexes that control the detrusor and sphincter muscles. This development gives the child the possibility to feel bladder fullness and initiate or inhibit a detrusor contraction voluntarily, thus suppressing voiding at socially inappropriate places and times. Normal urinary bladder control is mostly achieved by the age of 4 years. At this age the urethral sphincter reflexively constricts during bladder filling and relaxes during a voluntary detrusor contraction, allowing micturition to occur.

Nonneurogenic bladder-sphincter dysfunction is thought to originate from behavioral factors that affect toilet training and inhibit the maturation of normal urinary control. Since the gastrointestinal tract plays a prominent role in lower urinary tract dysfunction, the term dysfunctional elimination syndromes (Koff et al.1998) is applied, if functional bowel disturbances are associated in terms of chronic constipation and encopresis.

Conclusion

Toilet training is a highly complex process that is normally completed during the first 4 to 6 years of life. The development of continence and voluntary micturition needs maturation of the nervous system and behavioral learning. Cognitive perception of the maturing urinary tract is a prerequisite for toilet training. This implies a high susceptibility to the development of nonneurogenic bladder-sphincter dysfunctions. Nonneurogenic bladder-sphincter dysfunction is thought to originate from behavioral factors that affect toilet training and inhibit the maturation of normal urinary control.

14.6 Pathophysiology

If abnormalities of toilet training and aberrations in the development of normal urinary control persist, pathologic significance increases as the child becomes older.

For purposes of a better understanding of the pathophysiology and enabling comparative research on the impact on therapeutic efficacy, on outcome, on cost effectiveness and life quality and referring to the above-mentioned discussion on categorization, two main types of dysfunction can be subdivided according to whether the dysfunction occurs during bladder filling or during bladder emptying (or both).

Detrusor-sphincter dysfunction during bladder filling (unstable bladder or overactive bladder). The primary abnormality is the failure to suppress involuntary detrusor contractions due to the inability to exert complete voluntary control over the micturition reflex. This dysfunction ranges from minor unstable detrusor contractions at high filling volumes to the severe type with high-amplitude unstable detrusor contractions at lesser bladder filling volumes, frequently but not always combined with an urge to void.

The child, attempting to maintain continence during such contractions, must voluntarily and tightly constrict the external urethral sphincter to stay dry. This results in simultaneous and unphysiological contraction of both the bladder and external urethral sphincter. During this event functional urinary obstruction and high intravesical pressure

develop and persist until the bladder either relaxes or empties.

In about 70% of cases this dysfunction leads to (urge) incontinence, which is clinically manifested as wetting (mostly daytime, but nighttime as well). But even in severe cases the obligatory voluntary contraction of the striated urethral sphincter against the contracting detrusor can prevent leakage in up to 30% of cases.

The clinical symptoms of unstable bladder (overactive bladder) are frequency, urge and urge incontinence. Uninhibited detrusor contractions leading to symptoms such as urgency, frequency and urge incontinence can be called overactive bladder syndrome (Staskin and Dmochowski 2002).

Unstable bladder (overactive bladder) is the most common nonneurogenic bladder-sphincter dysfunction, accounting for 175 cases out of 226 children in a study by Hellerstein and Linebarger (2003). Children with this dysfunction use various posturing maneuvers (e.g., Vincent's courtesy) to avoid urinary incontinence. Children who are able to avoid incontinence showed a significantly higher incidence of urinary tract infections than those who did not attempt to obstruct urine outflow (Hellerstein and Linebarger 2003). This means that the lack of wetting does not exclude unstable bladder. These children may present with irritating voiding symptoms such as frequency and urge with UTI, with and without vesicoureteric reflux, reflux nephropathy, constipation and/or fecal soiling. Especially in cases of primary nocturnal enuresis that do not respond to treatment, unstable bladder not only during sleep, but also during the daytime may be detected.

Detrusor-sphincter dysfunction during micturition (dysfunctional voiding). The primary abnormality of this dysfunction is overactivity of the urethral closure mechanism during voiding. The most severe form of dysfunctional voiding in childhood is the Hinman syndrome (Hinman 1986) or the so-called nonneurogenic neurogenic bladder (Allen 1977). This syndrome includes fecal retention and soiling, emotional disturbances with family psychosocial problems, bladder trabeculation, diverticula, vesicoureteral reflux and upper-tract dilatation. In addition, there is a large post-void residual urine volume. Unstable bladder is mostly associated. This severe type of dysfunction is uncommon; more commonly seen are children with less severe symptoms of dysfunctional voiding. Dysfunctional voiding can be subdivided into the following types:

Staccato voiding is caused by bursts of pelvic floor activity during micturition resulting in peaks in bladder pressure together with interruption in urinary flow.

Fractionated voiding is caused by hypoactivity of the detrusor muscle and voiding consists of several unsustained detrusor contractions each with its own flow. Voiding frequency tends to be low; bladder capacity is large.

Lazy bladder syndrome is the consequence of longstanding dysfunctional voiding. It results from detrusor decompensation. Abdominal pressure is mostly responsible for voiding. Large residual urine volume can be observed (Nørgaard et al. 1998).

It is important to consider that with any type of bladder-sphincter dysfunction, an obstruction of the lower urinary tract is associated. In the case of unstable bladder, this occurs during bladder filling; in the case of dysfunctional voiding, this happens during bladder emptying. Resulting high intravesical pressure is the main mediator that leads to morphologic changes of the urinary bladder in terms of trabeculation and formation of diverticula with negative consequences for the ureteric orifices. The development of vesicoureteric reflux probably has its main cause in the anatomical distortion of the vesicoureteric junction as a consequence of chronic high pressure; high pressure itself does not cause vesicoureteric reflux (Koff 1992). In cases of borderline competent ureteric orifices, chronic high pressure itself may directly induce and perpetuate VUR.

Especially in cases of dysfunctional voiding with upper-tract dilatation and even reflux nephropathy, high intravesical pressure and morphologic distortion of the bladder are associated (Naseer and Steinhardt 1997). It has to be underlined that the clinical expression of dysfunctional voiding is not only staccato voiding or fractionated incomplete voiding, but also clinical symptoms such as frequency and urgency with and without incontinence as well. Wetting in fractionated voiding is probably intrinsically a form of overflow incontinence.

Conclusion

Functional obstruction is the central problem in nonneurogenic bladder-sphincter dysfunction. Bladder distortion, VUR, upper urinary tract dilatation, UTI and reflux nephropathy are potential consequences.

14.7 Constipation

Worldwide constipation is a common problem in children. Estimated prevalence rates have varied from 4 to 37% (Yong et al. 1998; Van der Wal et al. 2005; De Araújo Sant'Anna and Calcado 1999; Zaslavsky et al. 1988, Maffei et al. 1997). Constipation may vary from mild and short-lived to severe and chronic and is sometimes associated with fecal and urinary incontinence, urinary tract infections and abdominal pain. The prevalence of fecal incontinence ranges in children from about 0.3% to 8% (Van der Wal et al. 2005; Bellman 1966; Howe and Walker 1992). In a study by Loening Baucke (2006), a prevalence rate of 22.6% for constipation, 4.4% for fecal incontinence and 10.5% for urinary incontinence in a US primary care clinic was found. In this study on 482 children the fecal incontinence was coupled with constipation in 95% of their children. From the 10.5% prevalence rate for urinary incontinence, 3.3% were found for daytime only, 1.8% for daytime with nighttime and 5.4% for nighttime urinary incontinence. And it was concluded that fecal and urinary incontinence was significantly more commonly observed in constipated than non-constipated children.

Koff (1998) termed functional bowel and bladder disorders, including unstable bladder, constipation and infrequent voiding, dysfunctional elimination syndromes. He considers nonneurogenic bladder-sphincter dysfunction as only one part of the spectrum of functional disturbances that affect vesicoureteric reflux and UTI. In his study on 153 children with primary vesicoureteric reflux, he showed that 56% had dysfunctional elimination syndromes. The phenomenon of an association of overactive bladder, infrequent voiding, recurrent UTI, anatomic bladder distortion, upper urinary tract dilatation, vesicoureteric reflux, residual urine and a negative effect upon the reimplanted ureter with constipation remains incompletely understood (Blethyn et al. 1995; Dohil et al. 1994; O'Regan et al. 1986; Savage 1973; Loening-Baucke 1997; Shopfner 1968). It is postulated that a mechanical effect of the full rectum displacing the bladder, distorting the bladder base and elongating the urethra might be responsible (Shopfner 1968; Dohil et al. 1994). Another explanation might be the similar spinal innervation of the urethral and anal sphincters. Although the precise causal relationship remains unknown, a study by Loening-Baucke (1997) showed that the treatment of constipation played an important role in successful treatment of daytime and nighttime urinary incontinence and recurrent UTI in children without urologic anatomic abnormalities. Therefore, for evaluating and treating UTI and primary vesicoureteric reflux, the assessment of bladder and bowel function disturbances is essential. In addition dysfunctional elimination syndromes might lead to idiopathic urethritis, which is a common childhood problem characterized by blood spotting in the underwear between voiding (Herz et al. 2005). The authors showed a higher cure rate when children with idiopathic urethritis were treated according to dysfunctional elimination syndrome guidelines.

Dysfunctional elimination syndromes in childhood may have a negative impact on bladder and bowel function later in life. Women with urogynecological symptoms had significantly higher childhood dysfunctional elimination syndrome scores than normal women.

Conclusion

Fecal and urinary incontinence are significantly more commonly observed in constipated than non-constipated children. Constipation and/or encopresis is commonly associated with nonneurogenic bladder-sphincter dysfunction. Comprehensive treatment is mandatory for successful management of affected children. Idiopathic urethritis might be a manifestation of underlying dysfunctional elimination syndromes.

14.8 Urinary Tract Infection and Vesicoureteric Reflux

As mentioned above nonneurogenic bladder-sphincter dysfunction is one important risk factor among others in the disease complex urinary tract infection-renal damage (Van Gool 1995). It has a strong correlation with recurrent UTI and breakthrough infections and may also delay the spontaneous resolution of reflux (Allen 1979; Bachelard et al. 1998; David et al. 1998; Hellström et al. 1987; Hinman and Baumann 1973; Koff 1982; Koff and Murtagh 1983; Koff et al. 1979; Lapides and Diokno 1970;

Naseer and Steinhardt 1997; Smellie et al. 1988; Snodgrass 1998; van Gool et al. 1984; Wan et al. 1995; Mazzola et al. 2003; Feldman and Bauer 2006; Chen et al. 2004; Schulman et al. 1999, Chiozza 2002; Hoebebke et al. 2001; Nijman 2000; Chandra 1995). The well-known combination of primary vesicoureteral reflux and urinary tract infection predisposing to pyelonephritis, renal scarring, hypertension and chronic renal damage has formed the basis for diagnostic and therapeutic concepts over the last 25 years (Fanos and Cataldi 2004).

Girls evaluated for UTI after toilet training have in 50–60% of cases typical symptoms of unstable bladder. Koff and Murtagh (1983) reported that unstable bladder was present in 54% of children with VUR. Snodgrass (1998) reported an incidence of 33%. These authors concluded that unstable bladder might be the most common nonneurogenic bladder-sphincter dysfunction associated with VUR. Similarly, Homsy et al. (1985) demonstrated a doubled VUR resolution rate in children treated with anticholinergics compared to that in a historical control.

In a study by Penido Silva et al. (2006) nonneurogenic bladder-sphincter dysfunction was identified in 94 (19.1%) girls and in 20 boys (11%) with VUR. The main clinical implication of this multivariate analysis was that an isolated variable gender is a poor predictor of clinical outcome in an unselected series of primary VUR. Although boys in this study had a more severe VUR pattern at baseline, girls had a greater risk of recurrent UTI and nonneurogenic bladder-sphincter dysfunction during follow-up.

Koff (1992) describes two patterns of dysfunction that have important implications on patients with VUR: the nonneurogenic neurogenic bladder (Allen 1977; Hinman 1986) and unstable bladder (Bauer et al. 1980; Koff and Murtagh 1983). The greatest degrees of VUR and the severest changes of the upper urinary tract including reflux nephropathy were found at the lowest bladder pressure. This can be explained by the sustained effect of chronically increased bladder pressure that produces anatomical changes, including bladder-wall thickening, bladder diverticula and alterations of the ureterovesical junction. It is the chronic effect of high pressure on the bladder that produces bladder decompensation, leading to the lazy bladder syndrome with infrequent voiding and high residual urine volume.

There are many studies dealing with the close association between VUR and nonneurogenic bladder-sphincter dysfunction (Van Gool et al. 1984; Hellström et al. 1987; Seruca 1989; Van Gool and Dejonge 1989; Griffith and Scholtmeijer 1987; Fotter 1992; Pfister et al. 1999). An interesting study in this context was presented by Noé (1988), who showed the relationship between siblings' VUR and dysfunctional voiding. He concluded that VUR is indeed polygenetic in its inheritance and significantly influenced by environmental factors such as dysfunctional voiding.

In his publication on the relationship among dysfunctional elimination syndromes, Koff (1998) suggested that all children with VUR be carefully and specifically evaluated for unstable bladder, constipation and infrequent voiding, because successful management may significantly improve the outcome of VUR and prevent breakthrough UTIs, thereby reducing the need for reimplantation surgery and ultimately better ensuring kidney health.

But children with VUR, nonneurogenic bladder-sphincter dysfunction and dysfunctional elimination syndromes remain at significant risk for a breakthrough UTI despite antibiotic prophylaxis, anticholinergic therapy, timed voiding and regular bowel evacuation (Koff et al. 1998).

Of greatest importance is the observation by Naseer and Steinhardt (1997) who, in their study on 538 patients with a history of daytime urinary incontinence, identified 51 children with VUR, UTI and dysfunctional voiding in whom new renal scars had developed while they were under care. They concluded that voiding dysfunction is a significant risk factor not only for UTI and VUR development and perpetuation, but also for the development of new renal scars when associated with infection and VUR. An association between urinary tract dysfunction and reflux nephropathy was also demonstrated by Nielsen (1984).

In their 1987 publication, Griffith and Scholtmeijer described two different reflux/dysfunction complexes. One type included unstable bladder and VUR that frequently occurred on one side only; reflux nephropathy or upper urinary-tract abnormalities were rare in this group. The other group included poorly contracting bladders during voiding and overactivity of the external urethral sphincter. The bladder was usually stable and VUR occurred frequently on both sides; reflux nephropathy and upper urinary-tract abnormalities were relatively common. VUR in unstable bladder occurred as a direct consequence of abnormally high detrusor pressure occurring during unstable bladder contrac-

tions. In the second group with a poorly contracting bladder (lazy bladder syndrome) VUR occurred at low detrusor pressure and often was bilateral.

In the multivariate large-scale analysis of the relationship between dysfunctional elimination syndromes, UTI and VUR by Chen et al. (2004), the authors believe that both VUR and UTI are not independently associated with nonneurogenic bladder-sphincter dysfunction. The authors conclude that only together are UTI and VUR associated with nonneurogenic bladder sphincter dysfunction. This is in agreement with the concept that nonneurogenic bladder-sphincter dysfunction together with chronic constipation and/or encopresis (dysfunctional elimination syndromes) causes urinary tract infection, and abnormal voiding pressures cause VUR to develop, which would result in the observed association (Chen et al. 2004).

In a study by Yeung et al. (2004) it could be shown that the resolution of VUR significantly correlated with renal and bladder functional status at diagnosis. Normal renal and bladder functions at diagnosis were highly predictive of complete resolution of VUR, whereas abnormal renal and bladder functions were prognostic for persistence of VUR.

Nonneurogenic bladder-sphincter dysfunction in patients with renal transplantation may have a negative effect on the transplanted kidney (Van der Weide et al. 2006; Luke et al. 2003; Adams et al. 2004). In a study by Luke et al. (2003) comparing the long-term outcomes of graft survival between children with dysfunctional lower urinary tract and children with a normal lower urinary tract, it was found that lower urinary tract pressure plays an important role in graft survival.

Conclusion

Nonneurogenic bladder-sphincter dysfunction ("voiding dysfunction") has a strong correlation with UTI and breakthrough infections, as well as with VUR and renal scarring. Successful management of nonneurogenic bladder-sphincter dysfunction and bowel dysfunction significantly improves the outcome of VUR, allows VUR resolution, prevents breakthrough infections, thereby reducing the need for reimplantation surgery, and ultimately better ensuring kidney health. VUR and nonneurogenic bladder-sphincter dysfunction are important risk/predisposing factors of the disease complex urinary tract infection-renal damage.

14.9 Enuresis and Incontinence

For therapeutic and prognostic reasons it is important to distinguish between enuresis and incontinence. Enuresis is defined as normal voiding occurring at an inappropriate time or place. Primary nocturnal enuresis is defined as bed wetting that is lifelong and that does not have an intervening dry period of 6 months. If there was a dry period of 6 months before recurrence of nighttime wetting, it is called secondary nocturnal enuresis. Monosymptomatic nocturnal enuresis is bed wetting with normal daytime voiding; in polysymptomatic nocturnal enuresis bed wetting is associated with daytime symptoms of frequency, urgency with or without incontinence.

Incontinence is the involuntary loss of urine together with nonneurogenic bladder-sphincter dysfunction often in combination with UTI, constipation and fecal incontinence.

The causes of enuresis are always functional; the causes of incontinence may be organic or functional, but are mostly functional (Kelleher 1997). Functional causes can be divided as mentioned above in this chapter into overactive bladder (unstable bladder) and dysfunctional voiding in particular.

At least one nocturnal enuresis event per month has been reported in over 10% of children 6 years of age (Lackgren et al. 1999), in 2–5% of 10 year olds (Norgaard et al. 1998; Chiozza et al. 1998; Lackgren et al. 1999) and 0.5%–3.0% of adolescents (Spee-van der Wekke et al. 1998). The incidence of nocturnal enuresis is 1.5%–2%-fold more frequent among boys than among girls (Hellstrom et al. 1990).

Only monosymptomatic bedwetting without urge and UTI should be termed monosymptomatic (or isolated) enuresis nocturna. Chandra (1998) states that children with isolated nocturnal enuresis have a lower prevalence of constipation and/or encopresis. Urge incontinence, mostly as a daytime symptom of bladder instability, may be combined with nighttime wetting. In this case bedwetting should not be categorized as enuresis, but as incontinence.

Several causal mechanisms in nocturnal enuresis have been described. Nørgaard et al. (1995) describe insufficient nocturnal production of arginine vasopressin and impaired renal sensitivity to this substance and to desmopressin. This leads to

nocturnal polyuria, which might be one of the most important etiologic factors in nocturnal enuresis. Koff (1995) describes an afferent and efferent developmental delay in terms of a failure of the CNS to recognize bladder fullness or contraction and to suppress the micturition reflex arc during sleep. He underlines that this developmental delay is not responsible for all cases of nocturnal enuresis; etiology is indeed multifactorial.

Chandra (1998) underscores that nocturnal enuresis results from an interaction of unstable detrusor contractions, delayed arousal from sleep and nocturnal polyuria. Some children with nocturnal enuresis can hold urine well for several hours during the day and have isolated nocturnal enuresis, while others manifest diurnal voiding symptoms as well, including urinary frequency, urgency, urge incontinence and pelvic withholding. Pathogenesis of isolated nocturnal enuresis may be different in comparison to children with daytime and nighttime wetting. In the latter, unstable detrusor contractions of overactive bladder may play a major role, whereas delayed arousal from sleep at bladder fullness may be the cause in patients with isolated nocturnal enuresis. In children with isolated nocturnal enuresis, sleep cystometry has also disclosed unstable bladder (overactive bladder) in 50% of cases (Nørgaard et al. 1989). Therefore, among several pathological factors that have been described in association with isolated enuresis nocturna, there may be a significant underlying nonneurogenic bladder sphincter dysfunction, especially in children in whom treatment has failed (Medel et al. 1998; Yeung et al. 1999; Yeung et al. 2004; Kajiwara et al. 2006; Yeung et al. 2006b).

Chandra (1996) and Hellstrom et al. (1990) reported that 60% of girls and 50% of boys with nighttime wetting manifested daytime wetting symptoms as well. In bed wetting the bladder may get full because of large production of nighttime urine or because of reduced bladder capacity. This reduced capacity could be the result of incomplete bladder relaxation or from uninhibited detrusor contractions while sleeping. If the child is a deep sleeper or manifests delayed sleep arousal the full bladder may empty itself during sleep (Hjälmas 1997; Wille 1994; Hjälmas 1995; Nevéus et al. 1999). In normal children contraction of the detrusor during sleep leads to a change from deep to light sleep followed by arousal for urination (Watanabe et al. 1994).

Another causal factor in enuresis nocturna might be rapid bladder filling (Nørgaard et al. 1989). In this context the rare anatomic abnormality of a completely duplicated ureteral system in which an ectopic ureter empties directly outside the bladder has to be kept in mind. In this case the upper renal moiety drains through a ureter that empties below the urethral sphincter or at some other ectopic site such as the vagina, uterus or even the perineum. Hence, these children are wet all of the time. This condition occurs exclusively in girls.

Altogether it can be concluded that for therapeutic and diagnostic reasons it is essential to focus on the distinction between enuresis and incontinence. The term enuresis should be reduced to the symptom of isolated (monosymptomatic) primary nocturnal enuresis. These children void in bed while asleep and generally are not aroused by the wetting. The problem is that occult daytime wetting of bladder instability or dysfunctional voiding may coexist. The polyetiologic mechanism may include daytime unstable bladder, nocturnal bladder contractions, failure of antidiuretic hormone nocturnal increase and disturbances in arousal mechanisms. All could be related to a developmental delay of the central nervous system control of micturition, partly genetic and partly due to environmental factors (Koff 1995).

Most cases of daytime and nighttime wetting are functional forms of urinary incontinence resulting from nonneurogenic bladder sphincter dysfunction, clinically manifested by frequency, urgency and urge incontinence. UTIs, covered bacteriuria, VUR, constipation, encopresis and structural abnormalities of the urinary tract are often associated.

It is accepted that evaluation of the child with wetting with a history of infection is indicated because some 30%–50% of children who present with UTI will have VUR demonstrated on voiding cystourethrography (VCU). However, no clear guidelines have been established for the evaluation of wetting children with sterile urine demonstrated at the time of admission or without a history of UTI. In a study on children with enuresis, Sujka et al. (1991) demonstrated that no one symptom or combination of symptoms segregated these patients likely to have VUR: 16% of their 83 patients with sterile urine and no history of infection had VUR; out of those, 16 showed reflux nephropathy as well. They concluded that one of six children who present with enuresis and sterile urine will have VUR.

And therefore screening these children with VCU should be considered. This corresponds to our results and roughly to our policy of performing kidney and bladder ultrasound in children of more than 6 years of age with persistent severe enuresis nocturna despite treatment and performing VCU with a history of urinary tract infection. Assessment of stool retention in terms of ultrasound measurement of the rectal diameter has to be done (Klijn et al. 2004). The authors found in constipated children a mean diameter of the rectum of 4.9 cm (95% CI 4.4:5.3); in the control group they found a mean diameter of the rectum of 2.1 cm (95% CI 1.8:2.4). This difference was statistically significant. Therefore, the transverse diameter of the rectum measured by lower abdominal ultrasound provides an additional accurate parameter with which to diagnose constipation in patients with nonneurogenic bladder-sphincter dysfunction.

Any attempt to make the important distinction between monosymptomatic nocturnal enuresis and incontinence based on the patient's history and clinical symptoms alone may fail and occult underlying functional disorders of the lower urinary tract may be overlooked. This may contribute to the different rates of success for a heterogeneous spectrum of therapeutic measures in different studies and may contribute to different statements regarding prognosis and associated disorders of enuresis.

Incontinence and clinical symptoms of nonneurogenic bladder-sphincter dysfunction can be found in children after *sexual abuse*. Ellsworth et al. (1995) found a 6% rate of sexual abuse in 300 children with nonneurogenic bladder-sphincter dysfunction. Abidare and Shortliffe (2002) mentioned that sexual abuse of children is not limited to penetration, but may include fondling, exhibitionism or pornography. Davila et al. (2003) report that sexual abuse survivors have a significantly higher incidence of genitourinary dysfunction symptoms, including urge incontinence and voluntary urinary retention.

Giggle incontinence is another type of incontinence in girls. Those girls wet with a coordinated full or partial void during laughter. According to a study by Chandra et al. (2002) giggle incontinence results from unstable detrusor contractions induced by laughter, and it improves with effective treatment of unstable bladder. In this study diurnal voiding symptoms were noted in 95% of patients with giggle incontinence, while giggle incontinence was noted in 23% of those with diurnal voiding symptoms.

It was reported that incontinence and clinical symptoms of nonneurogenic bladder-sphincter dysfunction occur in some genetic syndromes. In *William's syndrome* deletions on the long arm of chromosome 7 are associated with mild cognitive deficits, a highly social personality and vascular and visceral defects (Abidari and Shortliffe 2002). A 32% prevalence of genitourinary symptoms, predominantly daytime wetting and increased frequency, was reported in a series of 41 patients (Schulman et al. 1996).

Ochoa syndrome has an autosomal dominant pattern of inheritance. Children who have this syndrome exhibit all the clinical features of Hinman syndrome, and in addition they have an unusual inversion of facial expression when smiling is attempted. The face becomes contorted into a grimace that makes it appear that the child is crying. Therefore, this syndrome is also known as the urofacial syndrome. Treatment is the same as for the Hinman syndrome. Despite the concern of children and parents regarding urinary incontinence, there is little research into the *psychological problems* associated with daytime wetting. In a study by Joinson and Heron et al. (2006) it was reported that there is increased vulnerability to psychological problems in children as young as 7 years of age with daytime wetting. There should be awareness of the increased risk of disorders such as *attention-deficit/hyperactivity disorder in children* with daytime wetting because this is likely to interfere with treatment.

Conclusion

Distinction should be made between monosymptomatic enuresis nocturna and incontinence. Patients with persistent and severe monosymptomatic enuresis nocturna despite treatment should undergo kidney and bladder ultrasound and VCU as well, if there are positive ultrasound findings and/or a history of urinary tract infection. In wetting children (daytime with or without nighttime urinary incontinence) with urinary tract infection with/without urge, kidney and bladder ultrasound and a VCU have to be performed as well. Assessment of potential stool retention has to be part of the imaging studies.

14.10 Nonneurogenic Bladder-Sphincter Dysfunction ("Voiding Dysfunction") in Neonates and Infants

In a study by Yeung et al. (1995) a considerably greater rise in detrusor pressure with micturition was found, especially in male neonates and infants, than in older children. Sillen et al. (1992) described pronounced detrusor hypercontractility in male infants with gross bilateral VUR, and in a follow-up study they described a gradual decrease in this initial detrusor hypercontractility until the age of 38 months (Sillen et al. 1996). Bachelard et al. (1998) described low bladder capacity, high-frequency bladder instability, high voiding pressure and increased activity of the pelvic floor during voiding in male infants with UTI. Hiraoka et al. (1999) found that male neonates had larger residual urine volumes and smaller urinary flow rates than female neonates.

One potential explanation for the increased voiding pressure in male newborns and infants as described by Yeung et al. (1999), Sillen et al. (1992) and Bachelard et al. (1998) could be the change in the configuration of the external urinary sphincter after birth, which starts as a complete ring-like structure and changes its configuration into an omega-shaped or horseshoe-like posteriorly open muscle structure by splitting, which occurs during the 1st year of life. This sex-linked developmental anatomy seems to coincide in time with the observation of high voiding pressure reported predominantly in male newborns and infants (Kokoua et al. 1993).

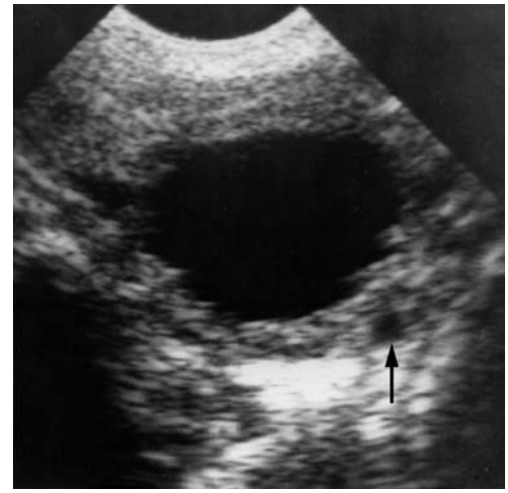
Unstable detrusor contractions combined with trabeculated thickened bladder wall, reduced capacity and somewhat dilated posterior urethra in male newborns with high grade dilating (bilateral) VUR can be detected on routine VCU performed for prenatally dilated upper urinary tracts. In these male newborns and young infants a highly dyscoordinated voiding pattern was observed (Fotter 1994; Allen and Bright 1978; Hjälmas 1988; Wen and Tong 1998) (Figs. 14.1, 14.2).

In a study by Godley et al. (2001) it was reported that VUR outcome in infants had a strong correlation with the initial renal functional status at diagnosis with a high incidence of early resolution of even high-grade VUR in infants. Bilateral abnormal kidneys associated with high grade VUR turned out to be a poor prognostic sign for VUR resolution. And Yeung et al. (1997) reported that resolution of VUR correlated with bladder function. A high VUR resolution rate was observed in infants with normal bladder function, and children with nonneurogenic bladder-sphincter dysfunction seem to have more breakthrough infections, which may have a role in new renal scar formation.

The coexistence of nonneurogenic bladder-sphincter dysfunction with VUR in infants and with kidney abnormalities could all arise from a single primary maldevelopment during differentiation of the ureteral bud and bladder trigone (Yeung et al. 2006a). Therefore, normal renal and bladder function seem to be highly predictive of complete resolution of VUR, on the other hand abnormal renal and bladder function would be associated with poor prognosis and persistence of VUR. This could be proved in a study by Yeung et al. (2006a).

Special attention must be paid to the critical assessment of adequate functional bladder capacity, since so-called covert instability manifests as significantly reduced bladder capacity. This means that after a short stable filling phase, the first unstable detrusor contraction is immediately transformed into a premature and forceful micturition contraction (Sillen et al. 1992). In this context it has to be taken into account that development of bladder volume in relation to age is not linear. There is a massive increase in bladder capacity after the 12th–18th month of life with a gain in perception and unconscious as well as conscious inhibition of detrusor contraction (Zerin et al. 1993).

Jayanthi et al. (1997) reported on seven patients (five males and two females), newborn to 2 months old, obviously with the severest form of neonatal bladder-sphincter dysfunction and called this pattern the nonneurogenic neurogenic bladder of early infancy. None of the infants had neurologic pathology or anatomical outflow obstruction. Five of the seven patients presented with thick-walled poorly compliant bladders and incomplete bladder emptying. Significant upper-tract pathology was found in all cases. Although the primary pathophysiological problem, low bladder capacity combined with detrusor hypercontractility during the filling as well as the voiding phase and abnormal contraction or perhaps nonrelaxation of the external urinary sphincter, is similar to the disorders encountered in older children, the clinical presentation is certainly more severe in infants. And since dysfunction has



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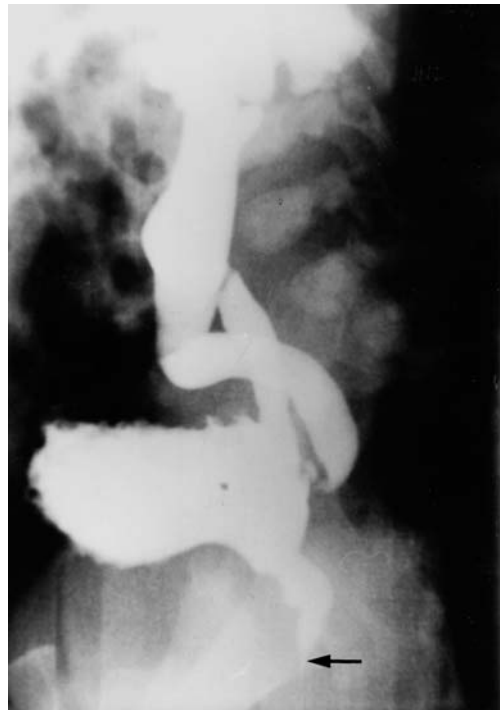

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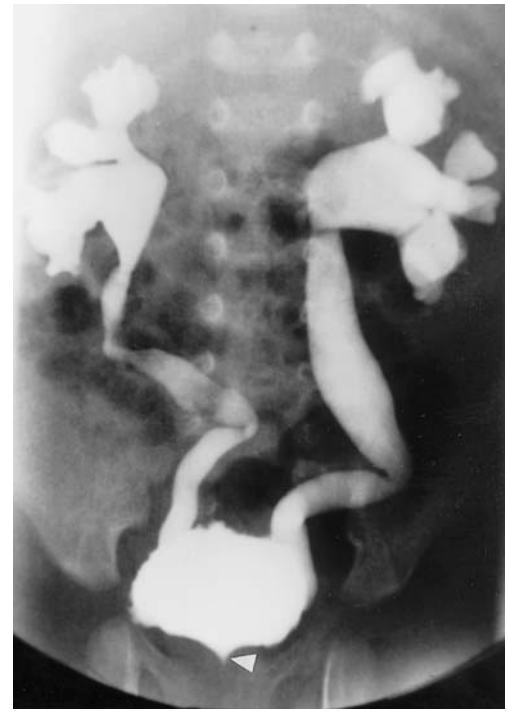


c

Fig. 14.1a–c. Male, 12 days old: bilateral high-grade fetal dilatation of upper urinary tract. **a** Transverse ultrasound scan of the bladder: bladder wall thickening, trabeculation, dilatation of left pelvic ureter (*arrow*), filling volume immediately before voiding 10 ml. **b,c** VCU: bladder trabeculation, diverticula, bilateral vesicoureteric reflux grade 5, wide bladder neck anomaly (*arrowhead*), unstable detrusor contractions, transformed into premature micturition, dyscoordinated voiding, contrast-filled posterior urethra up to contracted external sphincter (*arrow*), residual urine

started during development of nephrons prenatally, the risks for the upper urinary tract are much greater than in other forms of nonneurogenic bladder-sphincter dysfunction.

In 15 out of 25 baby boys with VUR, Avni and Schulman (1996) found a spectrum of bladder and urethral anomalies; they drew the conclusion that these findings may support the theory that a significant number of cases of VUR in baby boys results from a transient fetal urethral obstruction. But one central question remains in this context, if we consider a transient urethral obstruction between the 9th and 13th week of gestation as the cause of prenatal VUR and upper tract dilatation. How does the postnatally detected bladder-sphincter dysfunction fit into this hypothesis, how does it start, and why does it persist after birth? These questions can only be answered speculatively.

It is well known that subvesical obstruction leads to bladder hypertrophy, reduced bladder compliance and capacity, high detrusor pressure during bladder filling and voiding, and unstable detrusor contractions. Based on this well-known pathophysiological mechanism, the speculative conclusion could

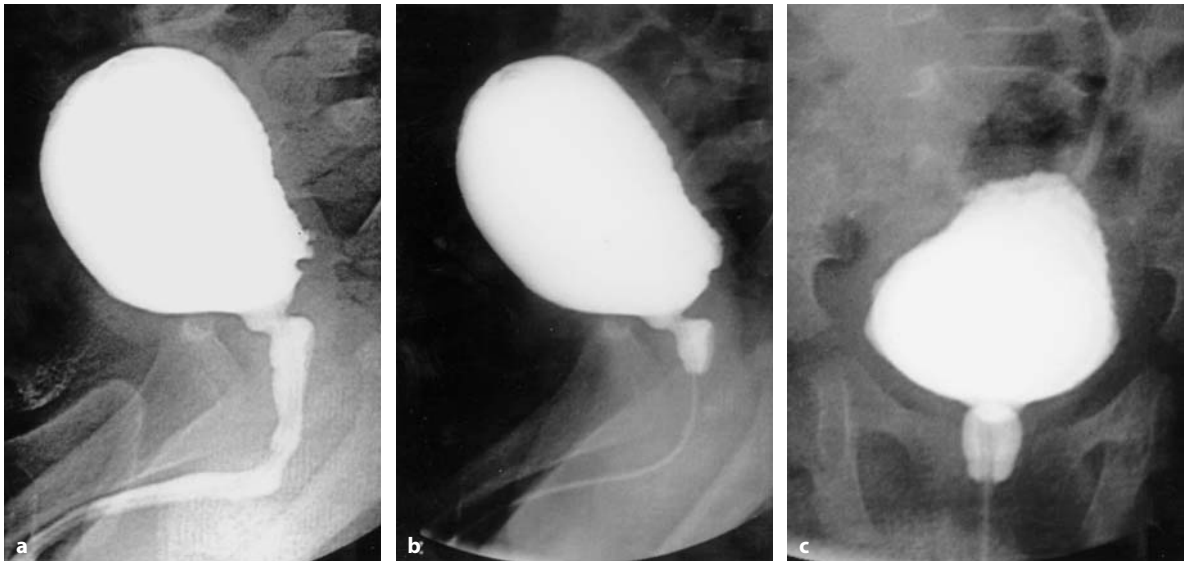


Fig. 14.2a–c. Male, 2 months old; moderate bilateral fetal hydronephrosis, VCU. Reduced bladder filling volume (20 ml); residual urine; early uninhibited detrusor contractions transformed into premature micturition. **a** Minor bladder trabeculation, short phase of normal micturition. **b**,**c** Dyscoordinated voiding, contraction of external urethral sphincter; dilated posterior urethra, male spinning top urethra

be drawn that after a transient early fetal urethral obstruction functional disturbances (bladder dysfunctions) could be induced and persist obviously at least until early infancy (Fotter 1994; Avni and Schulman 1996), and longer.

According to the results of the study by Sillen et al. (1996), either a delay in maturation of the coordination between the detrusor and the external sphincter with lacking sphincteric relaxation or reflexive contraction of the external sphincter could explain the high pressure waves without leakage of urine during unstable detrusor contractions in these newborn males.

The hypercontractile detrusor with altered tension of the bladder wall and/or longer-lasting elevated detrusor pressures during the remainder of pregnancy might be an important contributory factor for the development of VUR and megaureters in these children (Herndon et al. 1999; Kokoua et al. 1993).

It is interesting in this context that Risdon et al. (1993) found that in children with gross VUR submitted to unilateral nephrectomy, evidence of dysplastic renal development was confined to male patients. This corresponds to other studies that indicate a marked male preponderance among patients with reflux nephropathy diagnosed early in life, particularly those detected by antenatal ultrasound. Studies by Glick et al. (1993) and Beck (1971) have shown that upper-tract obstruction can cause dysplastic kidneys. Therefore, it seems likely that early fetal transient urethral obstruction in males followed by bladder-sphincter dysfunction with anatomic bladder distortion and persistent intrauterine high-pressure VUR may result in dysplastic kidneys.

Similar dysfunctional states can also be found in preschool children. This suggests that there may be a subgroup of children in whom nonneurogenic bladder-sphincter dysfunction may be congenital rather than acquired, as is postulated for the classical Hinman syndrome (Hinman 1986).

Summarizing these studies and observations it can be concluded that nonneurogenic bladder-sphincter dysfunction is not limited to childhood after toilet training; it can be observed more often in males with (bilateral) high grade VUR neonatally, as well as in infancy and early childhood. VUR resolution depends on renal status and bladder function. Unstable contractions of a hypercontractile detrusor with high filling and voiding pressure in utero may be an important contributory factor for the development of (bilateral) VUR and megaureters in these children. Another explanation could be that VUR, congenital kidney damage and bladder sphincter dysfunction could all arise from a single primary maldevelopment during dif-

ferentiation of the ureteral bud and bladder trigon. Male preponderance of bilateral high-grade VUR and of reflux nephropathy in early life and the high percentage of dysplastic elements in damaged kidneys in males may be explained by a causal relationship to a sex-linked in utero bladder dysfunction that persists after birth. Potential causes could be a transient fetal urethral obstruction (Avni and Schulman 1996) and/or the specific anatomical configuration of the striated external sphincter and its change with postnatal life in male infants (Kokoua et al. 1993).

Conclusion

Nonneurogenic bladder-sphincter dysfunction can be found more often in male neonates and infants with (bilateral) high-grade VUR and megaureters. Abnormal renal and bladder function is associated with poor prognosis and persistence of VUR. Reduced bladder capacity, trabeculation, dilated posterior urethra and a highly disturbed voiding pattern are characteristic VCU signs.

14.11 Voiding Cystourethrography (VCU)

A slightly modified VCU technique allows the diagnosis of (uninhibited) unstable detrusor contractions and therefore the diagnosis of unstable bladder with accuracy similar to that of urodynamic techniques (sensitivity 93%, specificity 90.7%) (Fotter et al. 1986).

For this technique the bladder has to be catheterized with a French 6–10 feeding tube and dilute contrast is dripped into the bladder from a constant height of 30 cm above the level of the bladder, at a rate of 5% of expected age-matched volume per minute (Fotter 1996). The radiologist has to maintain visual contact with the child and with the infusion bottle at all times. Bladder filling has to be carried out under brief intermittent fluoroscopic observation with the patient in a supine position. Additional fluoroscopic observations have to be carried out during slowing or spontaneous cessation of the infusion flow. Normally the bladder will fill to the expected age-matched capacity without significant slowing or cessation of the drip infusion flow. The drip infusion acts as a manometer of sorts.

If a first desire to void is announced, the point of bladder filling should be noted (normally greater than 20% of expected capacity). Drip infusion is stopped and the catheter removed if a strong urge to void is announced or when expected age-matched capacity is reached.

The combination of a transient opening of the bladder neck with a flow of contrast material into the posterior urethra up to the voluntarily contracted striated urethral sphincter (Fotter et al. 1986; Passerini-Glazel et al. 1992) together with cessation and/or back-up of contrast material drip flow suggests the presence of an uninhibited detrusor contraction (Fig. 14.3). These findings are valid; they can stand alone without urodynamic results. Modified VCU allows detection of the majority of these dysfunctions in neonates, infants and small children with the same reliability and in the same way as in older age groups.

Assessing dyscoordination between bladder and external sphincter during voiding without interrupted flow by VCU is a weak point of this technique. However, it is well known that electromyographic assessment of pelvic floor muscles assessment also is not reliable, with many artifacts noted (e.g., leg movements) (Höbecke et al. 1999).

Two specific cystographic signs have been found to be closely associated with unstable bladder (Saxton et al. 1988; Hausegger et al. 1991; Saxton and Robinson 1992; Naseer and Steinhardt 1997). The first is the so-called spinning top urethra (STU) (Combs et al. 1998; van Gool 1992a) (Fig. 14.4). In a retrospective VCU study on 102 girls Hausegger et al. (1991) found 28 to have STU, 16 of whom had unstable bladder as well (57%). There was a statistically positive correlation between STU and unstable bladder ($P<0.01$). Similar results were published by Saxton et al. (1988). Saxton's and Hausegger's studies confirmed the close association between unstable bladder and STU. Spinning top urethra was described in boys as well. This dilatation of the posterior urethra was found in male infants with high-grade VUR (Avni and Schulman 1996; Sillen 1992; Fotter 1994) (Figs. 14.1, 14.2) and boys with unstable bladder (Saxton 1992).

Second, the so-called wide bladder neck anomaly (WBNA) (Saxton et al. 1988; Hoebecke et al. 1999) is a permanent passive bladder-neck opening in the filling phase of the VCU independent of uninhibited detrusor contractions (Fig. 14.5). Wide bladder neck anomaly might be an acquired phenomenon and unstable bladder an important etiologic factor

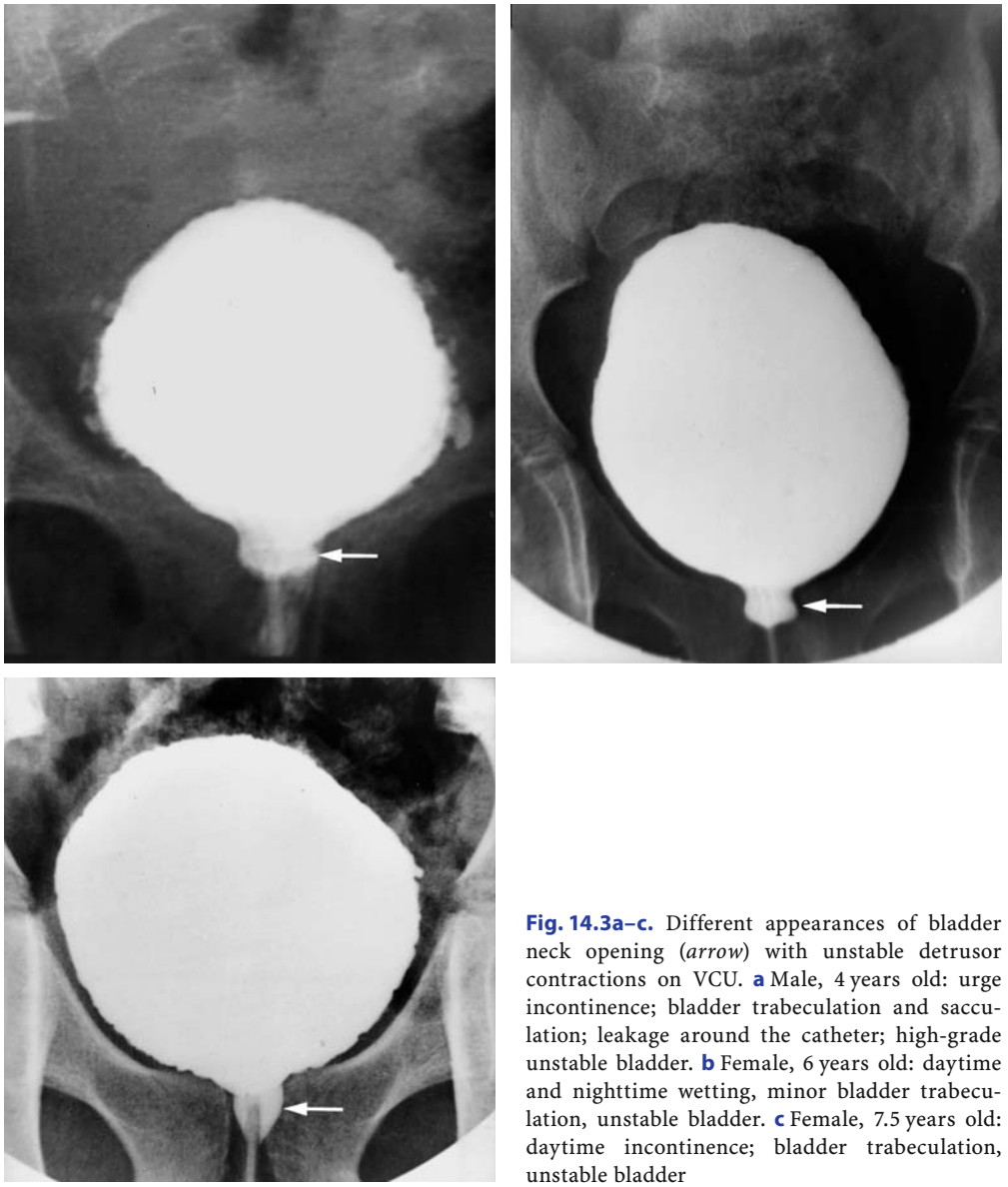


Fig. 14.3a–c. Different appearances of bladder neck opening (*arrow*) with unstable detrusor contractions on VCU. **a** Male, 4 years old: urge incontinence; bladder trabeculation and sacculation; leakage around the catheter; high-grade unstable bladder. **b** Female, 6 years old: daytime and nighttime wetting, minor bladder trabeculation, unstable bladder. **c** Female, 7.5 years old: daytime incontinence; bladder trabeculation, unstable bladder

contributing to WBNA. This is in contrast to the opinion of Saxton et al. (1988), who see in WBNA a congenital disorder. Both cystographic signs should alert the observer's attention to possible nonneurogenic bladder-sphincter dysfunctions, even in the absence of unstable detrusor contractions.

Careful attention must always be given to precise assessment of the urethral morphology in order to detect narrowing of the bulbar urethra (Cobb's collar) (Dewan et al. 1995; Nonomura et al. 1999) and congenital obstructing posterior urethral membranes (COPUM) (Dewan 1993; Dewan et al. 1997).

Altogether, assessment of lower urinary tract by VCU should include bladder and urethra morphology, detection and grading of VUR, bladder function during filling (unstable bladder?), age-matched bladder filling capacity (Zerin et al. 1993), residual urine, urinary flow if smooth or interrupted, and sphincter behavior during voiding (voiding dysfunction?).

In addition, an assessment of the fullness with stool of the entire colon and rectum (fecal retention?) and an evaluation for spinal defects must always be done.

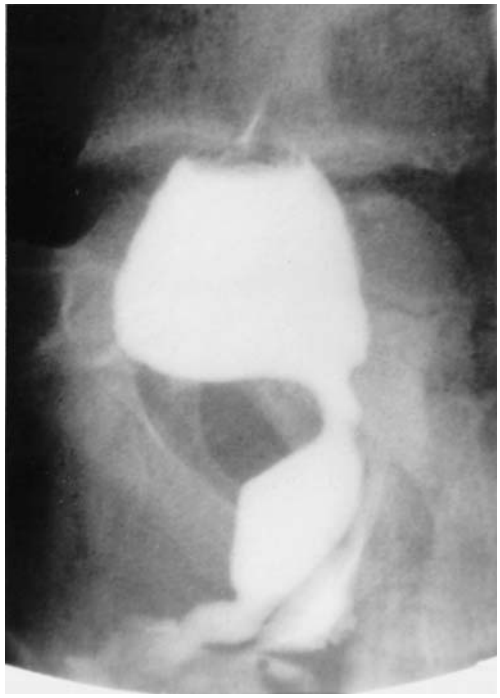


Fig. 14.4. Female, 6 years old: daytime wetting, VCU. High-grade spinning top urethra, marked widening of the muscular segment of the urethra during voiding

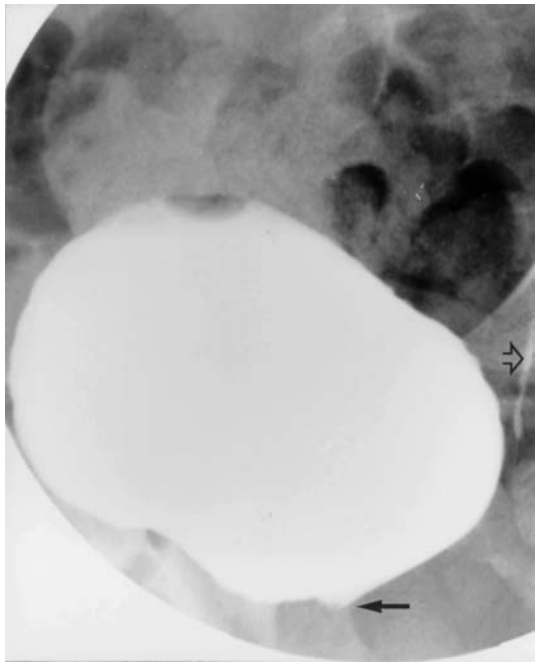


Fig. 14.5. Female, 6 years old: daytime and nighttime wetting, VCU. Wide bladder neck anomaly (*arrow*), vesicoureteric reflux grade 1 (*open arrow*)

Conclusion

A slightly modified VCU technique allows the diagnosis of unstable detrusor contractions with similar accuracy to urodynamic techniques. Spinning top urethra and wide bladder neck anomaly, even in the absence of unstable bladder, should alert the attention to occult or healed dysfunction.

14.12 Evaluation

The evaluation process begins with a good history. A standardized questionnaire using a scoring system for the quantitative evaluation of incontinence symptoms in children should be used to improve pretest probability, in particular, if we consider that routine urodynamics in children with nonneurogenic bladder-sphincter dysfunction in many cases do not change therapy or influence outcome (Akbal et al. 2005; Bartkowski et al. 2004; Sureshkumar et al. 2006; Parekh et al. 2001).

Equally important is the physical examination, which includes a careful inspection of the lower spine to look for a cutaneous manifestation of an occult spinal dysraphism and/or sacral agenesis and an examination of the external genitalia.

Radiological assessment of children with nonneurogenic bladder-sphincter dysfunction includes renal and bladder ultrasound and a modified VCU in children with persistent and severe dysfunction in particular if associated with urinary tract infection (Parekh et al. 2001) and breakthrough infections. In girls radionuclide cystography or echo-enhanced sonography may replace VCU.

For the evaluation of children with symptoms of nonneurogenic bladder-sphincter dysfunction by ultrasound, a careful examination of the urinary bladder has to be performed in particular. Not only structural abnormalities have to be searched for; bladder wall thickness, bladder volume and residual urine volume after voiding have to be assessed. Similar as described before for the modified VCU technique, the bladder base and bladder neck respectively have to be observed carefully by ultrasound as well. A transient opening of the bladder neck together with uninhibitetd detrusor contractions with filling of the posterior urethra up to the con-

tracted external sphincter can be seen sometimes with continuous observation of the bladder base by ultrasound as well (Fig. 14.6).

To overcome the weaknesses of urodynamics in children and the invasiveness and the radiation burden of VCU, several articles have been published recently describing various measurements and calculations in an attempt to detect nonneurogenic bladder-sphincter dysfunction by bladder ultrasound:

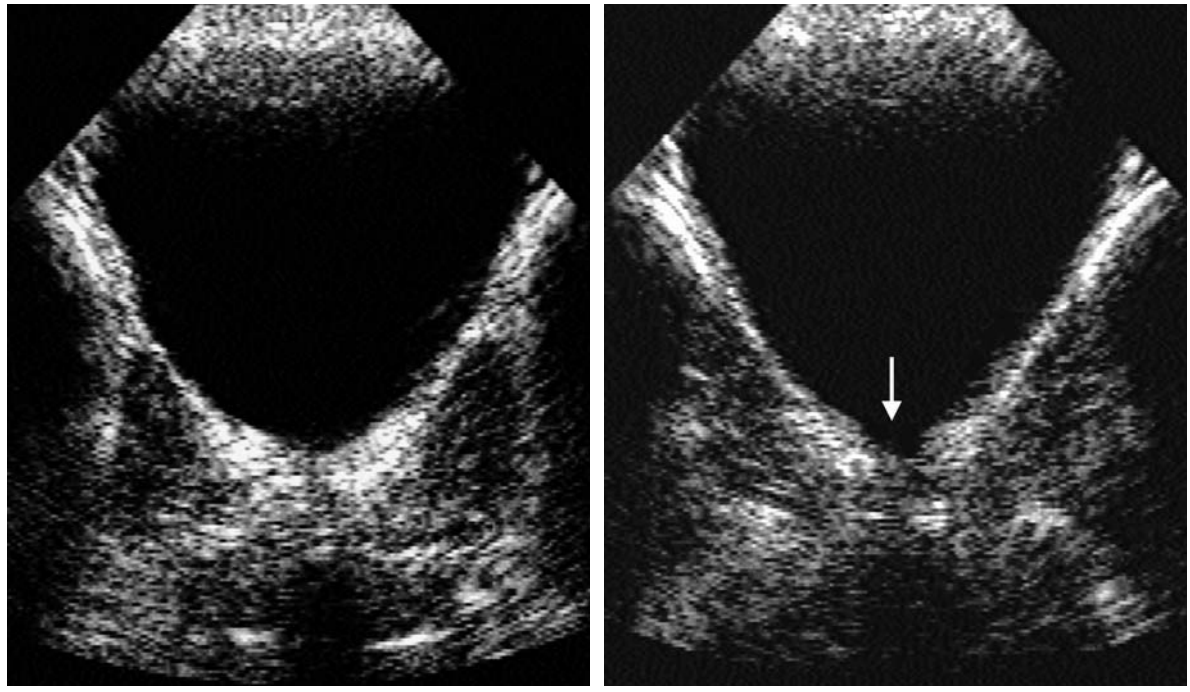
According to Leung et al. (2007) nomograms of total renal volume, urinary bladder volume index and bladder volume wall thickness index are described as useful indicators of bladder dysfunction in children with enuresis and urinary tract infection (Yeung et al. 2007).

In 1997 Kaefer et al. published that the bladder thickness index (bladder wall thickness was indexed to innerwall diameter) is a sensitive sonographic predictor of infravesical obstruction; application of this index could be a non-invasive screening tool for the patient with persistent nonneurogenic bladder-sphincter dysfunction.

Ukimura et al. (1998) described in 1998 that ultrasound-estimated bladder weight might be used to evaluate bladder compliance in children and concluded that this might be a suitable non-invasive urodynamic test in children with suspected urodynamic abormalities.

Another interesting feature of bladder ultrasound seems to be the assessment of the ureteric jet Doppler patterns (Leung et al. 2002a,b; Leung et al. 2006). The authors conclude that the persistence of an immature pattern was highly associated with urinary tract infection and VUR. Furthermore, the authors found that there was significant increase in the incidence of immature patterns in enuretic children when compared with controls. Enurectic children with bilateral immature ureteric jetwave forms and markedly thickened bladder wall showed multiple significant urodynamic abnormalities, which could be accounted for by immaturity of both vesicoureteric junction and detrusor muscle.

Pediatric radiologists performing ultrasound studies in children with clinical symptoms of nonneurogenic bladder-sphincter dysfunction and in enurectic children should not only evaluate for structural abnormalities, but should search for signs of unstable bladder (open bladder neck) and should measure residual volume after voiding and bladder wall thickness according to published standards (bladder wall thickness varies minimally with age,



a b

Fig. 14.6a,b. Female, 8 years old: urge incontinence, UTI, unstable bladder, bladder ultrasound. **a** Full bladder, minor bladder trabeculation, bladder neck closed. **b** Uninhibited detrusor contractions with bladder neck opening and filling the posterior urethra up to contracted external sphincter with urine (*arrow*)

with a mean of 3 mm, when the bladder is full and 5 mm when empty) (Leung et al. 2007). Calculating urinary bladder volume index, bladder volume wall thickness index and assessing the ureteric jet Doppler patterns seem to be useful adjuncts.

Important aspects in the evaluation process are the indications for VCU: Children with persistent and severe symptoms of nonneurogenic bladder-sphincter dysfunction including urgency, urge incontinence and infrequent voiding (lazy bladder syndrome) and positive findings in the kidney and bladder ultrasound study, in particular with (recurrent) UTI, should undergo VCU (Greenfield et al. 1997; Opsomer et al. 1998; Fotter 1994). A pelvic floor electromyography and uroflowmetry should be an obligatory part of the evaluation in those children. The role of urodynamics regarding sensitivity and specificity and impact on therapeutic efficacy and outcome is under debate.

Neonates and young infants with prenatally detected upper urinary tract dilatation or other uropathology who undergo kidney and bladder ultrasound and VCU must be carefully evaluated for signs of nonneurogenic bladder-sphincter dysfunction as well. Special attention to nonneurogenic bladder-sphincter dysfunction must also be given for infants and children with UTI who are referred for VCU because 30% of children with nonneurogenic bladder-sphincter dysfunction do not have urgency and/or incontinence.

Detection of nonneurogenic bladder-sphincter dysfunction is an important contribution for adequate management of these children. The radiologist must be aware of the important responsibility she/he has for these patients and must take charge in detecting nonneurogenic bladder-sphincter dysfunction, which otherwise could be overlooked. Since dysfunctional voiding and unstable bladder are often associated or coincide with the detection of unstable detrusor contractions on VCU, they can be a first and indirect sign indicating the need for further detailed examination, even video-urodynamics, which allows the most detailed assessment of the underlying, often complex, pattern of dysfunction for planning tailored and individualized treatment.

The close relationship between dysfunctional voiding and unstable bladder and urge with and without incontinence, recurrent UTI, breakthrough infections, VUR and constipation make kidney and bladder ultrasound and VCU (and video-urodynamics) an important part of the evaluation algorithm in these children. Successful treatment of these dysfunctions has a positive effect on the resolution rate and resolution time of VUR, of UTI, of (urge) incontinence and on costs (Benoit et al. 2002) and prevents kidney damage.

Videourodynamics remains the gold standard if a combination of a detailed functional assessment combined with a morphologic assessment of the urinary tract is desired (Glazier et al. 1997). But videourodynamic studies are seldom needed in children with nonneurogenic bladder-sphincter dysfunction. These studies are reserved for a selected group of patients with severe and/or persistent symptoms despite treatment. Video-urodynamics is not available in many institutions where children have to be assessed uroradiologically, and it is an expensive and time-consuming method. Therefore, the radiologist has to know a great deal about pediatric urology and urinary tract pathophysiology to exhaust all the possibilities that an adequate VCU technique provides.

Severe and persistent urgency and urge incontinence together with UTI suggest severe urinary-tract pathology. In these patients imaging with ultrasound and a VCU should be performed (Himsl and Hurwitz 1991). However, we have to keep in mind that VCU (and videourodynamics) are invasive methods and should not be used as screening tests in children.

We do not perform VCU for monosymptomatic, primary nocturnal enuresis or initially in children with daytime and nighttime wetting in the absence of severe urge, urge incontinence or UTI.

Altogether, it should be underlined that a slightly modified VCU technique allows the diagnosis of unstable bladder (overactive bladder) to be made in centers without urodynamic facilities with similar accuracy. Therefore, modified VCU is recommended in all children for the evaluation of symptoms of persistent and severe nonneurogenic bladder-sphincter dysfunction, in particular with (febrile) UTI and breakthrough infections and in all neonates and infants for the evaluation of upper urinary tract dilatation and extended ultrasound signs indicative of VUR.

There is still low general awareness of the problem of nonneurogenic bladder-sphincter dysfunction, especially among radiologists. There are still many children with nonneurogenic bladder-sphincter dysfunction, whose real problem has not been understood and who therefore receive delayed treatment or no treatment at all.

Conclusion

Evaluation of nonneurogenic bladder-sphincter dysfunction ("voiding dysfunction") begins with a careful history and a physical examination followed by urine analysis. Radiologic investigation starts with renal and bladder ultrasound. A VCU is performed in persistent and severe cases of nonneurogenic bladder-sphincter dysfunction and in children with associated urinary tract infection and breakthrough infections.

In primary monosymptomatic enuresis nocturna and in children with minor wetting before treatment and without irritative voiding symptoms and without urinary tract infection, VCU should not be performed.

14.13 Conclusion

The common pathophysiological denominator of all subtypes of nonneurogenic bladder-sphincter dysfunction ("voiding dysfunction") is functional urinary obstruction caused by detrusor-sphincter dyscoordination during bladder filling and/or micturition, leading to high intravesical pressure. Clinical manifestation in terms of irritative voiding symptoms and/or incontinence and urinary-tract pathology in terms of anatomical distortion, VUR and dilatation of the upper urinary tract are the consequences. Constipation, encopresis, urinary tract infection and breakthrough infections are part of a syndrome. To find a single common etiological denominator seems to be unrealistic; a complex polyetiologic concept has to be considered. Etiology may differ by age and gender. Pediatricians, pediatric urologists, and pediatric radiologists must learn to differentiate between symptoms such as enuresis nocturna and (urge) incontinence and signs such as unstable bladder or dysfunctional voiding. Unstable bladder is often the cause of (urge) incontinence in children, but it may be an associated sign of the symptom nighttime bed wetting (enuresis nocturna). The underlying etiology for both the symptom and the sign might be a disturbance of higher central nervous centers. The enormous complexity of this problem and rather divergent results of several treatment studies make treatment decisions still difficult. Even today, there is a major research deficit in this context due to the lack of systematic and large studies on the impact of various diagnostic tools and signs on the diagnostic and therapeutic efficacy, and there is still a lack of large comparable prospective and randomized treatment studies measuring outcome and life quality. The radiologist performing VCU and ultrasound studies of the kidneys and the bladder in neonates, infants and children has to know which functional and morphological findings are indicators of nonneurogenic bladder-sphincter dysfunction to bring out the crucial clues for further patient management.

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Urinary Tract Infection

15

Fred E. Avni, Michelle Hall, Marie Cassart, and Anne Massez

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F. E. Avni, MD, PhD, Professor and Chairman
M. Cassart, MD, PhD
A. Massez, MD
Department of Medical Imaging, Erasme Hospital, 808 route de Lennik, 1070 Brussels, Belgium
M. Hall, MD
Department of Pediatric Nephrology, University Childrens Hospital Queen Fabiola, Av. J.-J. Crocq 15, 1020 Brussels, Brussels, Belgium

15.1 Introduction

Urinary tract infection (UTI) refers to a condition in which there is growth of bacteria within the urinary tract. It is one of the most common bacterial diseases in children; 5% of girls and 0.5% of boys will experience at least one infection. Over the past few years, the approach to UTI has dramatically changed and is more focused on the pathogenesis, risk factors, indication for diagnostic tests and the appropriate uses of antimicrobial agents (Jodal 1994; Jodal and Lindberg 1999; Hellerstein 1995; Chang and Shortliffe 2006; Roberts 1990; Majd et al. 1991). Of special importance is the identification of individuals with complicated UTI, i.e., those with abnormalities of the kidneys, VUR or bladder dysfunction (Ditchfeld et al. 1994a,b). Symptomatic UTI must be differentiated into higher-tract infection, with lesions of the kidneys – acute pyelonephritis and pyelitis – and lower tract infections – acute cystitis. Upper UTIs usually present clinically with high fever and generalized symptoms, whereas lower UTIs present with voiding symptoms. It is often impossible to differentiate them or even sometimes to properly diagnose UTI (American Academy of Pediatrics 1999). Pathologically, in case of acute pyelonephritis (APN), inflammatory edema and microabscesses develop in the renal parenchyma; inflammatory lesions of the renal pelvic wall are often associated. If left untreated, the lesions evolve toward necrosis of the renal parenchyma, loss of nephrons and formation of scars (Talner et al. 1994). Long-term complications include reflux nephropathy (RN) (also called chronic pyelonephritis), renal hypertension, renal failure and end-stage renal disease. Risk factors for development of pyelonephritic scars include urinary tract obstruction, VUR with dilatation, low age, uncircumcised neonates, bladder dysfunction,

delay of treatment and recurrent attacks even with bacteria of low virulence (Chambers 1997; Van Howe 1998; Ring and Zobel 1988).

Imaging is important in that it will ascertain the diagnosis in patients with equivocal symptoms, while in others it will determine those at risk for developing recurrent UTI. Imaging will also allow efficient follow-up (Dick and Feldman 1996; Smellie et al. 1994, 1995; Gleeson and Gordon 1991).

15.2 Epidemiology of UTI

The prevalence of UTI varies with age and sex. UTIs are much more common in infant boys (2.7%) than in infant girls (0.7%); furthermore, there is a peak incidence of UTI in newborns boys that justifies a cautious and systematic approach (including a systematic VCU) once an infection is suspected. The origin of this difference is probably multifactorial, but uncircumcised boys could be more vulnerable (Cohen et al. 1992; Van Howe 1998).

The prevalence of asymptomatic bacteriuria in school-age girls is about 1.2% and about 0.04% in boys; in this age group, UTIs occur mainly in girls. Voiding dysfunction seems a favoring condition (Larcombe 1999; Lindert and Shortliffe 1999; Smellie 1991; Smellie 1994).

15.3 Imaging Acute Pyelonephritis

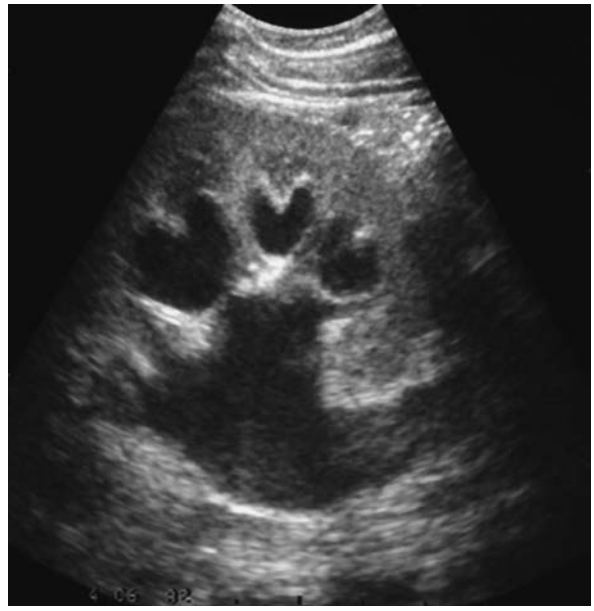
A great number of controversies persist on the difficult topic of imaging acute pyelonephritis (APN). No clear-cut studies have shown the investigations that must be performed, the patients who must be studied and the ideal timing. In most studies imaging techniques compete one against another; however, it is clear that no single study gives a complete evaluation of the diseased urinary tract and brings all the information needed. In other words, is there renal involvement? Is it irreversible? Is VUR present? Therefore, several techniques must be used in a complementary way for the assessment of a patient with an established case of UTI. Furthermore, their use must be optimized so that maximum yield is achieved (Lebowitz and Mandell 1987; Belman 1997; Stark 1997; Franz and Hörl 1999a, 1999b; Smellie 1994; Smellie and Rigden 1995; Pennington and Zerin 1999; Jakobsson et al. 1992; Beattie 2004).

15.3.1 Ultrasound

The need for a systematic use of US in case of suspected APN is controversial. Some authors advocate it, while others think it is unnecessary (Zamir et al. 2004; Giorgi et al. 2005; Jahnukainen et al. 2006).

The most widely accepted role of ultrasound (US) in cases of suspected APN is to determine whether there is an underlying renal malformation that has favored the UTI (Figs. 15.1a,b; 15.2a) (Dinkel et al. 1986; McKenzie et al. 1994; Hiraoka et al. 1997).

Besides this detection of congenital uropathies, US can and should have a supplementary role in diagnosing doubtful cases of APN. Surely, a so-called normal US does not exclude APN. Yet the analysis of the US appearances of the urinary tract must be very detailed and meticulous since there are many ancillary US signs that may result from an inflammatory involvement of the urinary tract that render the examination contributory (Table 15.1) (Picrillo et al. 1987; Avni et al. 1988a). Measuring the kidneys is important since in the case of APN the global renal volume is increased (Johansson et al. 1988; Schmidt et al. 2004); this is best evaluated by measuring the kidney on a transverse rather that on a longitudinal scan (Figs. 15.3; 15.4). As mentioned above, inflammatory infiltrates of the pelvic wall (pyelitis) and of the peripelvic fat are always present on pathological studies. These infiltrates may determine other interesting sonographic signs such as pelvic wall thickening and renal sinus hyperechogenicity (Figs. 15.3, 15.4) (Dacher et al. 1999). Thickening should be considered when the pelvic wall exceeds 0.8 mm (Alton et al. 1992; Robben et al. 1999). The thickening may extend into the ureter (ureteritis) (Avni et al. 1988b). It should be stressed that thickening of the renal pelvis wall may be encountered in other conditions such as VUR, postoperative uretero-pelvic obstruction and renal transplant rejection (Alton et al. 1992; Robben et al. 1999). Its presence must be analyzed according to the clinical data. Other signs of infection and especially sinusal hyperechogenicity would make



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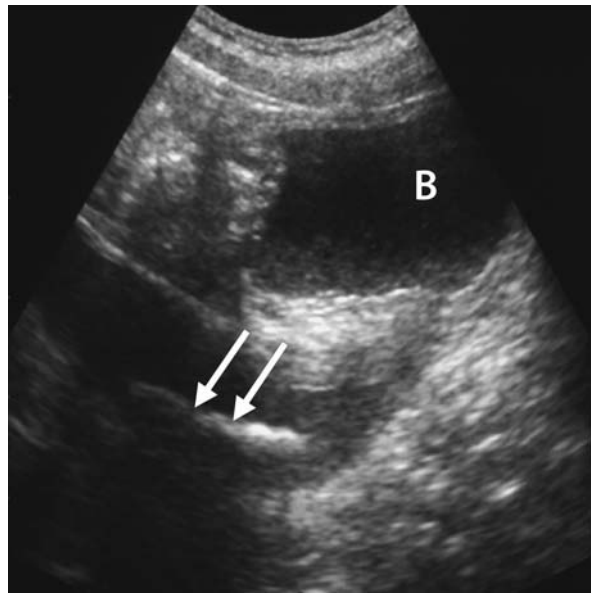

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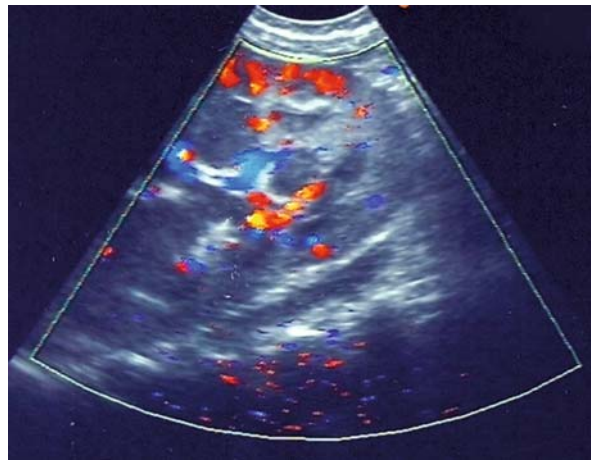

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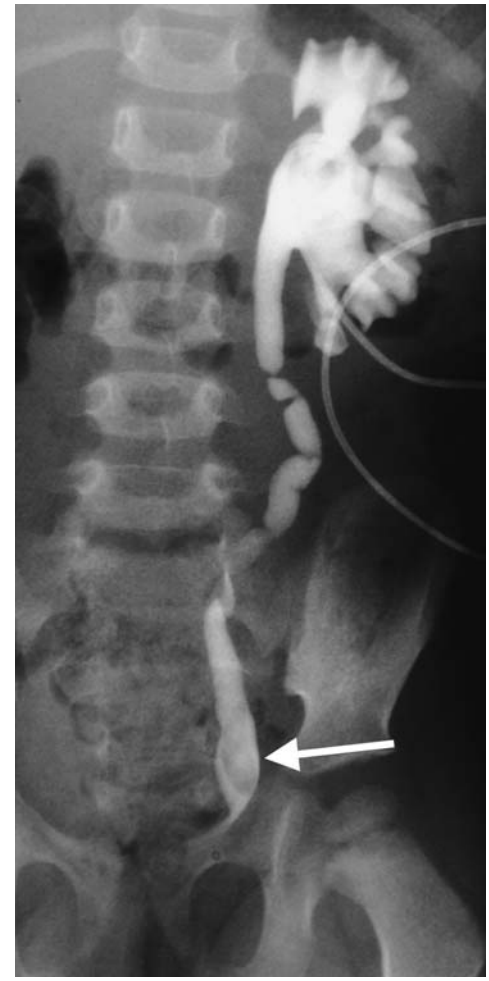
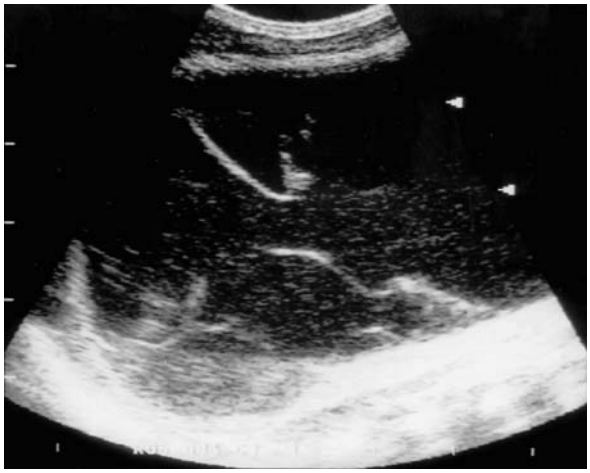


d

Fig. 15.1a–d. Acute pyelonephritis and pyonephrosis associated with ureterohydronephrosis and ureteral lithiasis. **a** Ultrasound: sagittal scan of the left kidney. Pyelo-calyceal dilatation; the urine appears echogenic suggesting pyonephrosis. **b** Ultrasound: left latero-sagittal scan of the U-V junction. A lithiasis is visible (*arrows*) in the dilated ureter; the urine in the bladder (**b**) and in the ureter is echogenic. **c** Ultrasound: color Doppler. Lack of color enhancement of the lower pole corresponding to inflammatory changes. **d** Opacification of the left urinary tract after placement of the nephrostomy tube. The urolithiasis is visible (*arrow*)



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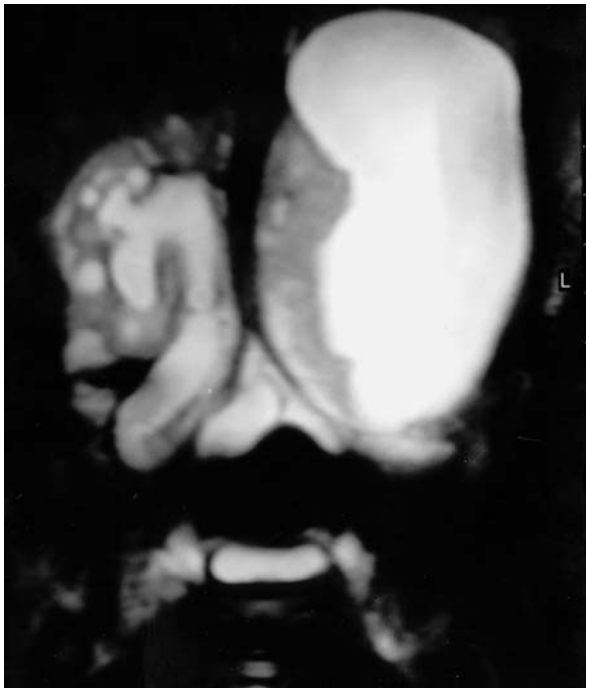


b

Fig. 15.2a,b. Infected perirenal urinoma. **a** US of the left flank: the huge urinoma contains echoes resulting from pus. **b** MR urography (SPIR T2 coronal sequence) showing right side ureterohydronephrosis and left huge urinoma

Table 15.1. Signs of APN on conventional US

• Increased renal volume
• Areas of increased or heterogeneous echogenicity
• Loss of CM differentiation
• Thickening of pelvic wall
• Renal sinusal hyperechogenicity
• Increased perirenal fat echogenicity

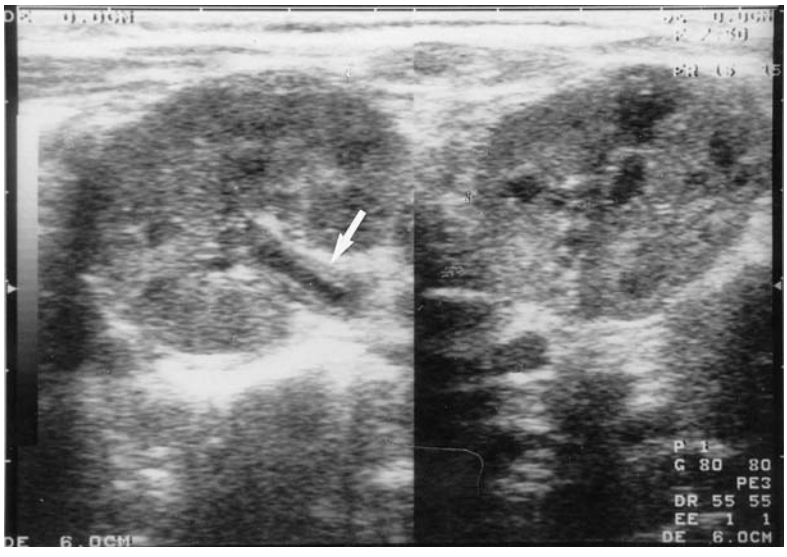
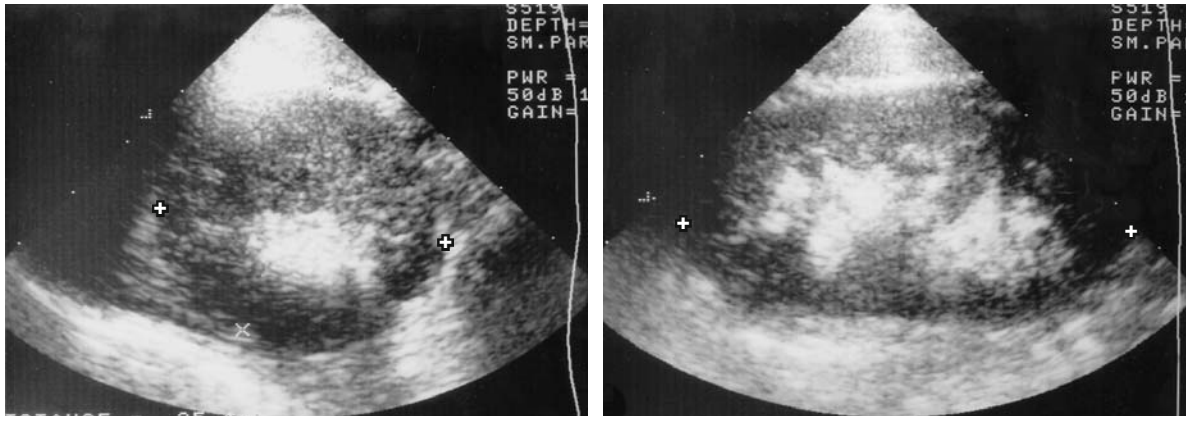


Fig. 15.3. Acute pyelonephritis (APN) and US. Transverse prone scan of both kidneys. The left kidney appears more globular, somewhat more echogenic with pelvic wall thickening (*arrow*)



a b

Fig. 15.4a,b. APN and US. **a** Transverse scan of the left kidney (*between crosses*). The kidney appears globular and there is a striking sinusal hyperechogenicity. **b** Sagittal scan of the kidney (*between crosses*) showing the sinusal hyperechogenicity

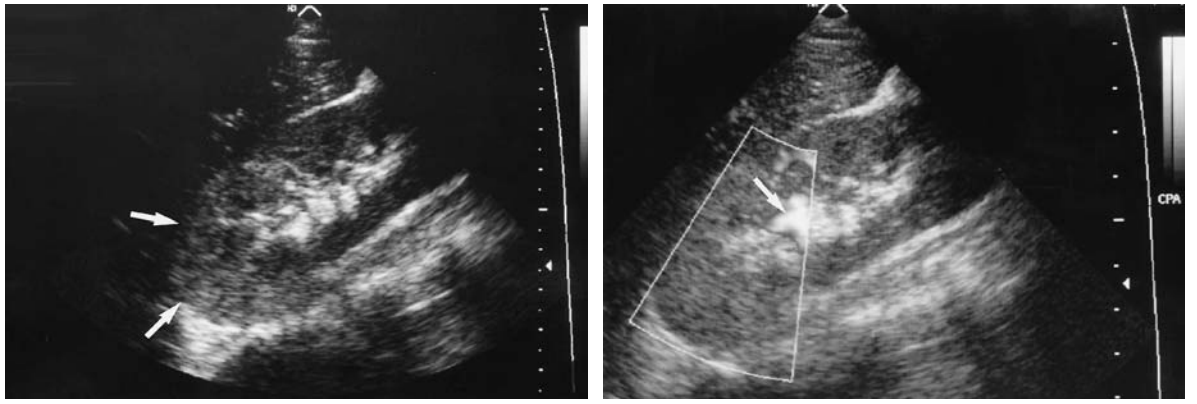


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Fig. 15.5a,b. APN and US. **a** Tumefactive hyperechogenicity of the upper pole of the right kidney (*arrows*). **b** Power Doppler (*arrow*) reveals lack of vascularization of this area

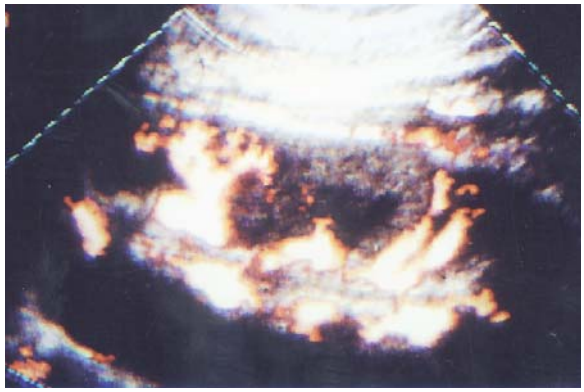


Fig. 15.6. APN and US. Power Doppler demonstrates an area of parenchymal devascularization (Courtesy of D. Dufour, MD)

this sign more suspicious. Other signs suggesting renal involvement include areas of parenchymal hyperechogenicity and corticomedullary dedifferentiation (Fig. 15.5a). The sensitivity of conventional US in detecting APN is about 50%–60%.

Several studies have shown that the use of color or power Doppler may increase the detection rate of the method to 85%. The contribution of Doppler is based on the lack of vascularization of diseased areas due to inflammatory edema and ischemic lesions (Figs. 15.1c; 15.5b, 15.6). The problem with Doppler techniques is that they require good cooperation from quiet patients; therefore, in some institutions, sedative drugs are administered to the patients before a Doppler examination (Eggli and Eggli 1992; Winters 1996; Dacher et al. 1996; Halevy et al. 2004).

15.3.2 DMSA Scanning

DMSA scanning is considered as the gold standard for the detection of renal involvement in UTI. The main feature of renal involvement is lack of uptake of the tracer in diseased areas. This may be localized or more diffuse (Fig. 15.7). The sensitivity of the technique reaches over 90%, and it is quite specific. It should be stressed, however, that at least half of the lesions seen in the acute phase of a UTI are no longer present on subsequent examinations. Furthermore, the lesions that are significant are those that will remain on follow-up. In addition, the DMSA scanning technique has the disadvantage of not differentiating old from new lesions unless a previous examination exists. Therefore, its use during the acute phase of the disease is not universally advocated (Kass et al. 1992; Rosenberg et al. 1992; Morin et al. 1999; Björgvinsson et al. 1991; Benador et al. 1994).

15.3.3 Computed Tomography

Contrast-enhanced CT appears as efficient as DMSA scanning for the demonstration of renal lesions of APN. The lesions are best demonstrated on the late post-injection phase and appear as hypodense striated triangular-shaped areas within the renal parenchyma (Fig. 15.8). Due to the corticomedullary differentiation of the early postinjection phase, the extension of the renal disease may be underestimated if the images are obtained too early. The ionizing hazards and the need of contrast injection prevent a routine use in the acute phase (Dacher et al. 1993; Dacher et al. 1996). On the contrary, CT is most helpful and should be used systematically if the clinical progression under appropriate therapy is not favorable or if an abscess is suspected (Fig. 15.9) (Auringer 1997). CT may also be helpful in cases of a poorly functioning kidney (Fig. 15.1b) and in case of underlying lithiasis.

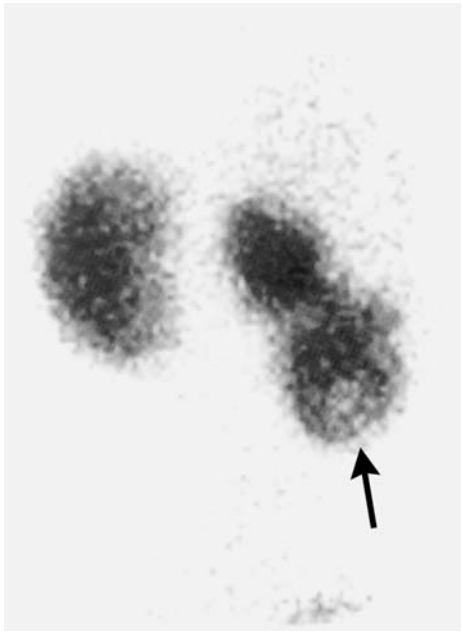


Fig. 15.7. APN and DMSA scanning. Posterior view area of decreased uptake at the lower pole of the right kidney (*arrow*)

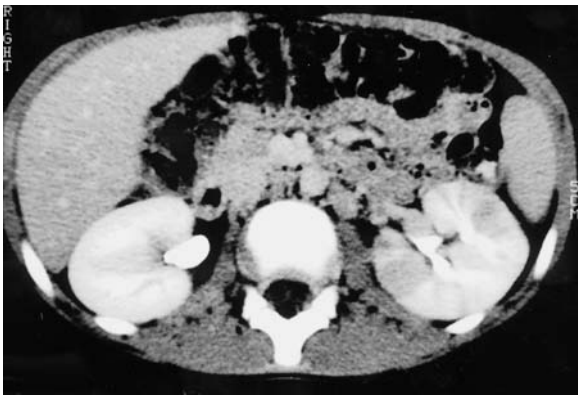


Fig. 15.8. APN and CT. Contrast-enhanced CT: triangular-shaped areas of decreased enhancement corresponding to the diseased parenchyma

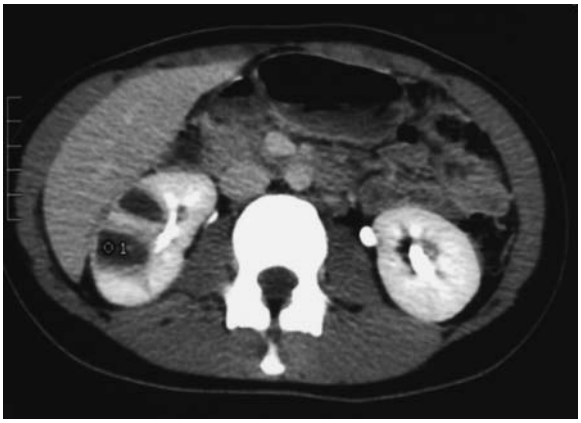


Fig. 15.9. APN and CT. Contrast-enhanced CT: evolution towards an abscess formation at the right middle and upper pole. The renal parenchyma appears necrotic and does not enhance

15.3.4 Magnetic Resonance Imaging

MRI has great potential for detecting areas of infected renal parenchyma. Both experimental and clinical trials have shown a good correlation between MRI and DMSA scanning. After contrast enhancement, the diseased areas appear hypointense on T1 sequences (Fig. 15.10). Newest diffusion weighted sequences are able to ascertain abscess formation, and the technique is able to differentiate between acute and more chronic inflammatory lesions. Another advantage of the technique is that it provides information on the morphology of the collecting system (Figs. 15.2b). To date, the biggest problem with this technique results from restricted access to the presently available equipment (Pennington et al. 1998; Lonergan et al. 1998; Poutschi-Amin et al. 1998; Weiser et al. 2003).

15.3.5 Voiding Cystourethrogram

The percentage of VURs occurring in patients with UTI varies according to age and sex and is evaluated to about 30%–40% (Fig. 15.11), and clearly, there is a significant association between UTI and VUR. Yet, VCU cannot be performed systematically since it is a relatively invasive and irradiating technique. Therefore, the decision tree should be based upon the age and sex of the patients. VCU should be performed systematically in infant boys, but less systematically in girls unless DMSA scan or US examination is positive for parenchymal lesions (Tseng et al. 2007). If decided upon, the examination must be performed once the treatment has been proven effective. If necessary, the examination can be performed as early as 4 days after intravenous antibiotic therapy once the urine has become sterile. Many teams prefer to perform it up to several weeks later under prophylactic antibiotic therapy. If decided upon, the technique should be performed reducing the irradiation in as much as possible (i.e., by using pulsed fluoroscopy). As mentioned above, the advantages of VCU include

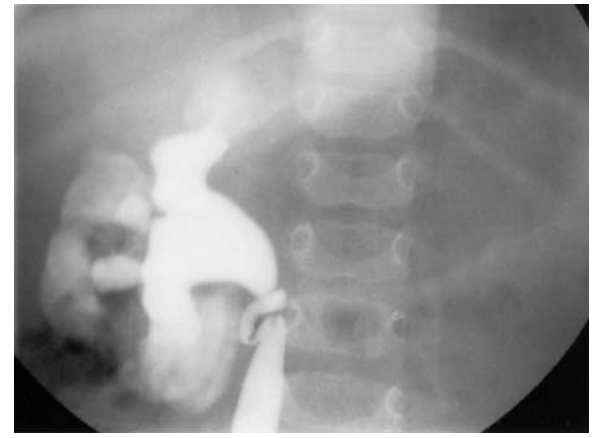
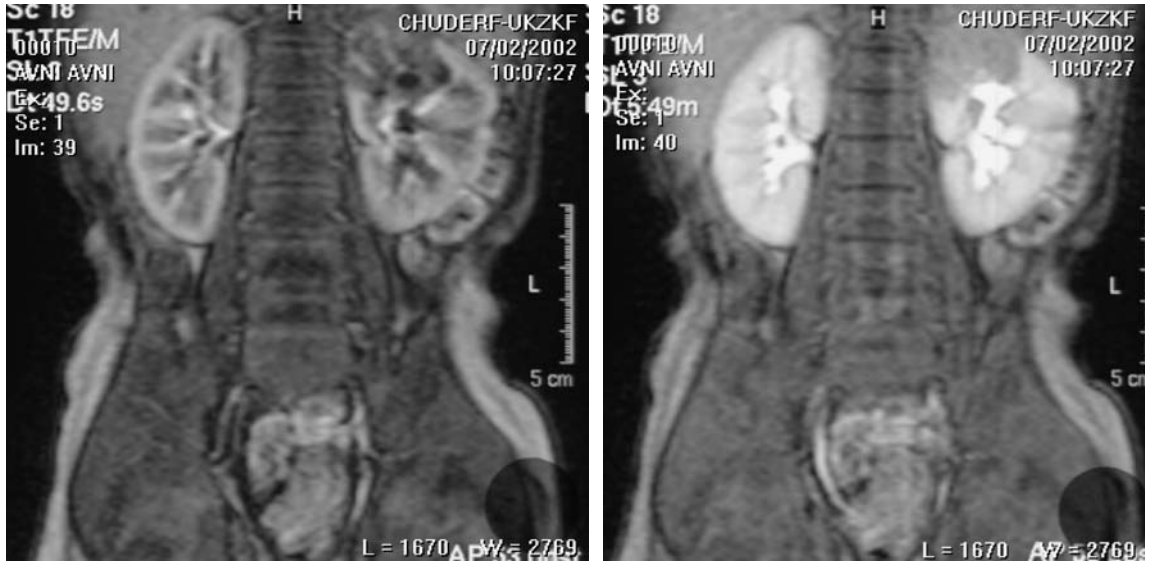


Fig. 15.11. Scarred kidney associated with massive right-sided intrarenal VUR on this VCU



a b

Fig. 15.10a,b. MR imaging of APN. **a** T1 sequence post-Gd enhancement. Early phase. Heterogeneous enhancement of the left upper pole. **b** T1 sequence post Gd. Late phase. No enhancement of the upper pole parenchyma is visible

the possibility to grade VUR, to visualize intrarenal VUR, to evaluate the bladder function and to display urethral anomalies. If the bladder capacity appears small compared to what is expected, cyclic filling of the bladder should be performed in order to increase the detection rate of VUR (Gelfand et al. 1998; Pennington and Zerin 1999; Jodal and Lindberg 1999). Contrast-enhanced sonocystography is an acceptable alternate study in girls with UTI.

15.3.6 Radionuclide Cystography

Radionuclide cystography (RC) is an interesting alternative to VCU in that the irradiating doses delivered are low. However, the technique does not allow evaluation of intrarenal VUR, of the bladder wall or of the urethra. Some teams advocate its use in girls rather than in boys (Piepz and Hamm 2006).

15.3.7 Intravenous Urography

Increased renal size, a delayed nephrogram, a striated nephrogram and striated ureters have been reported, among other findings, in APN (Fig. 15.12). However, since many other techniques can provide much more and more precise information on urinary tract involvement, this examination should no longer be performed in the acute phase (Kenda 1989).

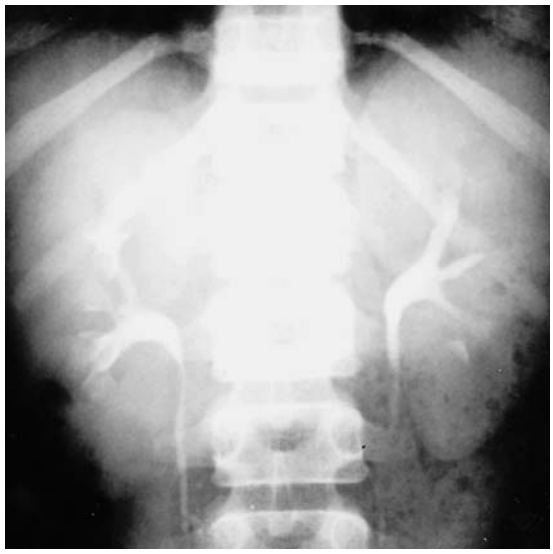


Fig. 15.12. IVU appearance of left APN. The left upper pole is swollen. The middle calyx is incompletely filled

15.3.8 Who Should Be Investigated?

A large number of studies have been published on optimizing the workup of children with UTI. As mentioned above, newborn boys and preschool-aged girls present the highest rate of renal involvement in UTI. Therefore, several teams have suggested restricting the investigations to these age groups and to groups at risk. To date, however, it is still not known why some patients develop renal involvement while others do not. Other unanswered questions include the origin of recurrent infections and the age and sex prevalence of new renal scars.

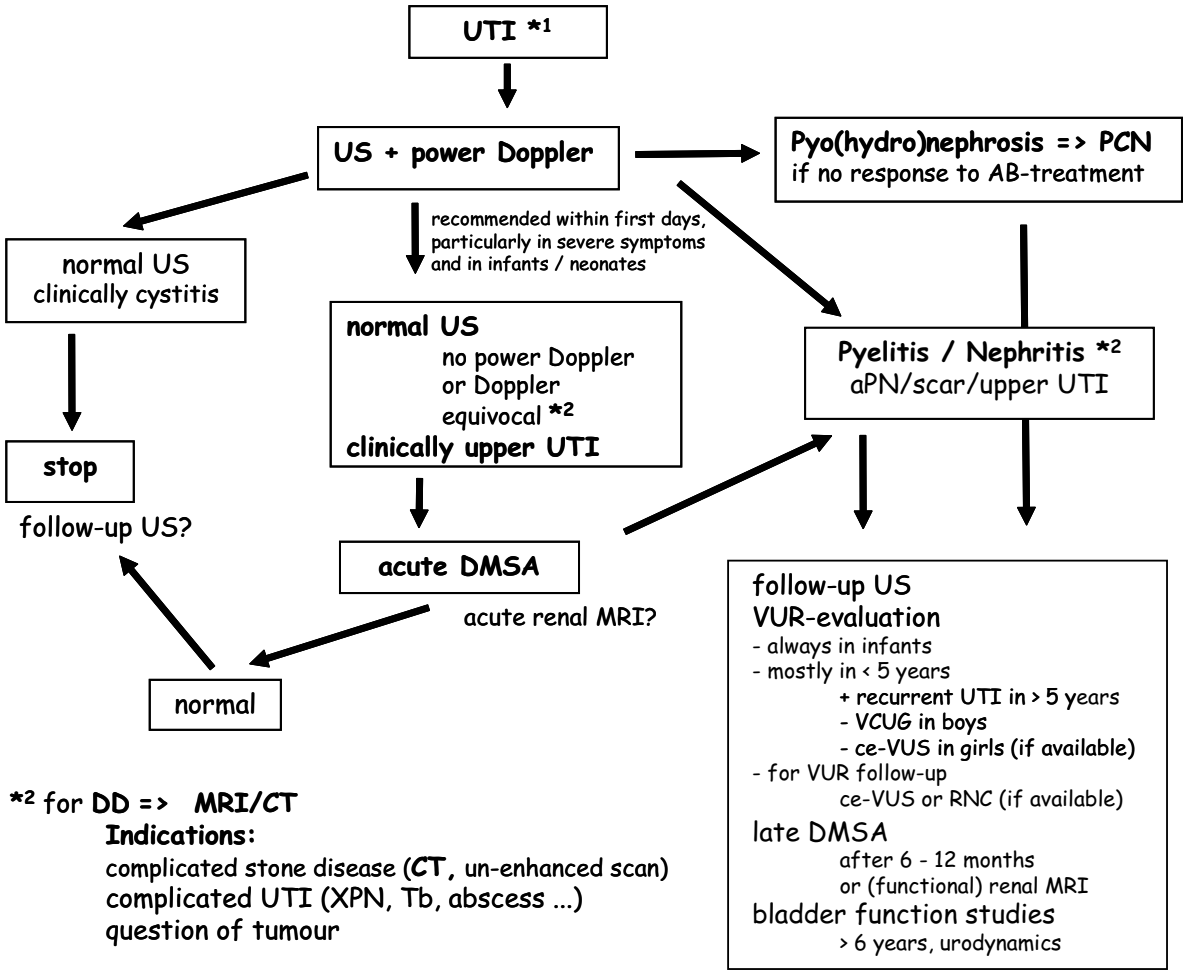
No prospective study has been performed that can answer these questions; therefore, until there is further evidence, any patient with proved UTI, whatever her/his age or sex, should undergo an imaging evaluation (Dick and Feldman 1996; Larcombe 1999; Wennerström et al. 2000; Olbring et al. 2003; Smellie and Rigden 1995). A recent consensus workshop has suggested a decision tree based on clinical data and US (Table 15.2) (Riccabona et al. 2006).

The first examination is usually US, which will demonstrate an underlying uropathy and possibly signs of renal involvement. The necessity of DMSA scanning should be decided during the acute phase if a clinical doubt remains concerning the diagnosis. VCU should be performed on an individual basis taking into account clinical and imaging data (Pennington and Zerin 1999; Jodal and Lindberg 1999; Stark 1997). These three examinations constitute the basis of the initial workup. It should be completed according to the initial findings or to the local conditions (i.e., availability of MRI).

Conclusion

No single imaging technique answers all the questions regarding UTI. Elements that would alter the treatment and are important to diagnose are renal involvement, any favoring condition and the presence of VUR. Any patient with proved UTI should undergo an evaluation. US and VCU are mandatory examinations. DMSA, CT and MRI are complementary investigations and should be performed in case of clinical doubt.

Table 15.2. Imaging algorithm in children with urinary tract infection (Riccabona et al. 2006)



15.4 Satisfactory Progression of APN

Clinical symptoms resolve rapidly in patients with a favorable outcome. On the contrary, the findings described on imaging and especially on US may remain for several weeks, before the situation returns to normal, and this should not raise concern. For instance, the decrease in renal volume is progressive and takes about 4–5 weeks (Fig. 15.13). The progressive decrease is best monitored by US (Johansson et al. 1988; Pickworth et al. 1995). This means that the follow-up of renal growth by US must take into account this transitory phase and start only after complete normalization. Pelvic-wall thickening and sinusal hyperechogenicity remain for an even longer time.

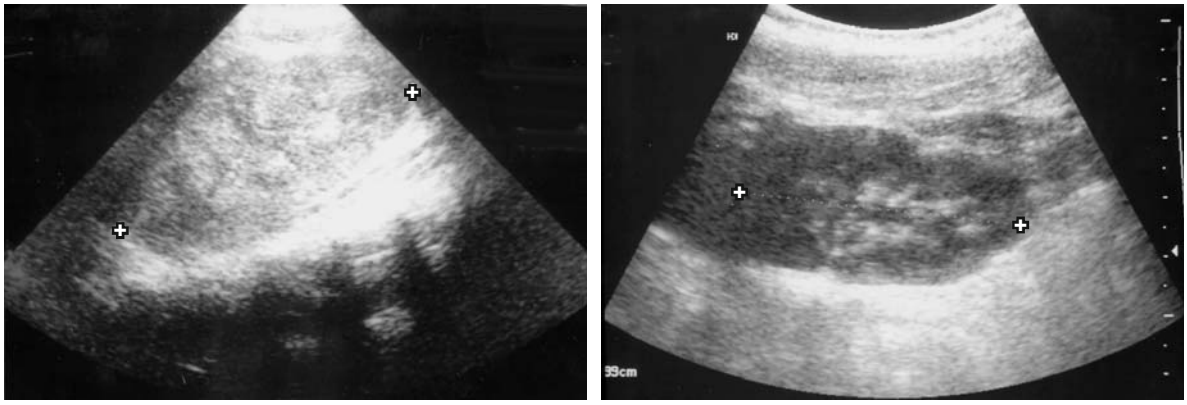


Fig. 15.13a,b. Satisfactory evolution of APN. US of the left kidney. **a** During the acute phase the kidney is swollen (length 7.5 cm *between crosses*) and diffusely hyperechoic. **b** Four weeks after treatment, the renal size has reduced (length 6 cm *between crosses*) and echogenicity has returned to normal

15.5 Early Complications of APN

15.5.1 Acute Bacterial Nephritis

Acute bacterial nephritis or acute lobar nephronia is an unusual form of APN and refers to a localized hemorrhage or necrosis superimposed on the local infection; on US, the area involved appears hyperechoic without clear limits (Fig. 15.14a) (Rigsby et al. 1986; Avni et al. 1988a). This probably corresponds to a pre-abscess formation stage (Talner et al. 1994).

15.5.2 Renal Abscess

In the event that the treatment of APN is delayed or not properly adapted, the pyelonephritic lesions may coalesce and form an abscess. This may remain limited to the kidney or extend first into the renal capsule and thereafter into the perinephric space. The progressive extension of the inflammatory process may be demonstrated by US (Figs. 15.14a, 15.15a); an increased echogenicity of the retroperitoneal fat or even of the perivesical fat on the right side will be demonstrated. The abscess itself appears as a mass with variable echogenicity depending on the degree of necrosis. Both CT and MR imaging are valuable techniques for the demonstration of the abscess and its extension (Figs. 15.14b, 15.15b, 15.16). Diffusion weighted sequences help for differentiating abscesses from other tumoral lesions (Fig. 15.16b) (Brook 1994; Thornbury 1991; Chen et al. 1995; Talaricco and Rubins 1990; Dacher et al. 1996; Thoeny et al. 2005).

15.5.3 Cystic Pyelitis and Ureteritis

In the years when treatment was not initiated rapidly and/or was not appropriate, more severe complications occurred corresponding to an extensive infection of the entire urinary tract. Small abscesses developed within the pelvis and the ureteral wall, leading to cyst-like defects within the collecting system that were best seen on IVUs (Fig. 15.17a). In even more advanced cases, dissecting air bubbles were visible within the walls of the collecting system. On US, cystic pyelitis and urethritis appear as a striated thickening of the wall of several mm (Fig. 15.17b) (Avni et al. 1988b).

15.5.4 Pyonephrosis

In pyonephrosis, fine echoes can be seen in the most dependent part of the dilated collecting system; their presence in UTI corresponds to thick infected urine or pus (Figs. 15.1a, 15.2a, 15.18, 15.19). It should be noted that echogenic urine may also correspond to lithiasis sand, hemorrhage or necrotic debris. The placement of a nephrostomy tube should be discussed in cases of pyonephrosis (Fig. 15.1d) (Yavascan et al. 2005).

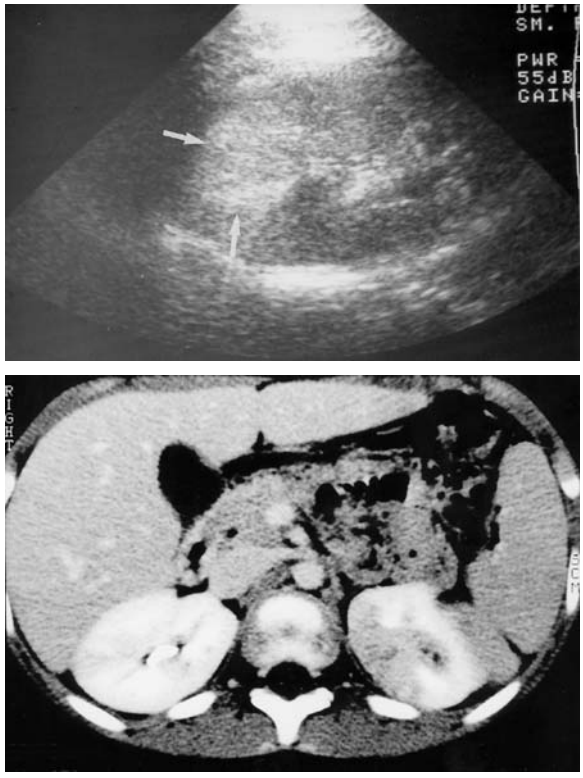


Fig. 15.14a,b. Acute nephritis, preabscess stage. **a** US: sagittal scan of the left kidney. There is an hyperechoic area at the upper pole (*arrows*). **b** Corresponding CT after contrast enhancement displays an area of decreased vascularization

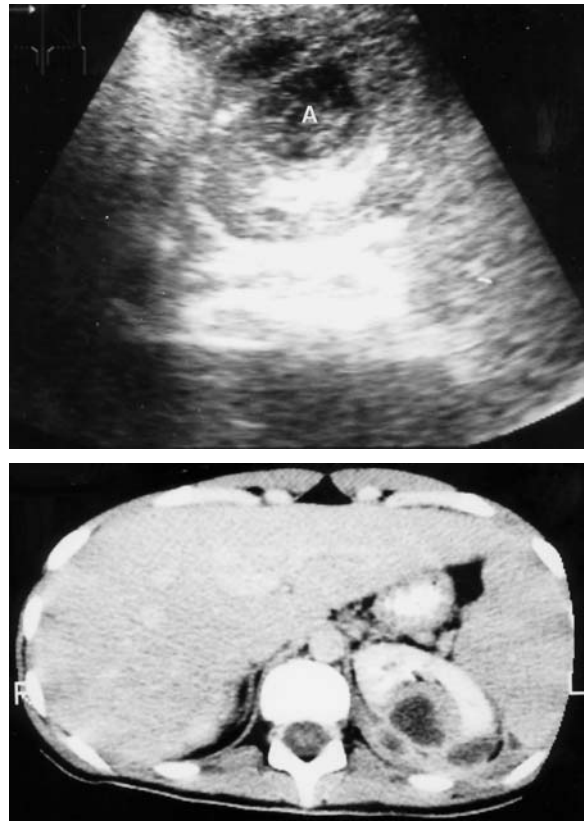


Fig. 15.15a,b. Renal abscess (courtesy of J.F. Chateil, MD). **a** US: transverse scan of the left kidney (prone) showing a hypoechoic abscess (*A*) formation with possible capsular extension. **b** Corresponding contrast-enhanced CT delineating the abscess formation and the perirenal extension

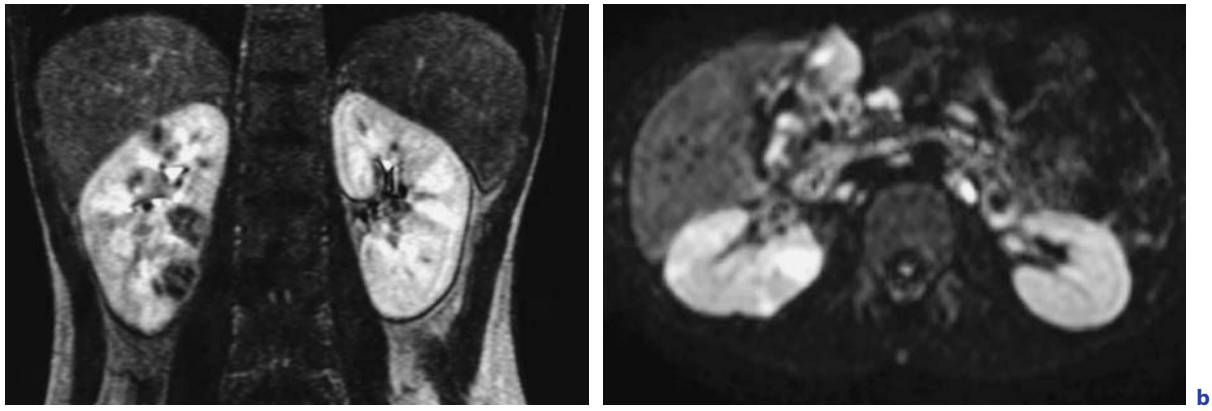
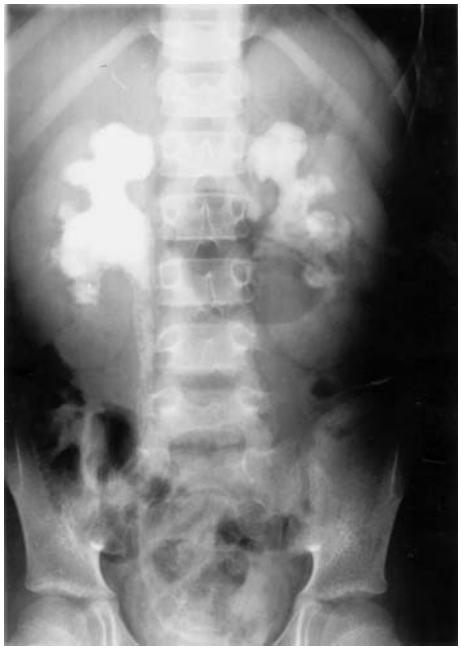


Fig. 15.16a,b. Diffusion weighted imaging and renal abscess. **a** MR imaging: T1-weighted sequence after Gd enhancement; inflammatory involvement of the right kidney. **b** MR imaging: diffusion weighted sequence; the abscessed areas highlight.



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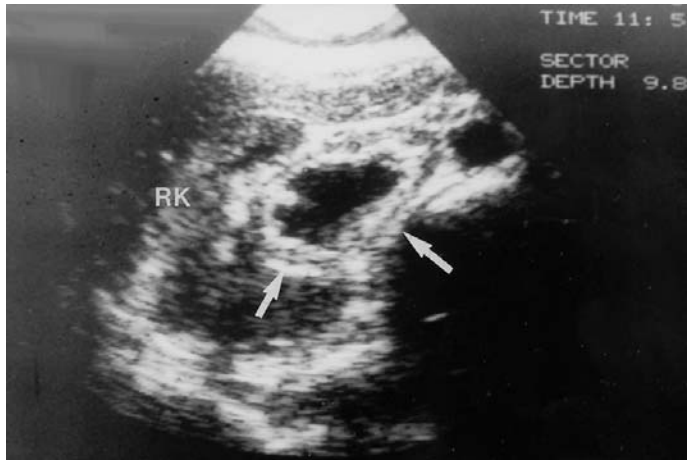

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Fig. 15.17a,b. Cystic pyelitis and ureteritis. **a** IVU: bilateral renal scars and cyst-like filling defects at the level of the collecting systems (especially the right ureter). **b** Corresponding US of the right kidney (RK) transverse scan, marked multilayered thickening of the renal pelvic wall (*arrows*)

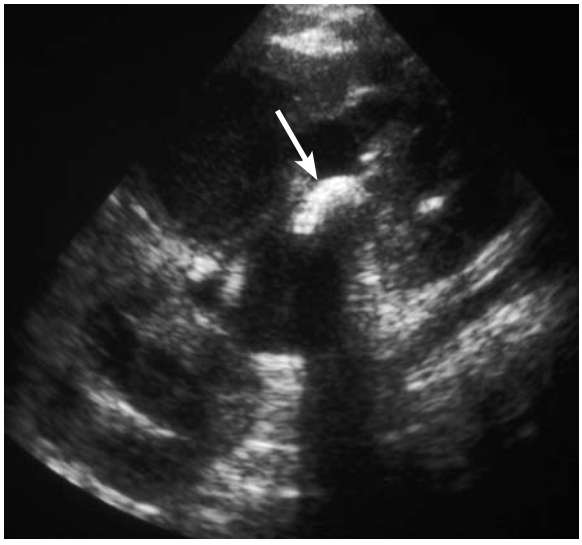
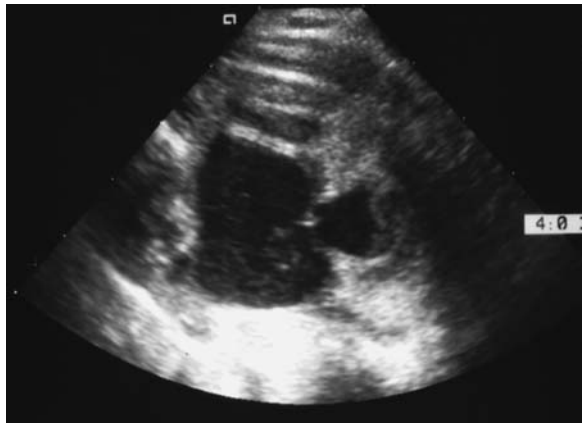


Fig. 15.18. Pyonephrosis, uro-lithiasis and obstructive uropathy. Ultrasound. Sagittal scan of the left kidney. A lithiasis is visible within the dilated urinary tract (*arrow*). The urine appears echogenic



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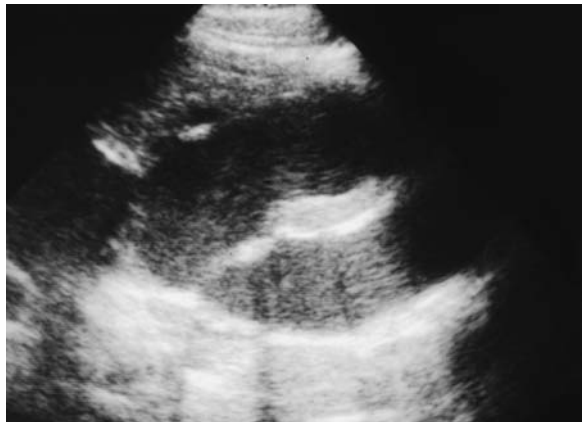

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Fig. 15.19a,b. Infected uretero-hydronephrosis. **a** Transverse scan of the left kidney. The urine within the dilated system is echogenic. **b** Sagittal scan of the left flank. It displays the highly dilated left ureter filled with echogenic urine

Conclusion

Abscess formation is the most common complication during the acute phase. CT and MR imaging is one the most valuable techniques for its evaluation.

15.6 Late Complications of APN

15.6.1 Scars and Chronic Pyelonephritis

The consequences of a delayed treatment of APN are the development of permanent lesions leading to a scarred kidney with chronic lesions of pyelonephritis (also called reflux nephropathy). Newer theories hypothesize that school-age girls have the highest risk of developing new scars, whereas in boys lesions that are demonstrated have developed in utero due to dilating VUR (Wennerström et al. 2000). Nevertheless, theoretically, patients presenting renal scars are at risk for developing renal hypertension, problems during pregnancy, renal failure and, more rarely, end-stage renal disease (Stokland et al. 1996; Jakobsson et al. 1994; Smellie 1994; Smellie et al. 1994; Berg 1992; Martinelli et al. 1995; Sreerarasimhalah and Hellerstein 1998). The role of imaging in the evaluation of RN is described in Chapter 11 on VUR. Presently, DMSA scanning is the most widely accepted and effective test for demonstrating the lesions once the acute phase of the disease has resolved (Fig. 15.20). IVU has become unnecessary (Shanon and Feldman 1992; Rushton and Majd 1992; Rushton et al. 1992; Risdon et al. 1994; Rushton 1997; Merrick 1995). US may also demonstrate scars (as thinning of the parenchyma and cortical irregularities) (Fig. 15.21), yet it underestimates the number and extent of the lesions. Contrast-enhanced US with harmonic imaging has been shown to improve the detection rate of US (Farhat et al. 2002). More recently, MRI has shown great potential for demonstrating RN; the advantage of the technique is that the collecting system can adequately be imaged as well (Chan et al. 1999) (see Chap. 11).

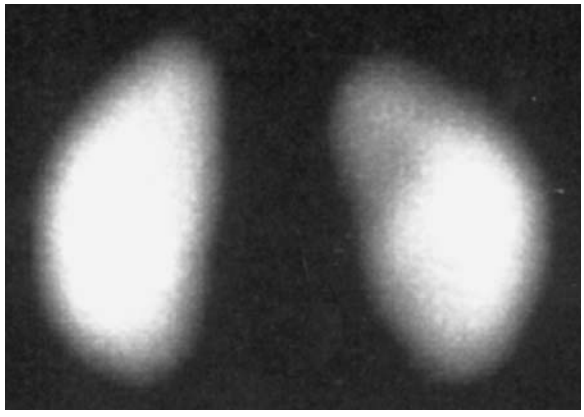


Fig. 15.20. DMSA. Scarring of the right upper pole (PA view)

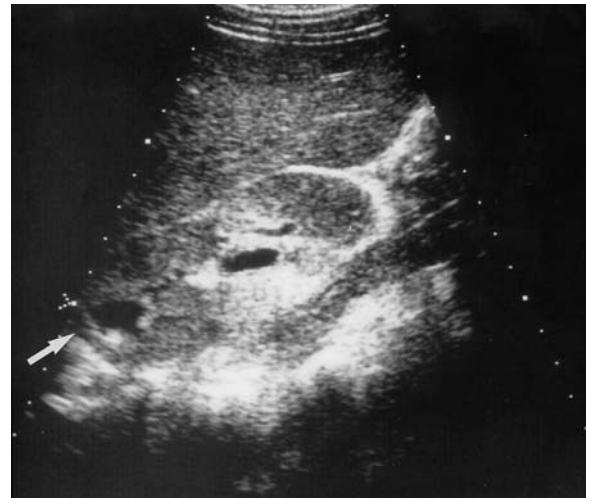


Fig. 15.21. US of a scarred kidney. Sagittal scan of the right kidney that appears small with thinning of the renal parenchyma and calyceal dilatation at the upper pole (*arrow*)

15.6.2 Xanthogranulomatous Pyelonephritis

Xanthogranulomatous pyelonephritis (XPN) is a severe atypical form of chronic renal parenchymal infection. Its origin is controversial and probably multifactorial. Pathogenesis includes calculus or noncalculus pyelonephritis, ineffectively treated APN, ischemia, alteration in renal metabolism and altered immune response to infection. It may appear as a localized tumor or under a more diffuse renal involvement pattern; calcifications are often present (Figs. 15.22, 15.23). The condition is usually mistaken for a true neoplasm, and preoperative diagnosis is rare. On US and CT, a calcified nodule within an otherwise normal-appearing kidney is the pattern encountered in the localized form. A large space-occupying lesion replacing the entire kidney and containing cystic necrotic areas can be found in the diffuse form. Calcifications may be present (Hugosson et al. 1994; Cousins et al. 1994; Schulman et al. 1997; Quinn et al. 1999).

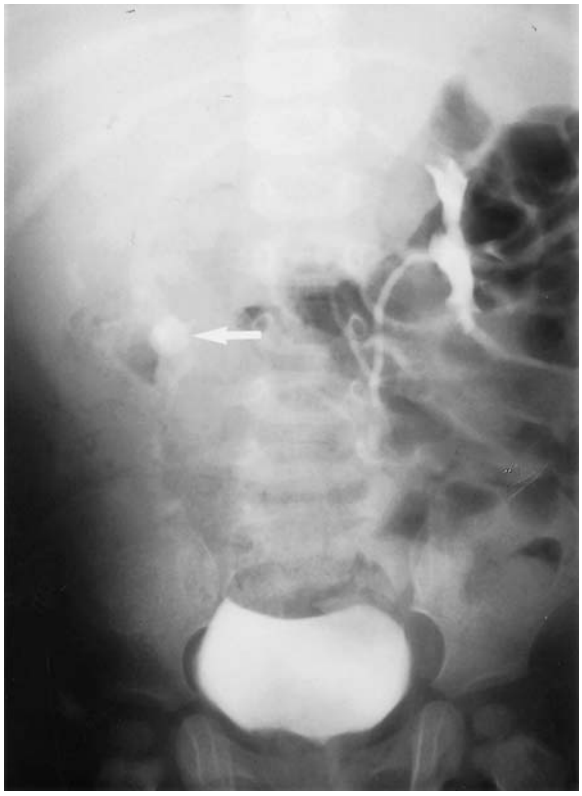


Fig. 15.22. Xanthogranulomatous pyelonephritis (XPN) IVU. Poorly functioning right kidney containing a central calcification (*arrow*) (courtesy of J.F. Chateil)

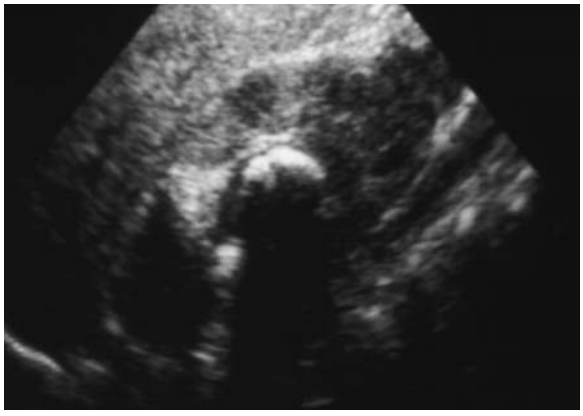


Fig. 15.23. XPN on US. Sagittal scan of the left kidney, highly distorted echogenicity and shape with central calcification (courtesy of C. Veyrac, MD)

Conclusion

Renal scars are the most feared complications of APN since they may induce complications later in life.

15.7 Cystitis

Cystitis refers to lower UTI without systemic symptoms. Sonographically, the bladder wall is thickened (more than 3.5 mm); it can be irregular and/or pseudo-tumoral (Figs. 15.24, 15.25). The urine within the bladder may be echogenic. These findings are not specific for a UTI, since bladder-wall thickening may appear in various conditions (Table 15.3) and urine echogenicity can be present in children without infection (Sutphin and Midleton 1984; Netto et al. 1999; Kaefer et al. 1997; Jécquier and Rouseau 1987; Friedman et al. 1983; McArville et al. 2000).

15.8 UTI and Lithiasis

Lithiasis may develop in association with a UTI; it can develop either with no other favoring factor (the pathogen involved is often Proteus mirabilis) or when there is any cause favoring renal stasis (Kraus et al. 1999) (Figs. 15.1, 15.18). The work-up must differentiate a metabolic and/or genetic origin from a specifically infectious origin (infectious stones). These stones are often poorly calcified and may appear stratified on CT.

15.9 UTI and Unusual Germs

15.9.1 Renal Candidiasis

Renal candidiasis develops in immunocompromised patients or in patients under massive and long-term antibiotic therapy. Patients with AIDS, premature babies and patients presenting complicated uropathies are most vulnerable to the germ. On US various patterns have been described, global renal hyperechogenicity, hyperechoic sludge (resembling small lithiasis) and fungus balls should suggest candidiasis (Figs. 15.26–15.28). Lesions may involve the renal vessels with secondary hypertension or even extend

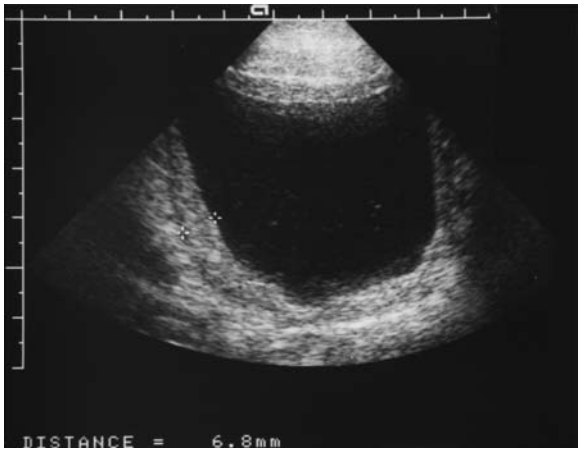
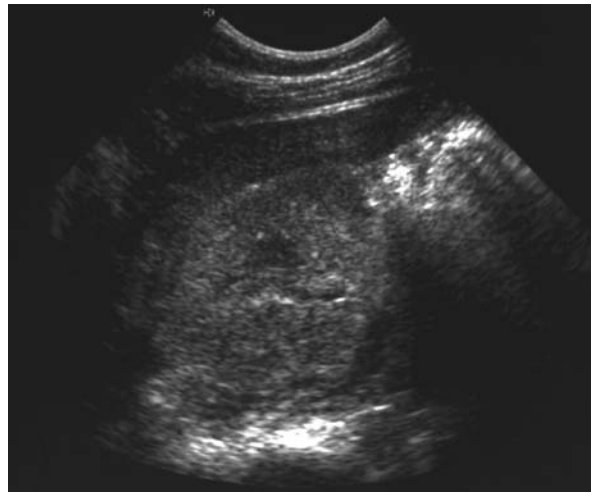


Fig. 15.24. Cystitis. Sagittal scan of the bladder showing thickening of the bladder wall (6.8 mm between *arrows*)

Table 15.3. Thickening of bladder wall

• Infectious cystitis (may be localized-pseudo-tumoral)
• Eosinophilic cystitis
• Drug-induced cystitis
• Neurogenic bladder
• Nonneurogenic bladder-sphincter dysfunction
• Posterior urethral valves
• Bladder outlet obstruction
• Megacystis-megaureter association

Fig. 15.25a–c. Pseudo-tumoral cystitis and APN. **a** APN: Ultrasound transverse scan of the right kidney that appears swollen and hyperechoic. **b** Cystitis: Ultrasound thickening of the bladder (*B*) wall affecting predominantly the posterior wall. **c** Cystitits: Power Doppler. Hypervascularization of the posterior bladder wall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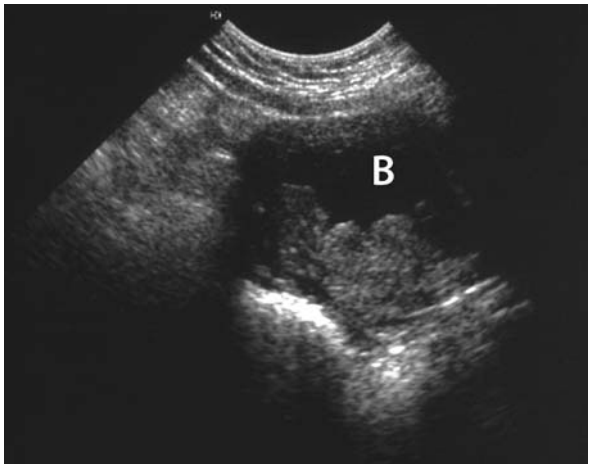

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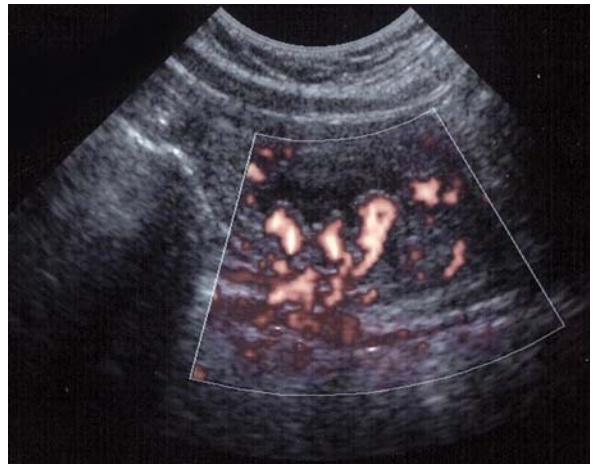
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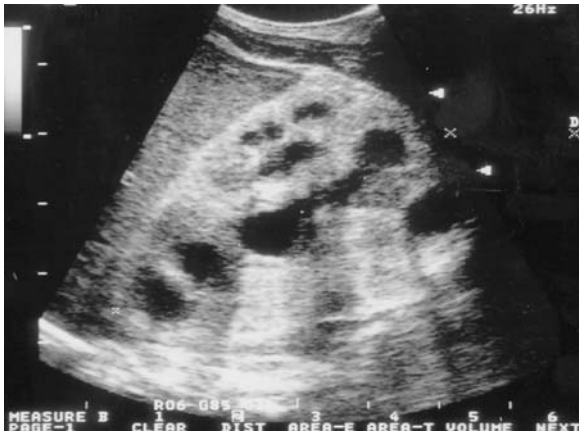

Fig. 15.26. Renal candidiasis and US. Diffuse hyperechoic pattern. Sagittal scan of the left kidney (case of ureterohydronephrosis related to a primary megaureter)

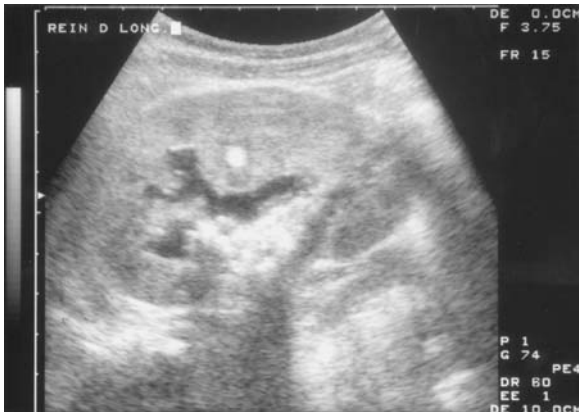

Fig. 15.27. Renal candidiasis and US. Sludge pattern. Sagittal scan of the right kidney; the cavities are filled with highly echogenic material (courtesy of J.F. Chateil, MD)

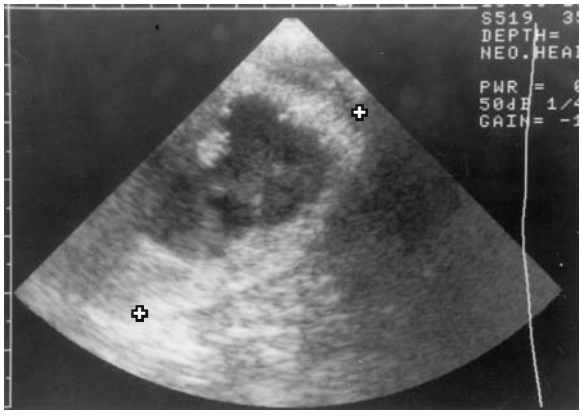

Fig. 15.28. Renal candidiasis and US. Fungus ball type. Sagittal scan of the left kidney (limited by the *crosses*). The dilated cavities contain echogenic ball-shaped material. The dilatation is related to grade V VUR

to the liver (Cohen et al. 1986; Shirkoda 1987; Yadin et al. 1998; Sirinelli et al. 1987; Berman et al. 1989).

15.9.2 Urogenital Tuberculosis

Tuberculous involvement of the urinary tract is uncommon. Radiological changes have mainly been described on IVU and include poor definition of a minor calyx or what is called the "drooping lily" appearance of pyelocalyceal system. It may evolve toward an acquired infundibular stenosis. It is followed by cavitation into the parenchyma. Finally, the kidney may be completely destroyed by ulcerocavernous caseation and calcify (Cremin 1987).

15.9.3 Hydatid Disease

Hydatid disease is a parasitic infection caused by larvae of tapeworms of the genus Echinococcus. The renal hydatid cyst is usually cortical and solitary. Such a diagnosis should be suggested in areas or patients presenting an epidemiological risk. CT or US demonstrates a thick-walled multiloculated cystic structure; it may be calcified. The falling snowflakes pattern within the cyst during patient mobilization is characteristic (Herta et al.1984).

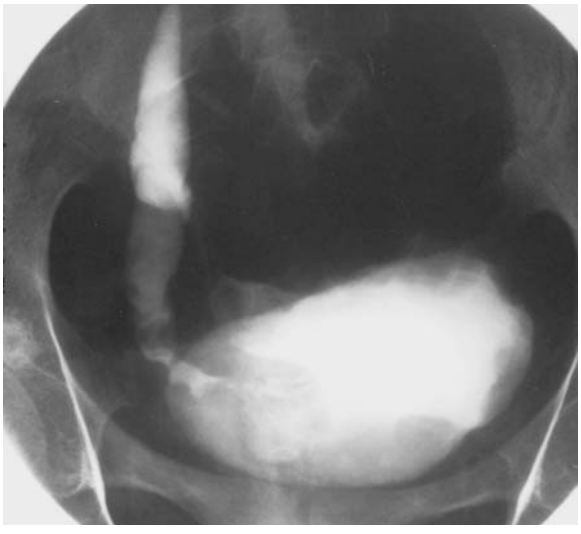

Fig. 15.29. Bilharziasis. On this IVU, the right lower ureter and the bladder wall appear thickened and irregular

15.9.4 Bilharziasis

Bilharziasis or schistosomiasis determines extensive inflammatory granulomatous reaction in the urinary tract. Renal involvement is usually asymptomatic, whereas ureteral involvement determines obstructive uropathy. Calcified thickening of the bladder wall is typical, and the bladder volume is markedly reduced (Fig. 15.29).

15.10 Conclusion

The topic of UTI remains controversial and the disease is not completely understood. However, the current imaging and therapeutic approach seems successful at least in terms of lowering the risk of renal scarring and late complications.

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Neurogenic Bladder in Infants and Children (Neurogenic Bladder-Sphincter Dysfunction)

16

Richard Fotter

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R. Fotter, MD
Professor and Chairman, Department of Radiology, Head, Division of Pediatric Radiology, University Hospital, Medical University Graz, Auenbruggerplatz 34, 8036 Graz, Austria

16.1 Introduction

Video-urodynamics, the gold standard for extended diagnosis in the neurogenic bladder, which combines urodynamics and VCU, has only limited availability, and significant involvement by radiologists is rare. Radiologists, however, are often involved in evaluating children with neurogenic bladder dysfunction. Radiologists performing VCUs and other imaging studies in children with neurogenic bladder should have an understanding of the pathophysiology and neurourology of these disorders, and they should be familiar with a modified VCU technique that can be accomplished with equipment currently available in radiological departments. This technique allows a more functional evaluation of the lower urinary tract and therefore allows detection of risk factors for upper urinary-tract deterioration. By incorporating aspects of modified VCU or urodynamic results, the ability to predict which neonates and infants are at risk for upper urinary-tract deterioration can be improved. Medical and surgical treatment can begin prior to the onset of urinary tract deterioration.

16.2 Anatomy of the Lower Urinary Tract

Urine is stored and evacuated by the bladder. The smooth muscle component of the bladder wall is termed the detrusor. The detrusor consists of interlacing muscle bundles that interdigitate with one another, resulting in a complex meshwork of smooth muscle. Viscoelastic properties of the normal detrusor allow it to stretch significantly without a significant rise in tension pressure. Detrusor fibers

continue into the bladder neck and surround the proximal urethra. These smooth muscle fibers are under voluntary control. The urethral sphincter mechanism has smooth and striated muscle fibers. The smooth muscle fibers are the continuation of the detrusor into the vesical neck and proximal urethra. This structure is called the internal urethral sphincter. The external striated sphincter surrounds the urethra, where it passes through the urogenital diaphragm extending up the posterior urethra to the level of the verumontanum. This can be seen endoscopically and radiologically (Dewan 1993; Dewan et al. 1997). The smooth muscle at the bladder neck (the internal sphincter) is the primary continence mechanism.

Lower urinary-tract function is under the control of the somatic and autonomic nervous system. The latter is comprised of the sympathetic and parasympathetic nervous systems. Sympathetic nerves originate in the thoracolumbar region of the spinal cord at T10 to L1. Parasympathetic nerves arise from the sacral area of the spinal cord at the level of S2 to S4. Somatic nerves from the sacral cord course through the pelvic plexus and the pudendal nerve to the external sphincter region.

16.3 Physiology of Normal Micturition

It is beyond the scope of this chapter to discuss this subject in depth, so I will simply stress the points most important for our purposes. The urinary bladder acts as a reservoir for urine between episodes of micturition. Resistance at the bladder neck and at the striated external sphincter allows for the retention of urine in the bladder until voiding occurs. Vesical pressure under normal conditions remains low during filling, even with high bladder volumes. Under normal conditions, the detrusor muscle, bladder neck, and striated external sphincter function as a unit for adequate storage and complete evacuation of urine. During bladder filling, there is unconscious inhibition of the micturition reflex. If maximum capacity is near, a need to void is transmitted to the sensory centers in the brain. When voiding is necessary and can occur in a socially acceptable situation, the micturition reflex is consciously activated and allows coordinated voiding. In normal voiding, there is a synergistic action between the detrusor and the internal and external sphincter mechanism, with contraction of the former and relaxation of the latter two muscle groups. Therefore, urine is expelled at low pressure.

16.4 Classification of Neurogenic Bladder

Children with neurogenic bladder-sphincter dysfunction may be unable to retain urine normally, unable to evacuate normally, or both. Multiple classification systems have been proposed to link various neurological diseases and their resultant lower urinary tract dysfunction. Classification systems for neurogenic bladder generally describe the pathologic condition in terms of the level of neurologic disorder or in terms of functional aspects of voiding. An example of the former is upper-motor neuron lesion and lower-motor neuron lesion. An example of a functional classification is based on the inability of the bladder to store urine properly or to evacuate itself properly of urine. Another functional classification that will be used in this contribution is based on the reflexive activity of the detrusor. For this classification three types are defined: contractile detrusor (detrusor hyperreflexia); acontractile detrusor (detrusor areflexia), which can be roughly linked to upper-motor neuron lesion and lower-motor neuron lesion, respectively; and intermediate detrusor (mixed type), when neurologic lesions overlap various portions of the micturition control centers or pathways as in many cases with myelodysplasia (Rickwood et al. 1982).

Conclusion

For prognostic and therapeutic reasons, only functional classifications based on the reflex activity of the different muscle groups involved in storing and evacuating urine should be used. One commonly used classification is based primarily on the reflex activity of the detrusor muscle, defining three types: contractile detrusor (detrusor hyperreflexia), acontractile detrusor (detrusor areflexia), and intermediate detrusor (mixed type).

16.5 General Background

Most neurologic conditions in children leading to a neurogenic bladder dysfunction including myelomeningocele, lipomeningocele, sacral agenesis, and occult lesions are congenital neurospinal dysraphisms (Goepel et al. 1999). Cerebral palsy is an acquired nonprogressive form of dysfunction occurring in the perinatal period as a consequence of cerebral anoxia from a variety of conditions. Children after sacrococcygeal teratoma resection commonly show neurogenic bladder as well (Ozkan et al. 2006). The neurourological changes could arise from the tumor itself and/or from the surgery. Traumatic causes of spinal cord or cerebral dysfunction resulting in neurogenic bladder are rare. In children, neurogenic bladder occurs in 80%–90% of patients who suffer from myelodysplasia. Myelomeningocele is the most common defect. The size of the myelomeningocele, the extent of the abnormality of the spine, and the degree of neurological symptoms do not necessarily correlate with the degree of neurourologic abnormalities. In addition, the neurourologic disturbance in myelomeningocele is dynamic and may change during a person's lifetime (Goepel et al. 1999).

With early and improved neurosurgical intervention, children with spina bifida are now suffering primarily from the urologic sequelae of the disease. The most common causes of morbidity and mortality among children with spina bifida who survive beyond the first 3 years of life are pyelonephritis and renal failure. About 50% will have evidence of upper-tract deterioration if left unattended over the first 5 years of life (Bauer and Joseph 1990). A central role in this problem is played by the neurogenic bladder, whose pressure volume characteristics determine the fate of the rest of the urinary tract. Upper urinary-tract deterioration, febrile urinary tract infections, and chronic renal failure are closely related to continuous or intermittent elevated bladder pressure. In terms of increased bladder pressure, there are three predictive indicators for upper tract deterioration: (1) detrusor sphincter dyssynergia, (2) high bladder-filling pressure, and (3) poor bladder compliance (Bauer and Joseph 1990; Galloway et al. 1991; Ghoniem et al. 1989, 1990; Kurzrock and Polse 1998; McGuire et al. 1981). In addition poor prognosis is determined by high leak point pressure and vesicoureteric reflux (Seki et al. 2004) and moderate to severe fibrosis of the detrusor (Özkan et al. 2005).

Therapeutic goals in children with myelodysplasia and associated neurogenic bladder are the preservation of renal function, avoidance of urinary tract infection, and achievement of appliance-free and social continence. Clean intermittent catheterization, administration of medication, and, in an increasing number of cases, surgical procedures such as continence procedures, bladder augmentation, vesicostomy, ileocaecal pouch with umbilical stoma, and the use of artificial sphincters have gained increasing importance to achieve these goals (Bauer and Joseph 1990; Kasabian et al. 1992; Rickwood et al. 1982; Stein et al. 2005a,b; Hayashi et al. 2006; Morrisroe et al. 2005). Operative reconstruction of the bladder has become a main stay for bladder rehabilitation, in particular, when pharmacological treatment and intermittent catheterisation have reached their usefulness. Xiao et al. (2003) developed a new approach for treatment, which could be the path into a new era of therapeutic management in refractory cases of neurogenic bladder. Microanastomosis of the fifth lumbal anterior route to the third sacral anterior route is undertaken to bypass the pathological etiology of spina bifida. With this approach the cause of neurogenic dysfunction is treated and not the end result of the neuropathy as with bladder reconstruction. Although the potential benefits have to be confirmed by others, pediatric radiologists should be aware of this new approach.

Altogether expectant treatment can no longer be advocated because morbidity with expectant therapy is high (Kaefer et al. 1999; Wu et al. 1997). To put treatment on an objective basis, it is essential to detect symptoms early and to take the abovementioned risk factors into account. Assessment of prognosis and treatment are without practical value if the neurourologic lesion is assigned to any neuroanatomic or functional classification without considering these risk factors.

Conclusion

Myelomeningocele is the most common cause of the neurogenic bladder in children. Pressure volume characteristics determine the fate of the urinary tract. There are three predictive indicators for upper tract deterioration: detrusor sphincter dyssynergia, high bladder-filling pressure, and poor bladder compliance. Expectant treatment can no longer be advocated.

16.6 Diagnostic Modalities

Many questions in this field can be answered by urodynamics and even better by video-urodynamics (Goepel et al. 1999). But because video-urodynamics is seldom available, especially in radiology departments, and because of the time-consuming nature of this technique, the main question for the radiologist today is how many and which of the above-mentioned essential features for planning treatment and prognosis in the neurogenic bladder can be detected by VCU. The role of VCU in evaluating children or infants with a neurogenic bladder should no longer be only morphologically descriptive. A modified VCU technique performed with a background of expertise in the pathophysiology of the neurogenic bladder provides functional assessment similar to urodynamics (Fotter et al. 1986; Fotter 1996). The role of VCU has to be redefined to include functional assessment of the neurogenic bladder in addition to the morphologic and descriptive role that it has played in the past. In the light of recent advances in our knowledge of which factors contribute to the deterioration of the upper tracts in myelodysplastic children, radiological functional assessment and classification of the neurogenic bladder must be done according to the following steps: (1) estimation of critical storage pressure to define the safe storage period (Bauer and Joseph 1990), (2) estimation of leak point pressure and of bladder compliance (Bauer and Joseph 1990; McGuire et al. 1981; Miguelez-Lago et al. 1997), (3) classification of detrusor dysfunction and of external sphincter behavior (Mundy et al. 1985; Rickwood et al. 1982), and (4) calculation of age-matched bladder volume and of residual urine (Palmer et al. 1997).

Conclusion

Functional questions can be answered by urodynamics; video-urodynamics provide simultaneous analysis of functional and morphologic findings. A modified VCU technique can also assess both functional disturbance and morphologic alterations.

16.7 Remarks on Classical Morphologic VCU Findings

With recently improved treatment and because radiological investigation is performed within the first days or weeks of life in most cases, the radiographic pattern of fully developed disease is no longer seen, but ultrasound may reveal bilateral upper-tract dilatation in inadequately treated patients. In such cases, the bladder can show a vertical configuration with major trabeculations, leading to the so-called Christmas tree bladder. This configuration is not characteristic of certain types of neurogenic bladder. In longer-lasting cases, especially with sphincter-detrusor dyssynergia, chronic prostatitis (male adnexitis) may lead to reflux of contrast material into the prostatic ducts and may lead to prostatic concrements (see Fig. 16.1). Bladder calculi are common in patients who are treated with clean intermittent catheterization. In postpubertal girls, calculi can be formed from pubic hair that may be carried into the bladder on the catheter. The hair may act as a nidus for the bladder calculus.

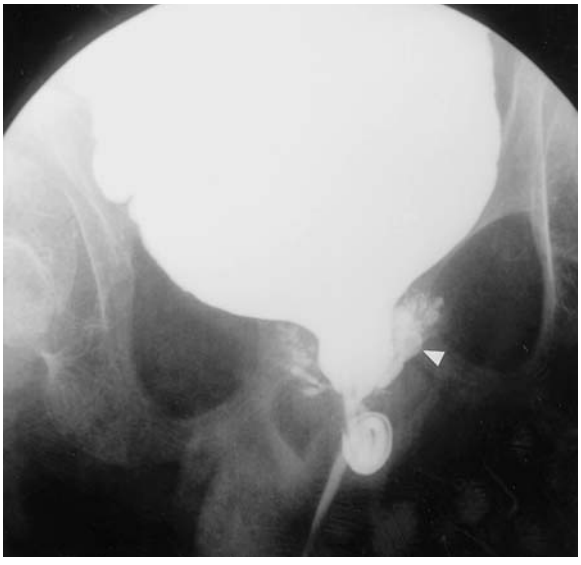

Fig. 16.1. Male, 15 years old. Lumbosacral myelomeningocele, contractile detrusor, sphincter detrusor dyssynergia: VCU. Contrast-filled bulging posterior urethra, minimal leakage around the catheter, massive reflux of contrast into dilated prostatic ducts. Filling defect (*arrowhead*) indicates prostatic concrement

Conclusion

Radiographic patterns of fully developed neurogenic bladder are seldom seen nowadays. Classical morphologic patterns such as the so-called Christmas tree bladder are not characteristic of certain types of neurogenic bladder.

16.8 Modified VCU

16.8.1 VCU–Relevant Bladder Physiology and Pathophysiology

In healthy bladders, the change in bladder-filling pressure between empty and full is normally less than 10–15 cm H_2O, and the normal filling pressure does not exceed this value. Even in the absence of reflux or upper urinary-tract dilatation, high intravesical pressure can impair drainage of urine into the bladder. A filling pressure of 40 cm H_2O is considered critical because ureteral peristaltic pressure rarely exceeds this level (Rickwood et al. 1982). Bladders with constant pressure values of more than 40 cm H_2O or intermittent pressure values of more than 90–100 cm H_2O are supposed to gradually lead to bladder-wall thickening, trabeculation, and subsequent diverticula formation. Such structural changes affect the elastic and viscoelastic properties of the bladder and may lead to ureterovesical junction obstruction or vesicoureteric reflux. Placement of the surface level of contrast material infusion is 30 cm above the level of the bladder. Therefore, under normal conditions, the bladder will fill to the expected age-matched capacity without significant slowing or cessation of the infusion flow. This indicates that intravesical pressure remains well below the critical vesical storage pressure of 40 cm H_2O. The speed of the infusion thus acts as a manometer of sorts, although without the capability of subtracting the effect of intraabdominal pressure. If intravesical pressure during the quiet filling phase or during unstable detrusor contractions reaches 30 cm H_2O or more, the flow will slow down and then cease, and the surface level will finally ascend when pressure significantly exceeds 30 cm H_2O. Changes in intraabdominal pressure must be identified as such by close and permanent observation of the patient and taken into account when estimating vesical pressure.

16.8.2 Technique

The modified VCU technique is described in detail in Chapter 14 on nonneurogenic bladder-sphincter dysfunction. Differences in handling and in VCU technique in children with neurogenic bladder do not start before the terminal phase of bladder filling and are described below. Drip infusion is stopped and the catheter removed if an urge to void or abdominal discomfort is announced or when expected age-matched bladder capacity is reached or if the drip infusion has completely stopped because of constantly increasing vesical pressure or as a consequence of massive uninhibited detrusor contractions. Catheter removal is done while the child is in a lateral position under fluoroscopic control. The way the child tries to empty the bladder is documented. If spontaneous micturition cannot be achieved, an attempt is made to provoke sphincter weakness incontinence by raising intraabdominal pressure. In this phase, the position of the bladder neck in relation to the superior margin of the symphysis pubis is checked. Any descent of the bladder neck in boys or a mild descent in girls is an expression of denervation of the striated sphincter and allows exclusion of sphincter detrusor dyssynergia (Zerin and Lebowitz 1990).

16.8.3 Findings

A constant decrease until cessation of infusion flow at inadequate low filling volumes indicates high filling pressure (Fig. 16.2), and such slowing of infusion flow with only small gains in inadequate filling volumes roughly indicates a noncompliant bladder. Compliance can be expressed as the bladder pressure needed to store a volume of 100 ml (Fig. 16.3). Low terminal compliance has a high incidence of associated vesicoureteric reflux, deterioration of upper urinary tract, and impaired renal function (Ghoniem et al. 1989). The term "safe period of bladder storage" is used to describe such filling volumes

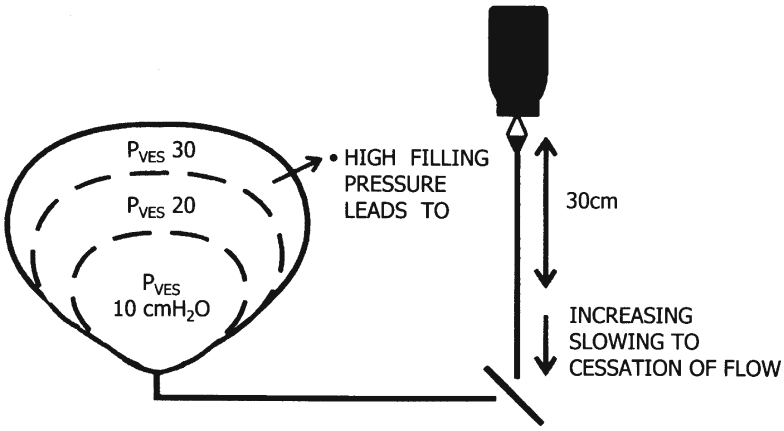

Fig. 16.2. Estimation of high bladder filling pressure by modified VCU. Increasing vesical pressure (P_{VES}) with bladder filling leads to decreasing flow and cessation of infusion flow if P_{VES} reaches 30 cm H_2O

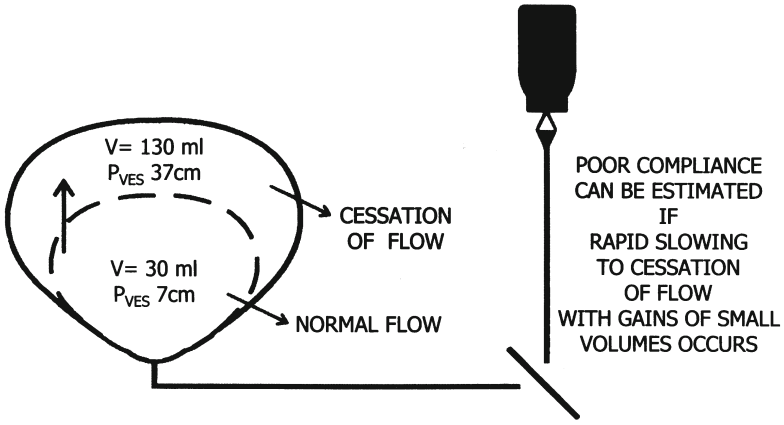

Fig. 16.3. Estimation of poor bladder compliance by modified VCU (V bladder filling volume; P_{VES} vesical pressure)

where bladder pressure does not exceed 40 cm H_2O (Bauer and Joseph 1990). In terms of modified VCU, the term safe storage period describes bladder volume before slowing or cessation or even before back-up flow occurs (Fig. 16.4). For bladders with a large safe storage volume, intravesical pressure does not reach 30 cm H_2O, and infusion flow does not cease until leakage occurs or age-matched estimated bladder capacity is reached, whichever occurs first. A leakage around the catheter must be noted and described in relation to the current filling volume and roughly estimated bladder pressure. If there is no leakage in a patient with continuous slowing or cessation of infusion flow, a high leak-point pressure can be estimated (>30 cm H_2O) (Bauer and Joseph 1990; Ghoniem et al. 1989; Ghoniem et al. 1990; McGuire et al. 1981) (Fig. 16.5). Abrupt and intermittent cessation or even reversal of flow indicates a rise in pressure that exceeds 30 cm H_2O, which is due to uninhibited detrusor contractions. Radiographically uninhibited detrusor contractions are manifested by a small or moderate amount of contrast agent flowing into the posterior urethra, where it is stopped above the pelvic floor by either a reflexive contraction of the external sphincter or a static distal sphincter obstruction (Mundy et al. 1985) (Fig. 16.6).

Based on the reflex activity of the detrusor muscle and the fact that most children with myelodysplasia do not fit into the classical anatomical and neurological categories, a classification system with three types of bladder dysfunction (contractile, acontractile, and intermediate) is in use (Rickwood et al. 1982).

In contractile bladders (hyperreflexive detrusor), uninhibited detrusor contractions lead to a sudden bladder-neck opening in a formerly normally configured bladder base, with bulging of the posterior urethra up to the contracted external sphincter. This VCU finding is the manifestation of sphincter detru-

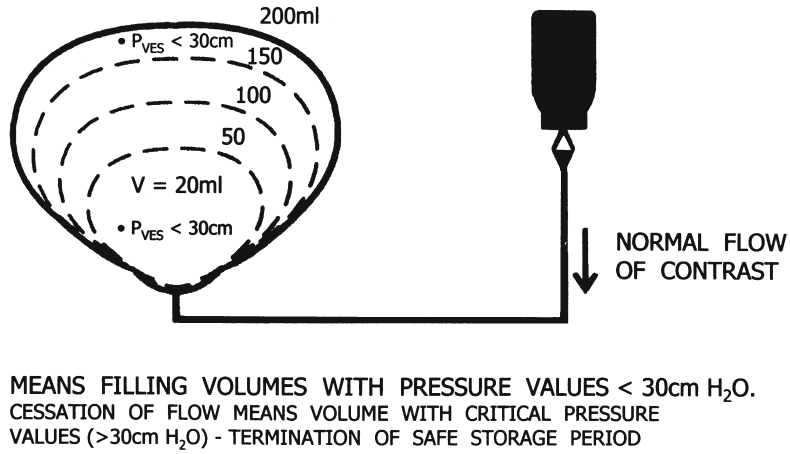

Fig. 16.4. Estimation of the safe storage period (the bladder volume at which vesical pressure remains well below 40 cm H_2O, the safe storage pressure) by modified VCU (P_{VES} vesical pressure; V bladder filling volume)

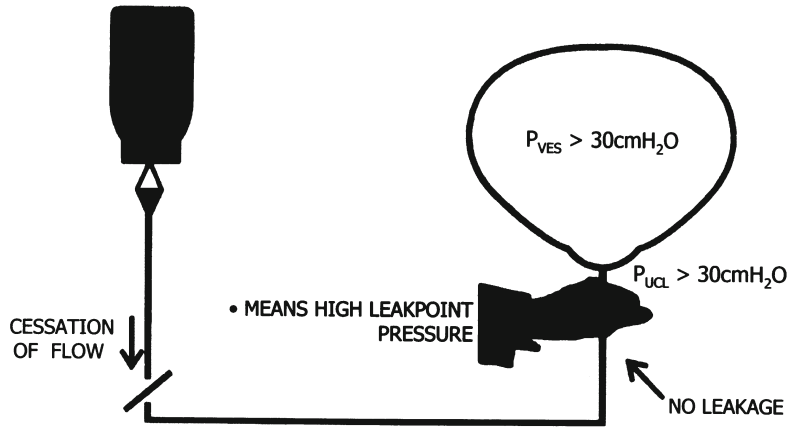

Fig. 16.5. Leak-point pressure estimation by modified VCU (P_{VES} vesical pressure, P_{UCL} urethral closure pressure

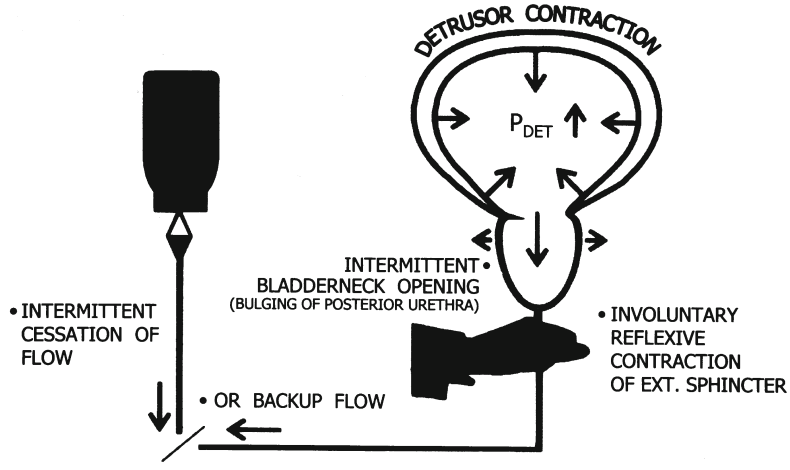

Fig. 16.6. Assessment of sphincter detrusor dyssynergia by modified VCU (P_{DET} detrusor pressure)

sor dyssynergia (Figs. 16.1, 16.6, 16.7). In sphincter detrusor dyssynergia a detrusor contraction is not accompanied by relaxation, but by reflexive tightening of the striated external sphincter. This results in a functional obstruction that produces high bladder pressure during voiding. Coexistence of detrusor sphincter dyssynergia and vesicoureteric reflux is the most common cause of rapid deterioration of the upper urinary tract in these children. In patients with sphincter detrusor dyssynergia without reflux, gradual deterioration in the form of obstructive hydroureteronephrosis will be the consequence. This may lead to a late onset of vesicoureteric reflux.

In intermediate bladders, the bladder neck can be closed at the beginning of filling, but the neck opens more and more with increasing filling volume and with increasing vesical pressure. Detrusor contractions lead to a transiently higher degree of the pre-existing bladder-neck opening, but the typical bulging of the posterior urethra is usually not seen in these cases. The urethra takes on a funnel-like appearance. In this situation, it is important to check the position of the bladder neck in relation to the superior margin of the symphysis pubis. Any descent of the bladder neck in boys or a mild descent in girls is an expression of denervation of striated sphincter and excludes sphincter detrusor dyssynergia (Fig. 16.8).

In acontractile bladders (detrusor areflexia), no signs of radiologically detectable detrusor contractions can be found. The bladder neck is open during the entire filling phase in these cases. Sphincter-weakness incontinence is indicated by leakage around the catheter, usually during the rise in intraabdominal pressure or coughing.

The bladder neck is usually competent in infants and children with contractile detrusors, whereas it is mostly nonobstructive and incompetent in children with intermediate or acontractile bladders at their usual bladder volumes.

Conclusion

In addition to morphologic assessment, modified VCU provides rough and sufficient assessment of the underlying neurogenic dysfunction including assessment of the so-called risk factors for the deterioration of the upper urinary tract.

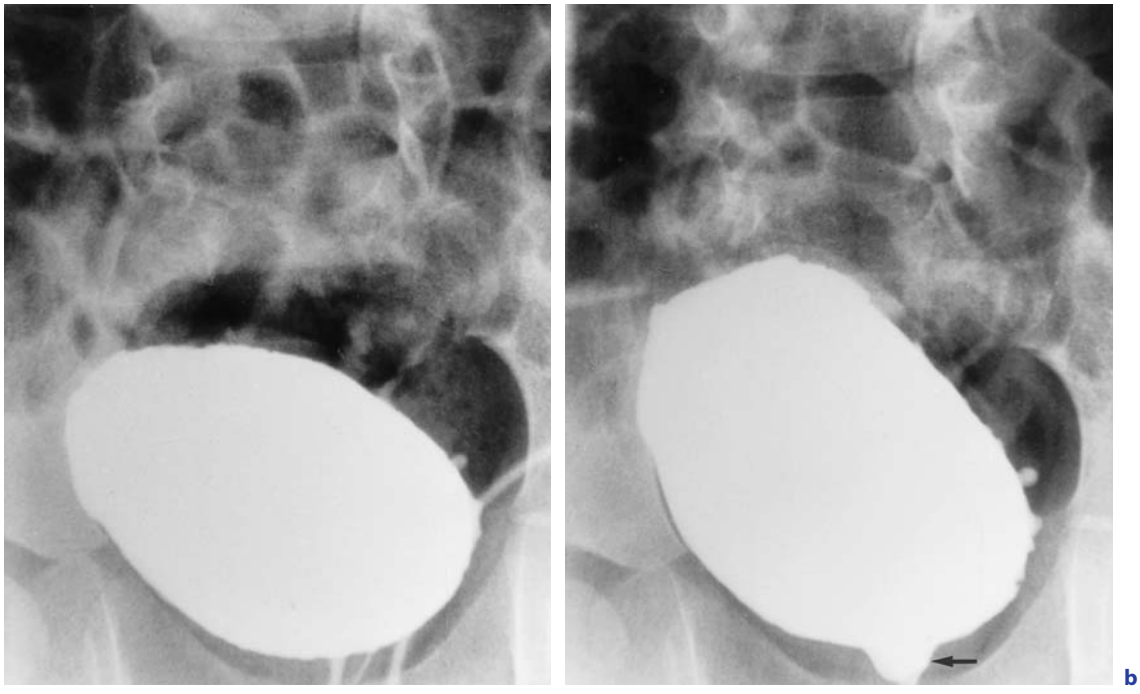

Fig. 16.7a,b. Male, 4 years old. Lumbar myelomeningocele, contractile detrusor: VCU. **a** Closed bladder neck during bladder filling, bladder trabeculation, and sacculation. **b** Uninhibited detrusor contractions, massive back-up flow of contrast infusion; contrast filled bulging bladder neck (*arrow*) up to contracted external sphincter (sphincter detrusor dyssynergia), some leakage around the catheter

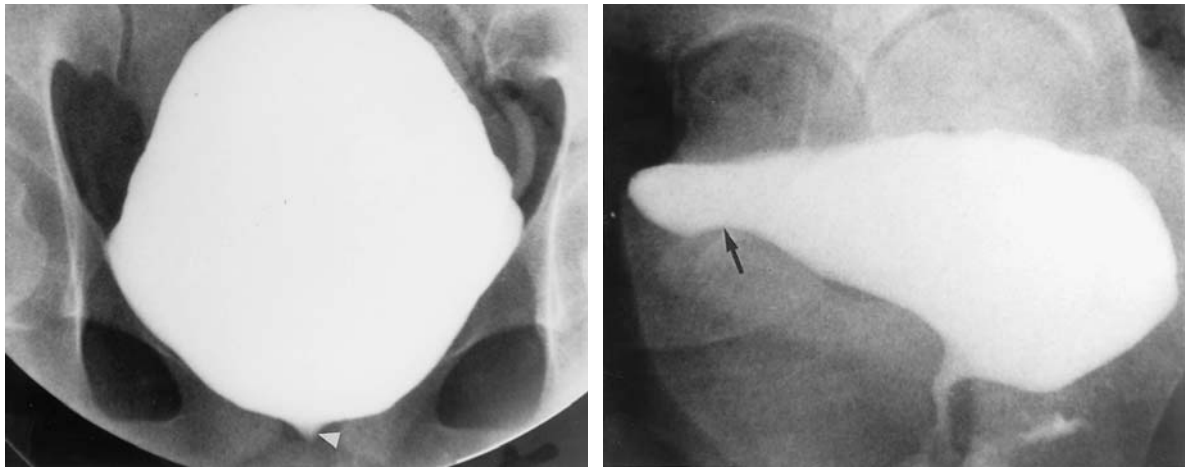

Fig. 16.8a,b. Female, 15 years old. Lumbosacral myelomeningocele, intermediate detrusor: VCU. **a** Open bladder neck during bladder-filling phase (*arrowhead*). Grade-2 reflux is shown at left. Minor detrusor activity with intermittent slowing and cessation of infusion flow. Otherwise, infusion flow was normal. **b** Terminal insufficient bladder emptying with funnel-like outflow. Severe descent of the bladder neck with concomitant abdominal straining. Superior margin of symphysis (*arrow*)

16.9 Autonomic Dysreflexia

Children with lesions of the spinal cord above T5 (major sympathetic splanchnic outflow between T5 and L2) may manifest autonomic dysreflexia during bladder distention in cystography (Erickson 1980). This is a life-threatening condition that is characterized by severe hypertension, anxiety, sweating, piloerection, headaches, and bradycardia. It can also be stimulated by urethral catheterization and pressure on the glans penis. The radiologist performing VCU in children with neurogenic bladder should be aware of autonomic dysreflexia, recognize it when it occurs, and be able to perform treatment when necessary. The bladder should be immediately evacuated and any catheter removed. The head of the fluoroscopy table should be elevated and the blood pressure checked at regular intervals. The majority of acute autonomic dysreflexia cases can be treated by these measures without pharmacological intervention. In severe cases, pharmacological treatment is urgently indicated.

Conclusion

Autonomic dysreflexia is a life-threatening condition characterized by severe hypertension, anxiety, sweating, piloerection, headaches, and bradycardia. Immediate treatment is mandatory.

16.10 Diagnostic Management

A standardized protocol for the evaluation of the urinary tract must be established in every radiological department caring for neonates, infants and children with myelodysplasia. Such a protocol might be as follows: After the myelomeningocele has been repaired and the hydrocephalus has been relieved by a shunt device, ultrasound studies of the kidneys and the bladder should be performed. During the first 6 weeks of life, a video-urodynamic study, if available, or a modified VCU study must be performed. In hospitals where only urodynamics is available, we suggest a modified VCU study as well.

In any case of deterioration of bladder function and/or new onset or worsening of symptomatic UTI and fecal soiling, which might not be accompanied by orthopedic deterioration, secondary spinal cord tethering has to be ruled out by urodynamic testing and radiological studies including spinal MRI, bladder, and kidney ultrasound and VCU, since secondary spinal cord tethering can be found in up to 32% of cases of spinal repair (Tarcan et al 2006).

Since this complication may manifest itself till the age of 15 years, close neurourological surveillance including ultrasound and VCU is mandatory. Diagnostic and therapeutic management should be tailored individually over time, if possible. Continuous follow-up of children with myelodysplasia by a multi-

disciplinary team is highly important (Dik et al. 2006). Ultrasound follow-up studies should be performed every 6 months, and a video-urodynamic or modified VCU study should be repeated once a year. Modifications of this protocol depend on the patient's clinical status or on urodynamic and imaging findings.

Conclusion

A standardized protocol should include early ultrasound studies of the urinary tract and a VUD study, if available, or a modified VCU within the first 6 weeks of life. If VUD is not available a VCU study should be complemented by urodynamics. The follow-up protocol should include ultrasound studies every 6 months and video-urodynamics or a modified VCU study once a year.

16.11 Conclusion

Preservation of the upper urinary tract is the central goal in the treatment of neurogenic bladder in children with myelodysplasia. Predictive indicators for upper urinary-tract fate are detrusor sphincter dyssynergia, high bladder-filling pressure, poor bladder compliance, moderate to severe fibrosis of the detrusor (Özkan et al. 2005), high leak-point pressure, and vesicoureteric reflux (Seki et al. 2004).

The role of radiology in the care of infants and children with a neurogenic bladder, especially in treatment planning and in the prevention of upper urinary-tract deterioration, has changed. It has expanded from a morphologically descriptive to a more functional role. A standardized and modified VCU technique allows the radiologist to promptly detect children at high risk for upper urinary-tract deterioration and allows for the planning of adequate treatment in facilities where urodynamics and video-urodynamics are not available. It has to be kept in mind that agreement between detrusor dysfunction and bladder morphology is poor.

Treatment modalities such as clean intermittent catheterization, surgical continence procedures, bladder augmentation, and the use of artificial urinary sphincters in addition to pharmacological treatment have significantly improved the quality of life for neurourologically impaired children. Since renal and bladder function can deteriorate after childhood, a long-term follow-up program is mandatory.

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Prune Belly Syndrome

17

Wolfgang Rascher and Gundula Staatz

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W. Rascher, MD
Professor, Department of Pediatrics and Adolescent Medicine, University of Erlangen-Nürnberg, Loschgestrasse 15, 91054 Erlangen, Germany
G. Staatz, MD
Professor, Department of Radiology, Division of Pediatric Radiology, University of Erlangen-Nürnberg, Loschgestrasse 15, 91054 Erlangen, Germany

17.1 Introduction

Absence of the abdominal musculature, urinary tract dilatation, and bilateral undescended testis is known as prune belly syndrome (Eagle and Barrett 1950; Greskovich and Nyberg 1988; Williams 1982). The classical syndrome is also known as triad syndrome, Eagle-Barrett syndrome, or abdominal muscular deficiency syndrome. There is a broad spectrum of malformations with severe dilatation of the urinary tract as a consequence of aplasia of the musculature. The pathogenetic mechanism is different from that of dilatation as a consequence of supra- or infravesical obstruction. Some patients with prune belly syndrome have a real obstruction, such as urethral aplasia with oligohydramnios syndrome. The prognosis of the malformations depends upon the degree of renal dysplasia (Duckett and Snow 1986). There is no consensus as to the pathogenesis of this complex abnormality, although most investigators consider prune belly syndrome a distinct entity.

Unfortunately, the term prune belly syndrome is inconsistently used in the literature. The incomplete form of the syndrome has been occasionally described as pseudo-prune belly syndrome (Bellah et al. 1996). However, the term pseudo-prune belly syndrome in patients with massive, prune belly-like dilatation of the urinary tract but normal abdominal wall examination and incomplete cryptorchidism or normal testes is confusing and should be avoided. Furthermore, diagnosis of severe urinary tract anomalies with oligohydramnios by prenatal ultrasound often results in termination of pregnancies (Hoshino et al. 1998). In these cases the typical pathology of prune belly syndrome has not always been demonstrated sufficiently.

More than 100 years ago Parker (1895) reported on a male newborn infant with a parchment-thin and

flaccid abdominal wall with marked underdevelopment of both the oblique and transverse abdominal muscles, and a marked hypertrophy of the bladder with dilatation of the ureters and renal pelves. Obstructing urethral lesions were absent and the testes were undescended. Osler (1901) described a similar pathology in a 6-year-old child and likened the appearance of the abdominal wall to a wrinkled prune. The persistent use of this metaphor led to the unfortunate term prune belly syndrome for patients with this abnormality.

Eagle and Barrett (1950) reported urethral obstruction in five out of nine cases, and surgeons began to try correction of urologic abnormalities. Through the 1970s urologists experimented with detailed reconstruction of the enlarged urinary collecting system, the abdominal wall, and the undescended testes. Poor results and the lack of evidence of intrinsic urinary tract obstruction in many cases favored a more conservative approach. Up to now results have not demonstrated an obvious benefit for either method.

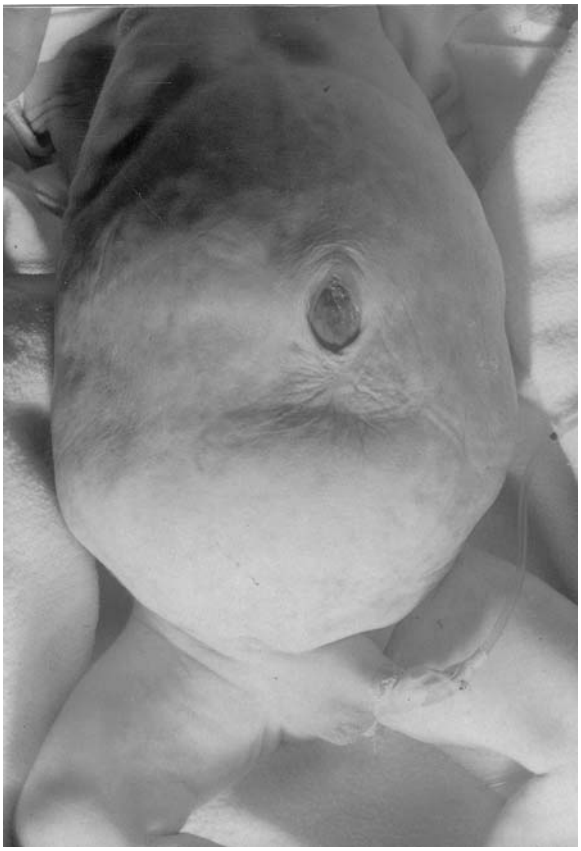


Fig. 17.1. Clinical presentation of abdominal muscular deficiency syndrome (prune belly syndrome)

17.2 Pathology

The incidence of prune belly syndrome is 1 out of 40,000 live births with a male predominance of 97%. By definition affected females cannot have the complete triad, and the urologic manifestations may often be less severe. In females, anomalies of the urethra, uterus, and vagina are usually present (Reinberg et al. 1991). Most cases occur sporadically, although familial occurrence has been described (Ramasamy et al. 2005). In selected cases, an association with trisomies 13, 18, and 21 has been reported.

The appearance of the abdominal wall is caused by a muscular deficiency (Fig. 17.1). In severe cases, muscle fibers are absent and replaced by a thick collagenous material. In many, but not all cases, the abdominal wall is simply a cosmetic problem. Urinary tract pathology is highly variable with ureteric dilatation, megacystis, and dilatation of the prostatic urethra. The anterior urethra may be dilated, resulting in a megalourethra, and the prostate is hypoplastic. A urethral stenosis or atresia is seldom present. The ureters are dilated, elongated, and tortuous and may show obstruction at the level of the pelviureteric or the vesicoureteric junction (Wheatley et al. 1996).

Renal involvement ranges from near-normal kidneys to a severe degree of dysplasia with primitive ducts in embryonic mesoderm, cysts, and metaplastic cartilage. Severe renal dysplasia may resemble type II cystic kidneys according to Potter (1972), but also small kidneys with subcortical glomerular and tubular cysts as a consequence of urethral obstruction have been reported, as seen in type IV cystic dysplasia.

17.3 Pathogenesis

Two main mechanisms have been proposed in the pathophysiology of prune belly syndrome: firstly, a primary defect of abdominal wall mesoderm formation during early embryogenesis; secondly, overdistension of the abdominal wall and urinary tract

as a consequence of severe bladder outlet obstruction. Despite extensive study of clinical and autopsy cases, no single theory can satisfactorily explain the entire spectrum of the prune belly syndrome.

17.3.1 A Primary Defect in Mesoderm Formation

A primary defect during the embryonic formation of the mesoderm may affect the muscles of the developing abdominal wall and urinary tract as well as the renal and prostatic primordia. Comparison of the bladder, urethra, and genital tract of specimens of patients with prune belly syndrome and of posterior urethral valves revealed differences in the pathologic anatomy (Stephens and Gupta 1994; Workman and Kogan 1990). The seminal ducts and vesicles and the prostatic glands were abnormal in the prune belly syndrome specimens and normally developed in the posterior urethral valve specimens. Figure 17.2 illustrates the different pathologies. This major difference points to a primary defect of the mesoderm formation in prune belly syndrome.

Bladder histology of fetuses with prune belly syndrome and no evidence of obstruction showed thin bladder walls with increased connective tissue. However, fetuses with posterior urethral valves or with prune belly syndrome and evidence of urinary tract obstruction had increased bladder muscle thickness (Popek et al. 1991). These results suggest that the phenotypic appearance of the prune belly syndrome may result from a mesenchymal defect, but urinary tract obstruction may contribute. Chest wall anomalies, gut malrotation, and orthopedic malformations are secondary to the abdominal wall defect or oligohydramnios.

17.3.2 A Primary Defect Leading to Urethral Obstruction

The basis of the theory of primary obstruction is the existence of a lesion at or distal to the prostatic urethra producing back pressure into the fetal urinary tract. Compression of the prostatic primordia may prevent normal development, and the

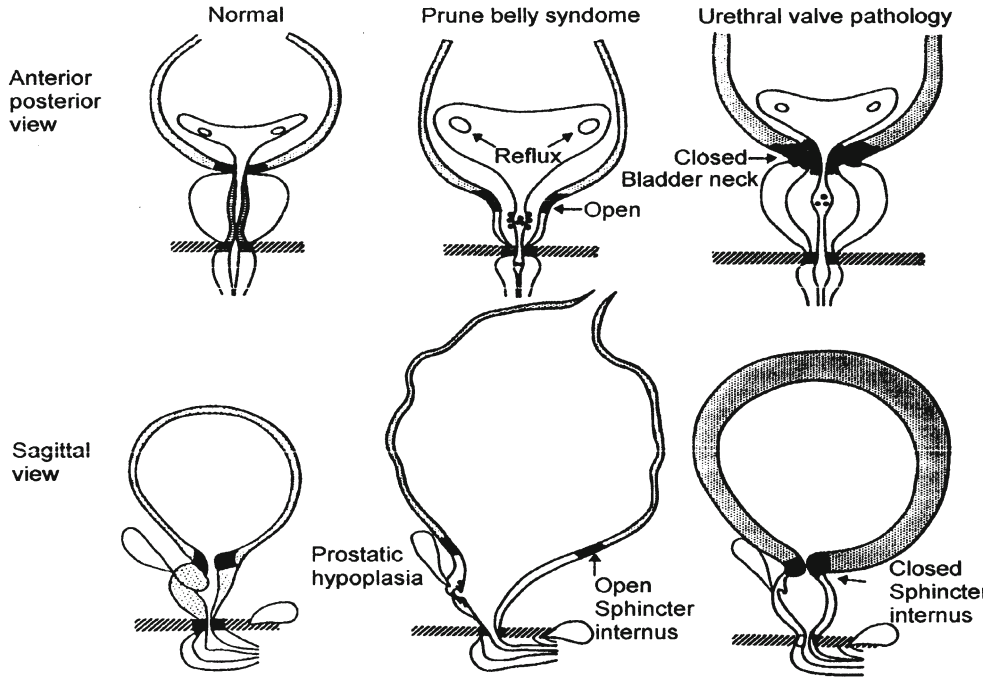


Fig. 17.2. Comparison between normal anatomy, prune belly pathology, and urethral valve pathology in anterior-posterior and sagittal view. Note the enlarged trigone in both pathologic conditions, whereas the detrusor muscle is thin in prune belly syndrome and hypertrophied in valve pathology. (Modified from Sigel and Rösch 1993)

prostatic urethra dilates. Gross distension of the bladder causes abdominal distension and degeneration of the abdominal wall muscles. The distended bladder prevents access of the testes to the inguinal canal.

Obstructive lesions exist in a considerable number of patients, although the proof of an urodynamically significant obstruction is difficult. As documented in 12 studies comprising 151 patients mainly studied postmortem, 84 had obstructive urethral lesions (Wheatley et al. 1996). If the theory of urethral obstruction as a primary defect in prune belly syndrome is correct, the timing and severity of the obstruction must be distinct from other obstructive uropathies, particularly from posterior urethral valves.

The common observation of an urachal diverticulum or patent urachus points to possible damage from high pressure in the urinary tract before the 15th week of gestation when the urachus closed. At that time urine production in the glomerular tissue has started. The first nephrons form at about 8 weeks after conception and the human embryo produces urine from the 12th week of gestation. Distension of the urinary tract at 13–15 weeks gestation may induce degenerative changes of the abdominal wall and urinary tract.

Significant high pressure in patients with posterior urethral valves occurs later when urine is excreted in large amounts. At that time the urachus is closed, and prostatic development and the abdominal wall are normal.

Conclusion

Prune belly syndrome is the combination of the absence of the abdominal musculature, urinary tract dilatation, and bilateral undescended testis as a consequence of aplasia of the musculature.

17.4 Clinical Presentation and Diagnosis

Diagnostic criteria of the prune belly phenotype are wrinkled skin, thinness, and laxity of the abdominal wall (Fig. 17.1) in the absence of palpable testes. Urinary tract abnormalities are demonstrable only by diagnostic procedures, e.g., ultrasonography, and vary widely in appearance and severity.

17.4.1 Obstetric Ultrasound and Antenatal Diagnosis

To date prenatal ultrasonographic screening has resulted in the identification of increasing numbers of patients with suspected prune belly syndrome (Yamamoto et al. 2001). However, it is difficult to define reliably whether urinary tract dilatation during gestation is associated with true prune belly syndrome. It is even more difficult to decide whether severe obstruction is present that will interfere with normal renal development. Obstetric ultrasound is unable to give reliable information on functional renal tissue and glomerular and tubular renal function. Whether prenatal vesicoamniotic shunting is beneficial, remains to be shown despite positive case reports (Biard et al. 2005).

Reduced urine production with early and persistent oligohydramnios (e.g., before 20 weeks of gestation) is strongly associated with an adverse outcome (Moore et al. 1989). Fetal compression due to a deficiency in amniotic fluid results in a recognizable constellation of clinical findings, including skeletal abnormalities, characteristic facies, pulmonary hypoplasia and perinatal death due to respiratory insufficiency (Potter's sequence). When this complication (severe persistent oligohydramnios) occurs before 24 weeks of gestation, it is associated with pulmonary hypoplasia. A deficiency in amniotic fluid prevents normal fetal lung expansion. Prognosis is poor if oligohydramnios occurs during early gestation (Mandell et al. 1992).

Although normal fetal kidneys can sometimes be identified by ultrasound in the 16th week of gestation, the adrenals are large and may be a source of misinterpretation. After 32 weeks of gestation, both kidneys can usually be visualized during maternal ultrasonography. The fetal bladder can be seen between 12 and 15 weeks gestation, when active urine production begins. The cyclical increases in size and emptying can often be seen during an examination. Repeat examinations will demonstrate adequate bladder filling.

The key problem in pre- and postnatal ultrasonographic examination is the limited information about renal function and urodynamics. There is no question that the experienced investigator is able to define anatomical details of urinary tract anomalies reliably. The term prune belly syndrome is frequently used for prenatally diagnosed severe urinary tract malformation that resulted in termination of pregnancy, although the pathologic examination

is incomplete, particularly due to lack of histologic examination of the prostate (Cazorla et al. 1997; Hoshino et al. 1998).

Fetal urinary indices, e.g., sodium, creatinine, microproteins, etc., are not precise predictors of subsequent renal function. Therefore, they are not helpful in the prediction of renal function after birth.

17.4.2 Postnatal Diagnostic Approach

As with other fetal urinary tract anomalies detected prenatally, suspected prune belly syndrome should be monitored by ultrasound and delivery should be carried out at a center where expert neonatal, nephrologic, urologic and pediatric radiological experience is available. The first postnatal physical examination clearly shows absent abdominal muscle wall (prune belly) syndrome (Fig. 17.1).

Ultrasound often suggests, in addition to the clinical examination, the diagnosis of prune belly pathology, but complementary radiological and radionuclide imaging is necessary to rule out a significant obstruction that will have to be corrected surgically. Radiological diagnostic procedures are rarely an emergency. Urine output and micturition can be monitored clinically, and serial determination of serum creatinine is important to assess renal function. Serum creatinine at day 1 represents the serum creatinine of the mother and falls to normal values of less than 0.3 mg/dl within 14 days. If serum creatinine remains high or rises, renal insufficiency can be diagnosed. After peaking between 1 and 2 weeks of age, serum creatinine may fall in the case of adequate urine production. If the serum creatinine level remains high under stable conditions, it indicates the degree of renal dysplasia.

17.4.2.1 Renal and Urinary Tract Ultrasonography

After the physical examination has been completed, ultrasonography should be performed. A realistic interpretation of an ultrasound examination is important since it provides only anatomic information: dilatation of the urinary tract is not necessarily induced by obstruction, particularly in patients with prune belly syndrome. In addition to dilatation of the renal pelvis and the ureter, bladder filling and bladder wall thickness can be determined by ultrasound (Fig. 17.3). Bladder outlet obstruction is usually associated with thickened and hypertrophied bladder wall. Typical prune belly syndrome presents with a thin bladder wall and dilatation of the ureter (Fig. 17.3).

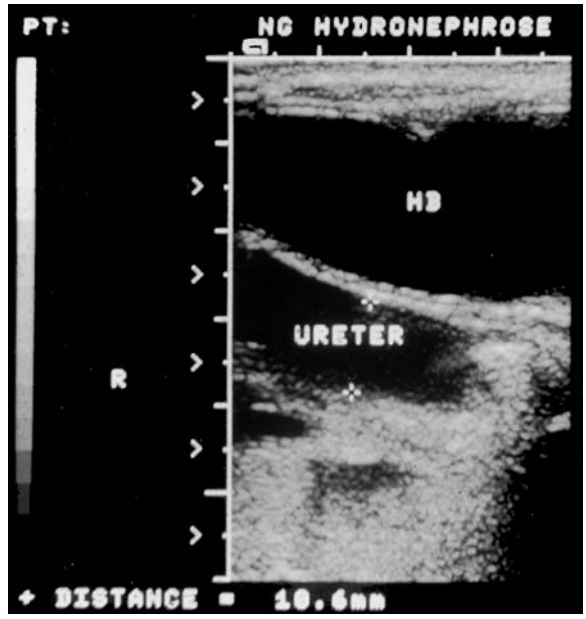


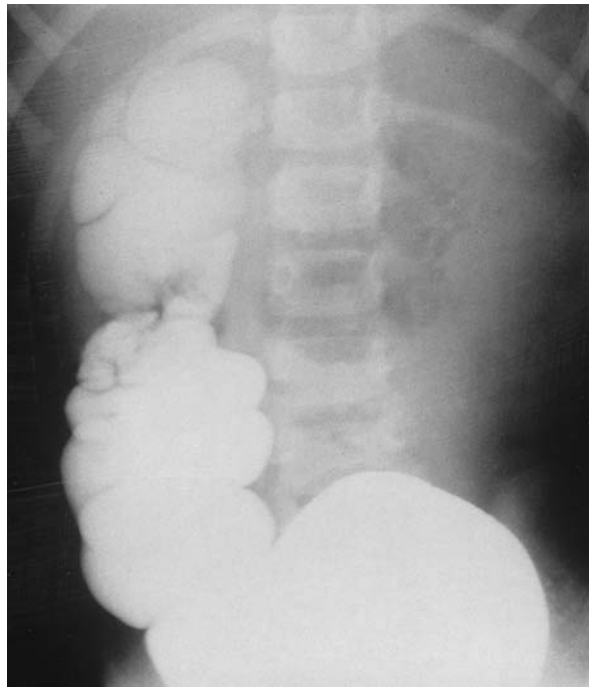
Fig. 17.3. Ultrasonographic demonstration of a large bladder (HB) with thin bladder wall and a dilated ureter in a newborn infant with prune belly syndrome

17.4.2.2 Voiding Cystourethrography

The first radiological examination performed in patients with prune belly syndrome should be voiding cystourethrography (VCUG), an investigation that is independent of the degree of renal function and gives valuable information regarding the lower urinary tract (bladder outflow) and whether vesicoureteric reflux is present.

Since megacystis can be expected in patients with prune belly syndrome, the investigator should be prepared for a large bladder volume (Fig. 17.4). A persistent urachus may be seen, and the bladder typically empties slowly and incompletely. Bilateral vesicoureteric reflux is commonly observed. The prostatic urethra is often dilated, presents in a V-shaped manner, and the prostatic utricle may be opacified.

With the combination of ultrasound and VCUG, adequate morphologic evaluation of the kidneys and collecting systems shortly after birth is possible and permits appropriate management to be instituted immediately (e.g., suprapubic drainage if urethral obstruction is present). Because of the high risk of



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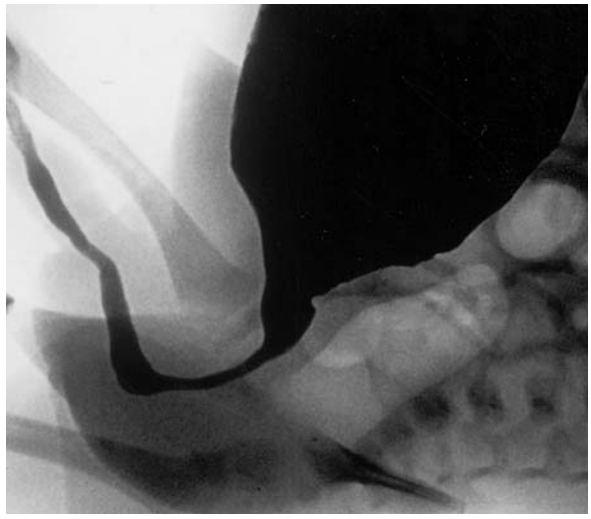

b

Fig. 17.4a,b. Voiding cystourethrogram in an infant with prune belly syndrome. **a** High-grade reflux into the enlarged ureter; **b** a wide bladder neck as a consequence of an open internal urethral sphincter

urinary tract infection, antibiotic prophylaxis should be given at the time of the diagnostic procedure.

17.4.2.3 Dynamic Renography

Further imaging may be planned when the neonate is stable and clinical and laboratory findings have been evaluated. Since normal renal function is necessary for further diagnostic procedures, it should be done only after the end of the neonatal period (after 4 weeks of age).

Dynamic renography with 99m technetium-mercaptoacetyltriglycine (^{99m}Tc-MAG3) is generally characterized by a continuously rising curve reflecting poor drainage of the kidney if a dilatation of the collecting system exists. In this condition furosemide should be administered (diuretic renography), which increases urinary flow and may distinguish between good and impaired drainage (for further details see Chap. 1.3).

The dynamic renogram is only of diagnostic value if glomerular renal function is normal and both kidneys appear normal in the ultrasonographic evaluation. It is important that dynamic renography is performed with an empty bladder to exclude an obstruction at the ureterovesical junction. Therefore, in infants the use of an indwelling bladder catheter that is not clamped is required. Adequate hydration is necessary to yield a reliable examination (Rascher and Rösch 2005).

17.4.2.4 Static Renal Scan

The 99mTc-dimercaptosuccinic acid (DMSA) scan, as a static renal scan, binds to functioning proximal tubular cells and indicates functioning renal parenchymal mass. This scan has an important role in identifying small, poorly functioning or nonfunctioning dysplastic kidneys and in obtaining information about split renal function.

In the newborn period, the ^{99m}Tc-DMSA scan is characterized by high background activity and relatively low fixation of the isotope in the renal tubules, but good evidence of differential function between the two kidneys can still be obtained during the first months of life.

17.4.2.5 Intravenous Urography

Intravenous urography has been previously used for further evaluation of prune belly syndrome, but nowadays it should be replaced by magnetic resonance urography (MRU). MRU is superior to the

conventional IVU in many aspects, particularly in evaluating renal parenchymal disease, for assessment of ureteral anatomy and ureteral orifice, and for evaluation of poorly functioning renal systems (Riccabona et al. 2002). If MRU is not applicable, intravenous urography is helpful to assess renal dysmorphy and ureteric pathology (Fig. 17.5), which is typically characterized by bilateral hydroureteronephrosis in children with prune belly syndrome.

Intravenous urography should not be performed in newborns within the first 4 weeks of life, because of the risk of contrast nephropathy, and not in children with impaired renal function.

17.4.2.6 Computed Tomography and Magnetic Resonance Imaging

Computed tomography is usually not indicated in children with prune belly syndrome. Magnetic resonance urography is the imaging modality of choice for the cross-sectional assessment of upper urinary tract dilatation in children (Nolte-Ernsting et al. 2003; Riccabona et al. 2004; Grattan-Smith et al. 2006). The combination of heavily T2-weighted (static) MRU and dynamic contrast-enhanced (excretory) T1-weighted MRU after administration of gadolinium and low-dose furosemid provides accurate anatomic information and functional information such as renal transit time or differential renal function (Rohrschneider et al. 2002; Grattan-Smith et al. 2006) (for further details see Chap. 1.2).

Conclusion

Postnatal physical examination with wrinkled skin, thinness, and laxity of the abdominal wall in the absence of palpable testes in combination with ultrasonographic and radiological demonstration of the massive urinary tract dilatation proves the diagnosis of prune belly syndrome.

17.5 Management

Treatment of prune belly syndrome is primarily conservative, and surgical management is seldom required. When obstruction is absent, the goal of treatment is the prevention of urinary tract infection.

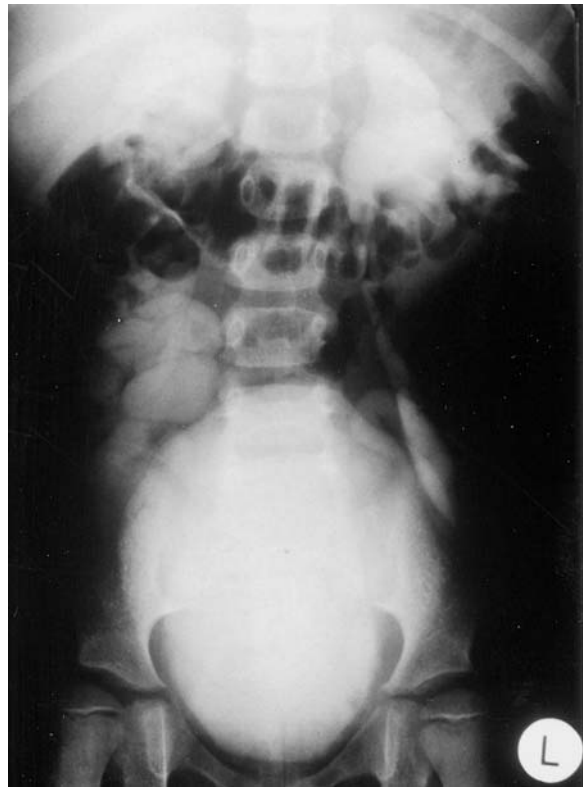

Fig. 17.5. Intravenous urography in an infant with prune belly syndrome. Note the enlarged bladder and right ureter

When obstruction of the ureters or urethra can be demonstrated or is strongly suspected, temporary drainage procedures, such as pyelostomies or vesicostomies, may help to preserve renal function until the child is old enough for reconstructive surgery.

Chronic renal failure is mostly due to the accompanying renal dysplasia and the deleterious effects of acute pyelonephritis that has been diagnosed and treated too late. Since massive bladder distension and megaureter often promote urinary tract infection, antibiotic prophylaxis is often logical and highly effective. Conservative management is more efficient than an extensive and aggressive surgical approach such as urinary diversion or ureteric remodeling (Burbige et al. 1987; Duckett and Snow 1986). Current practice is to correct the cryptorchidism surgically. Orchidopexy in these children can be quite difficult and is best accomplished at the end of the first year of life. Reconstruction of the abdominal wall may offer cosmetic and functional benefits.

The prognosis depends on the degree of pulmonary hypoplasia and renal dysplasia. Up to one-third of children with prune belly syndrome are stillborn

or die in the first few months of life as a consequence of pulmonary hypoplasia. However, early termination of pregnancies with severe prune belly pathology will reduce the proportion of patients with this syndrome and particularly reduce those cases with a poor outcome.

Of the long-term survivors, one-half will develop chronic renal failure from dysplasia or complications of infection or reflux and require renal transplantation. The results of renal transplantation in these patients are favorable (Fontaine et al. 1997; Fusaro et al. 2004).

Conclusion

Management of prune belly syndrome is primarily conservative (prevention of urinary tract infection, treatment of chronic renal failure when present). Surgical procedures are required only when obstruction is present.

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Postoperative Imaging and Findings

18

Veronica Donoghue

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V. Donoghue, FRCR, FFR.RCSI
Consultant Pediatric Radiologist, Departments of Radiology, Children's University Hospital, Temple Street, Dublin 1, Ireland
and
National Maternity Hospital, Holles Street, Dublin 2, Ireland

18.1 Introduction

The practice of pediatric urology and uroradiology has changed a great deal in recent years. The increase in the clinical use of antenatal ultrasonography and its ability to provide anatomic information about the developing fetus has led to the growth and development of perinatal urology. There has been a significant increase in the number of genitourinary anomalies diagnosed in the newborn period, and greater attention is paid to postnatal assessment, diagnosis, and management, including follow-up imaging of these infants. The urological conditions requiring surgery are varied, but the abnormalities that require the most frequent surgical intervention are those that give rise to urinary-tract dilatation.

18.2 Ureteropelvic Junction Obstruction

The pelviureteric junction is by far the most common site of urinary obstruction in children (see also Chaps. 5 and 26). The obstruction may be caused by some intraluminal lesion, by a functional abnormality of the proximal ureter leading to an intrinsic obstruction, by external compression, usually because of an aberrant renal vessel, or it may be secondary to some other urinary tract abnormality, usually vesicoureteric reflux causing secondary obstruction.

Among infants where a diagnosis has been made antenatally, improvement or resolution of the hydronephrosis occurs in approximately 30% (Arnold and Rickwood 1990; Freedman and Rickwood

1994) and more. These and other considerations have led to a more conservative approach to the surgical management of pelviureteric junction obstruction. The clear indications for active intervention are:

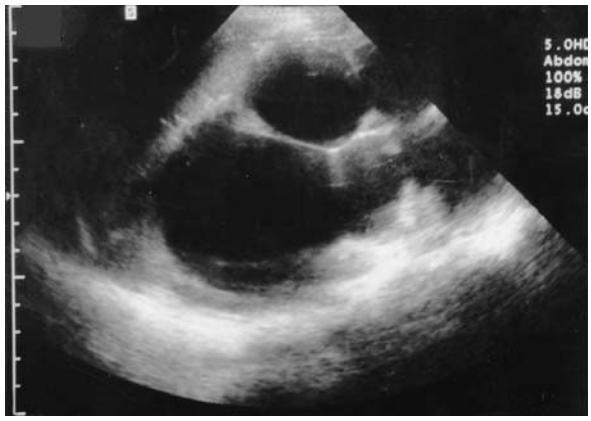
- Clinical symptoms.
- Impaired renal function. Less than 40% of the differential function in a unilateral lesion is the general consensus for surgical intervention.
- Complications such as renal calculi or hypertension.

Active intervention usually means surgical relief of the obstruction, though there have been some reports of successful balloon dilatation of the pelviureteric junction (Wilkinson and Azimy 1996; Doraiswamy 1994; McClinton et al. 1993). An exception may be a unilateral obstruction where kidney function is severely compromised at less than 20% differential function. The usual outcome in these patients is a kidney that still functions poorly, though perhaps a little less poorly than preoperatively. Sometimes function declines further despite technically satisfactory surgery, presumably due to significant vascular changes intrarenally (Grapin et al. 1990). The outcome of functional recovery is more satisfactorily predicted by static rather than dynamic scintigraphy (O'Flynn et al. 1993) and is less likely if the affected kidney is small and the contralateral kidney has undergone compensatory hypertrophy (Koff and Campbell 1992).

Percutaneous nephrostomy drainage can be performed in these patients and the function reassessed after 4 weeks (Fig. 18.1). Nephrectomy is usually the treatment of choice when the function remains poor (Ransley et al. 1990). Percutaneous nephrostomy drainage is also the initial treatment of choice in infants who present with a pyonephrosis.

Open pyeloplasty is the usual procedure to correct pelviureteric junction obstruction. Postoperative drainage may be carried out by extra-anastomotic drainage, nephrostomy with a transanastomotic splint (Fig. 18.2) or a double-J pyelovesical stent (Fig. 18.3). If extra-anastomotic drainage is used the drain can be removed approximately 24 h after urinary leakage has ceased. Alternatively nephrostography through the drain can be performed approximately 7 days postoperatively to assess satisfactory drainage down the ureter prior to removal of the drain. Transanastomotic splints are usually removed 7–10 days postoperatively. The nephrostomy is clamped at the same time and removed following contrast nephrostography through the tube to assess drainage down the ureter (Fig. 18.2). Early complications are uncommon and usually comprise prolonged urinary drainage where extra-anastomotic drainage has been employed or delayed drainage at the anastomosis site where a nephrostomy plus transanastomotic splint has been used. Persistence of either complication more than 2 weeks postoperatively can often be treated by retrograde passage of a ureteric catheter.

If more significant anastomotic failure is present, retrograde balloon dilatation (McClinton et al. 1993; Wilkinson and Azimy 1996) or rarely reoperation is carried out. Neither procedure is advisable before 1 month postoperatively, and in the interim the kidney can be drained if necessary by percutaneous nephrostomy. Rarer postoperative complications include urinomas following anastomotic leaks and hemorrhage collections. These can usually be monitored with sonography. As the vasculature of the kidney can be variable and anomalous, care must be taken during surgery not to damage the blood supply. If this is suspected it can be monitored with sonography (Fig. 18.4) and Doppler studies. In general, assessment of outcome following pyeloplasty is performed 3–6 months following reconstructive surgery. A satisfactory outcome is monitored by ultrasonography and dynamic radionuclide scintigraphy. A significant reduction in the degree of hydronephrosis and an increase in the parenchymal thickness on ultrasonography are a good indication of successful surgery (Fig. 18.5), but absence of this finding does not necessarily indicate a persistent obstruction (Kis et al. 1998). The use of the IVU to assess postoperative relief of obstruction has largely been replaced by dynamic nuclear scintigraphy using either Tc-99m DTPA or Tc-99m MAG 3 (Fig. 18.5). However, in the presence of massive hydronephrosis, where there is significantly impaired renal function, or following reconstructive surgery, scintigraphy may not be reliable (Chung 1993). There should therefore be close correlation between the preoperative and postoperative studies. A Whitaker test may be necessary to confirm or exclude residual obstruction (Kass and Majd 1985). In children where renal function is impaired postoperatively and where early postoperative nephrostograms indicate technically satisfactory surgery, reassessment of function can be deferred for up to 2 years because functional recovery before this time is generally slight.



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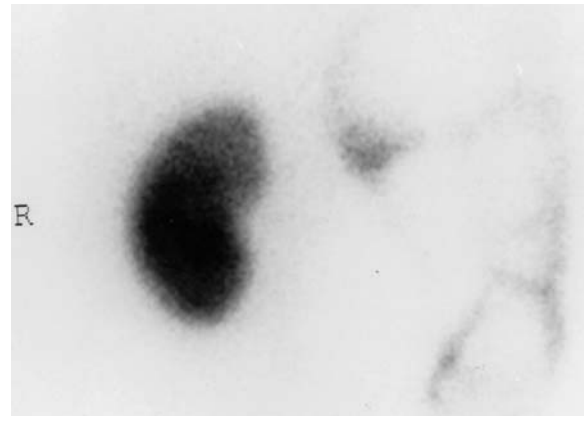

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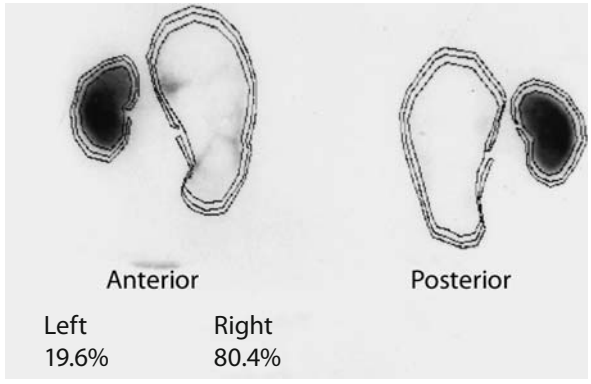

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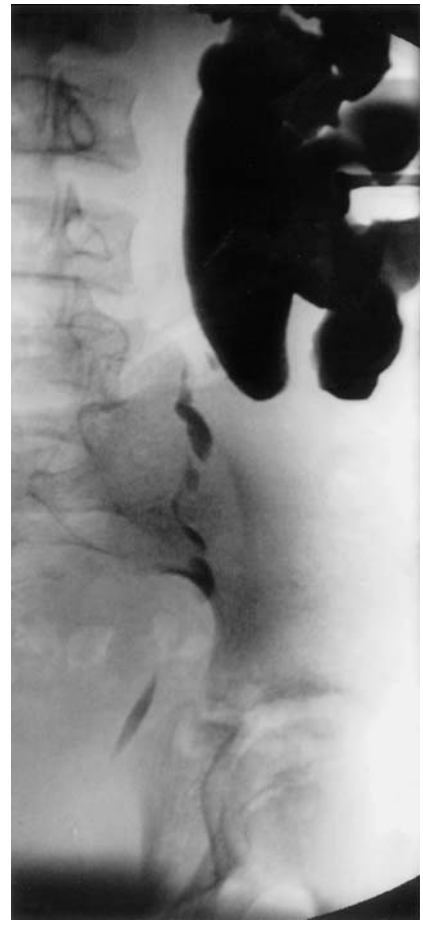

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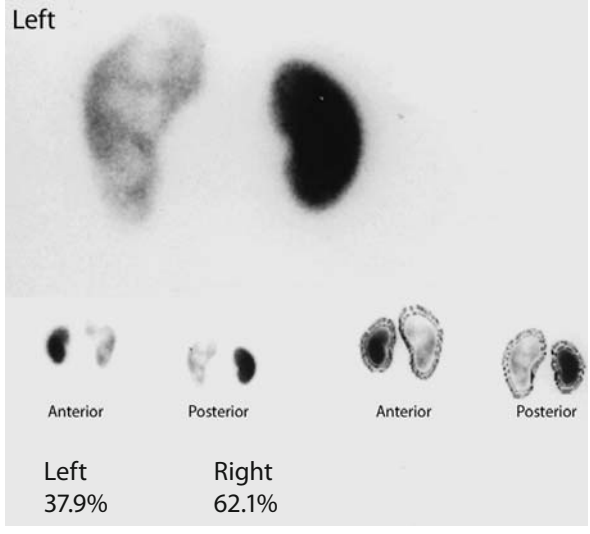


e

Fig. 18.1. **a** Ultrasonographic examination shows very marked hydronephrosis with a thin cortical rim. **b**,**c** DSMA renal scintigraphy shows an enlarged left kidney with very thin rim of functioning renal tissue. The percentage uptake of the radiopharmaceutical on the left side is 19.6%. **d** Nephrostogram outlining a hydronephrosis with drainage down the ureter 4 weeks after nephrostomy drainage. **e** DMSA scan 4 weeks after nephrostomy drainage. There is an improvement in left kidney function to 37.91%

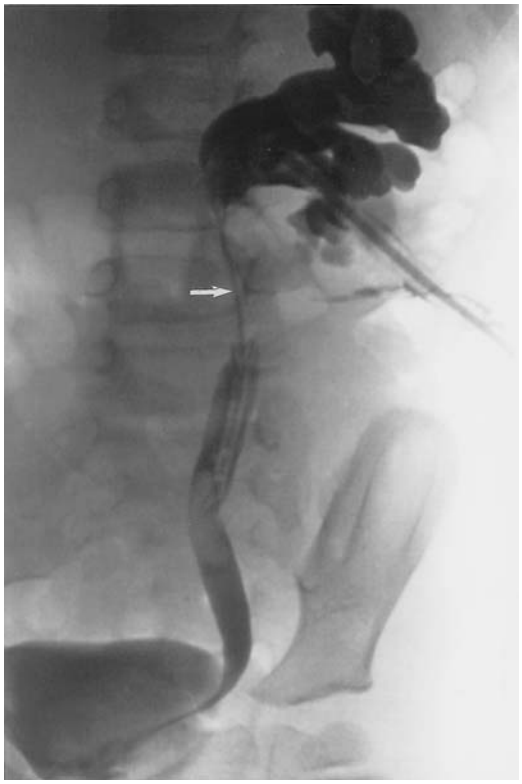


Fig. 18.2. Nephrostogram through a nephrostomy catheter after pyeloplasty. Contrast flows down the ureter. Transanastomotic splint in position (*arrow*)

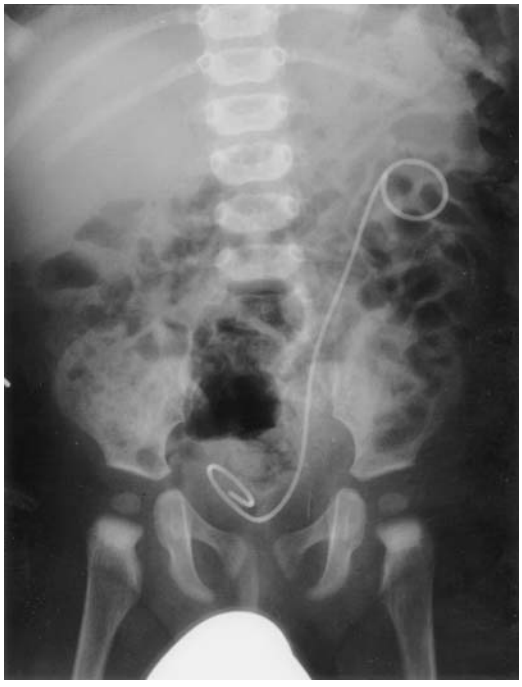


Fig. 18.3. Double-J pyelovesical stent in position after open pyeloplasty

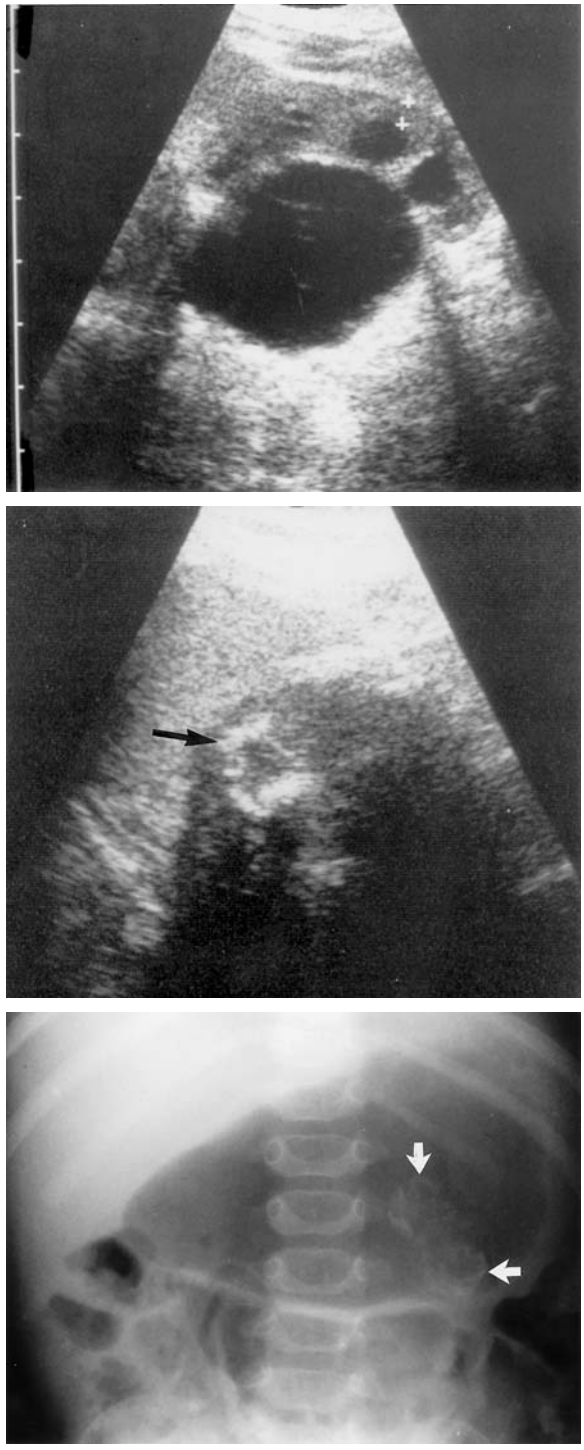


Fig. 18.4. **a** Ultrasonography demonstrating marked dilatation of the renal pelvis with dilatation of the calyces in a child with pelviureteric junction obstruction. **b** Ultrasonography 1 month after open pyeloplasty. There was damage to the kidney blood supply at surgery. The kidney is shrunken and is replaced by a rim of increased echogenicity compatible with calcification (*arrow*). **c** Plain radiography confirming a shrunken left kidney replaced by calcification (*white arrows*)

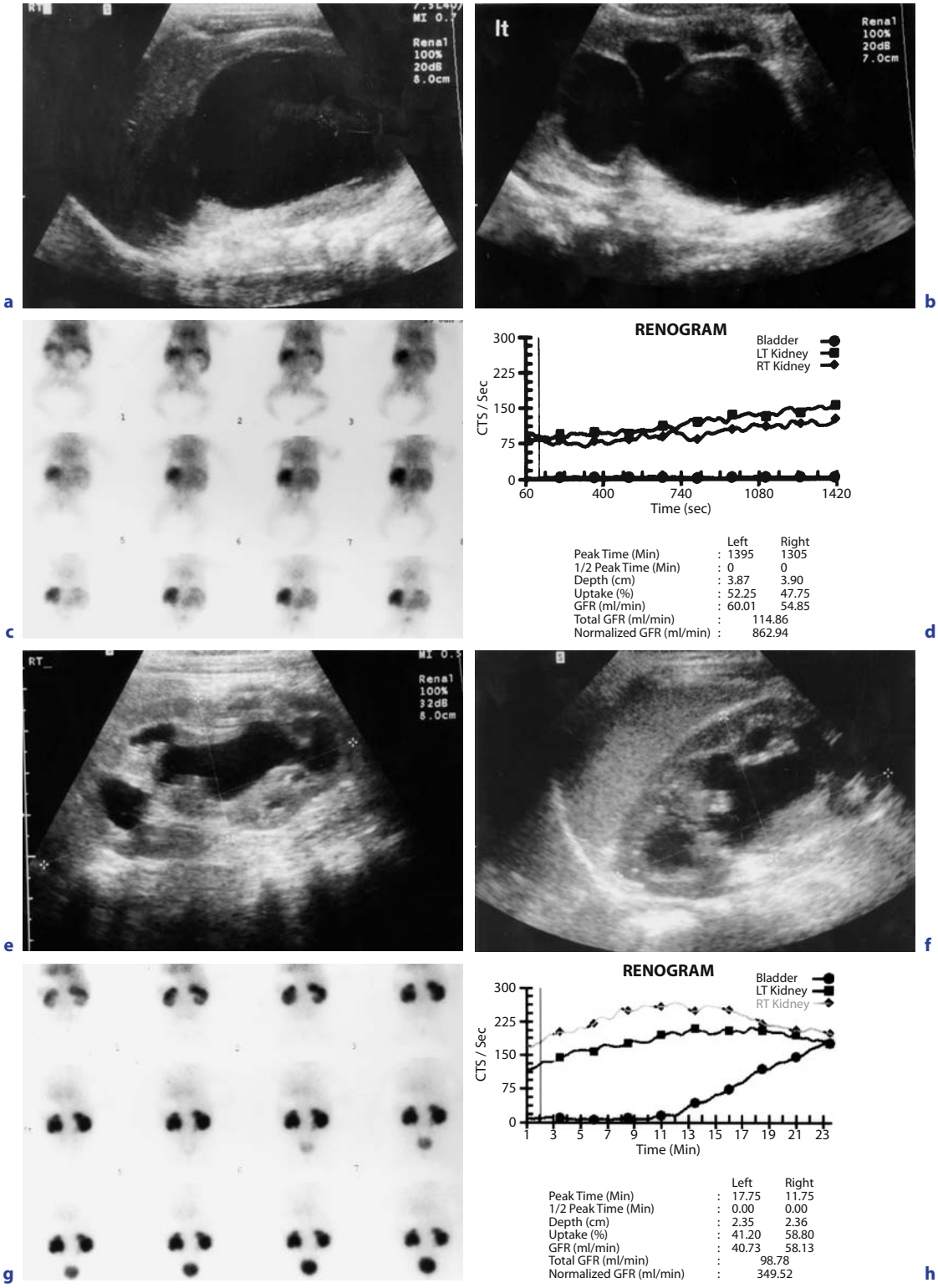


Fig. 18.5. a Right kidney and **b** left kidney outlining bilateral UPJ obstruction. There is dilatation of the calyces and renal pelvis on both sides. **c**,**d** Preoperative Tc 99m DTPA scintigraphy showing poor uptake of the radiopharmaceutical bilaterally with no significant detectable excretion. **e** Right kidney and (**f**) left kidney after pyeloplasty. There is a significant reduction in the degree of hydronephrosis and an increase in cortical thickness. **g**,**h** Postoperative Tc 99m MAG 3 renogram 1 year after operation. There is improved function in both kidneys, more on the right than on the left side, with an improvement in excretion

Conclusion

The outcome in children treated surgically for pelviureteric junction obstruction is best monitored by means of ultrasonography and dynamic radionuclide scintigraphy using either Tc-99m DTPA or Tc-99m MAG 3. The use of IVU to assess postoperative relief of obstruction has largely been replaced.

18.3 Congenital Disorders of the Ureter

18.3.1 Nonrefluxing Primary Obstructive Megaureter

In this condition there is an adynamic segment of the distal ureter just prior to its insertion into the bladder resulting in obstruction to urine flow. Rarely a patient may present with a pyonephrosis. If the patient is ill, a percutaneous nephrostomy catheter should be inserted to drain the pus. A functional assessment of the kidney is undertaken in approximately 4 weeks, and a decision taken as to whether to proceed to nephrectomy or a ureteric reimplantation.

If the ureter is very large, a low-end ureterostomy may be performed allowing the ureter to decompress before carrying out a reimplantation. Like pelviureteric junction obstruction, management of ureterovesical junction obstruction is often nonoperative initially. One study (Liu et al. 1993) found that 34% resolved spontaneously, 49% persisted, and only 17% required a reimplantation due to infections or deteriorating renal function.

The majority of dilated ureters less than 6 mm in diameter resolved, while 50% of those greater than 10 mm were treated with surgery.

The definite indications for surgery are:

- Deteriorating renal function on scintigraphy
- Recurrent urinary tract infections despite antibiotic prophylaxis
- Pyonephrosis or stones
- Clinical symptoms

The surgical treatment involves resection of the adynamic distal segment of the ureter with reimplantation of the dilated proximal portion possibly following a reduction in the caliber of the ureter and a hitching of the bladder onto the psoas muscle so that a long tunnel can be obtained. Any patient who has had a ureteric tailoring will most likely have the ureter stented and a bladder catheter in position for 8–9 days postoperatively. Ultrasonography or plain radiography can be performed prior to its removal to check the position of the stent (Fig. 18.6). Sonography is used to assess the degree of dilatation of the collecting system and ureter. If a tapering technique has been performed, attention should be paid to possible postoperative complications such as urinary leak. There is also a risk to the blood supply of the distal ureter, which results in ischemia and restenosis. After surgery patients usually remain on antibiotic prophylaxis until a follow-up voiding cystourethrogram excludes reflux.

In general, follow-up investigations using sonography and radionuclide imaging are carried out between 3 and 6 months after surgery.

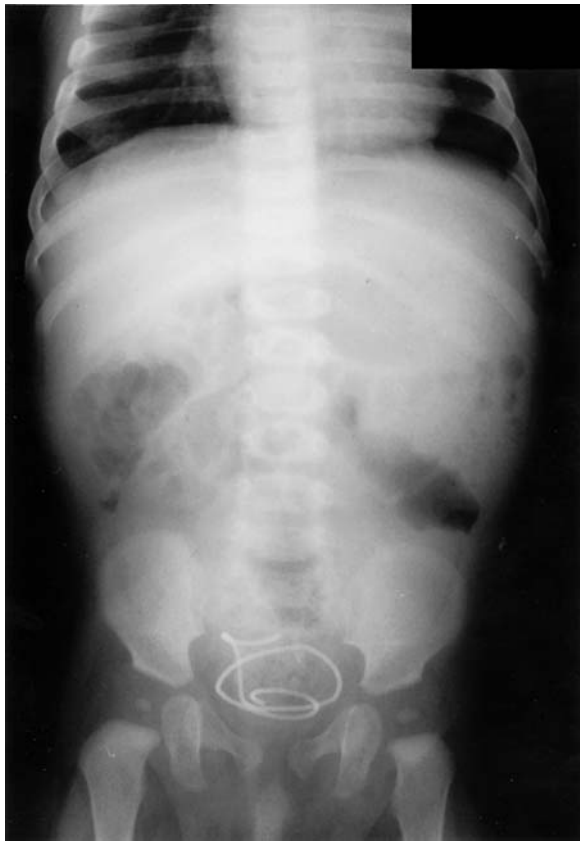


Fig. 18.6. Plain radiography after ureteric reimplantation. There is malposition of the ureteric stent, which lies in the urinary bladder

Conclusion

Postoperative imaging in children with primary obstructive megaureter includes a micturating cystogram to rule out reflux. Follow-up ultrasonography and radionuclide scintigraphy are performed at 3–6 months.

18.3.2 Ureteric Duplication, Ureteric Ectopia, and Associated Anomalies

Duplication of the renal collecting system is a common anomaly. The duplication may range from a bifid pelvis to incomplete or complete duplication. Ureteroceles are cystic dilatations of the distal segment of the ureter. Though they may be associated with single ureters, they most commonly occur at the distal end of the ureter, draining the upper pole collecting system in a complete duplication.

In most cases incomplete ureteric duplication is an incidental finding. However, it is occasionally possible that there is "yo-yo" reflux leading to stasis and ureteric dilatation. This can lead to flank pain and infection. In the rare cases requiring surgery, the type of operation depends on the level of duplication. If this is very low, it may be possible to carry out a reimplantation of the ureters with separate ureteric orifices into the bladder. If the duplication is higher, a high ureteropyelostomy or ureteroureterostomy with excision of most of the duplicated ureter is the treatment of choice.

Management of a refluxing duplicated ureter depends on the function of the lower pole. Lower grades of reflux with good function may resolve spontaneously as the child grows. Higher grades of reflux may benefit from reimplantations of the ureter. This is usually a double-barreled reimplantation of the ureters in their common sheath. Poor function of the lower pole (less than 10% of the individual renal function) is usually treated by a lower-pole heminephroureterectomy. This approach to treatment also applies to ectopic ureters.

Conclusion

The treatment of ureteric duplication depends on the level of duplication and the presence or absence of associated reflux.

The factors taken into account when planning treatment of ureteroceles are renal function, the intravesical or ectopic position of the ureterocele, whether there is a single or duplex system, the degree of ureteric dilatation, the presence of ipsilateral or contralateral reflux and the degree of detrusor covering of the ureterocele. The treatment of choice for an intravesical ureterocele is a small endoscopic incision just above its base (Fig. 18.7). Using this procedure the incidence of secondary reflux is rare (Blyth et al. 1993). Other surgical options include a nephrectomy for poor function. In some centers this procedure is now performed laparoscopically using either a retroperitoneal or transabdominal approach (Wallis et al. 2006; Sydorak and Shaul 2005). The procedure is safe with a low morbidity but complications have been reported which include urine leaks, retroperitoneal fluid collections and functional loss of the remaining ipsilateral moiety (Wallis et al.2006).

Persistent reflux documented by follow-up voiding cystourethrography will require reimplantation, and if the ureter caliber is very large, a tapered reimplantation may be required. If there is ureterocele prolapse mimicking a bladder diverticulum on the fluoroscopic imaging due to poor detrusor covering (Fig. 18.8), this should also be repaired. There are a number of options available to treat ectopic ureteroceles with a trend in recent years towards more conservative management. If the preoperative renal cortical imaging shows poor function of the upper pole of a duplex system with an ectopic ureterocele, its removal with decompression of the ureterocele and a staged approach to surgery at the bladder level is used in some centers. This approach avoids surgery on the ureterocele until it has a chance to reduce in size following decompression. This is best assessed using ultrasonography. Currently persistent ipsilateral lower-pole reflux is the most common indication for excision of the ureterocele and reimplantation of the lower-pole ureter. This procedure is required in approximately 50% of patients (Caldamone et al. 1984). There are other rarer cases where reflux into the ureterocele and upper ureteric stump leads to problems of infection and postmicturition dribbling. In these children the extent of the ureterocele and the ureteric stump may be imaged using ultrasonography and occasionally CT (Fig. 18.9). These patients also require surgery. When the upper pole associated with an ectopic ureterocele has sufficient function to require a salvage procedure, high ureteroureterostomy or ureteropy-

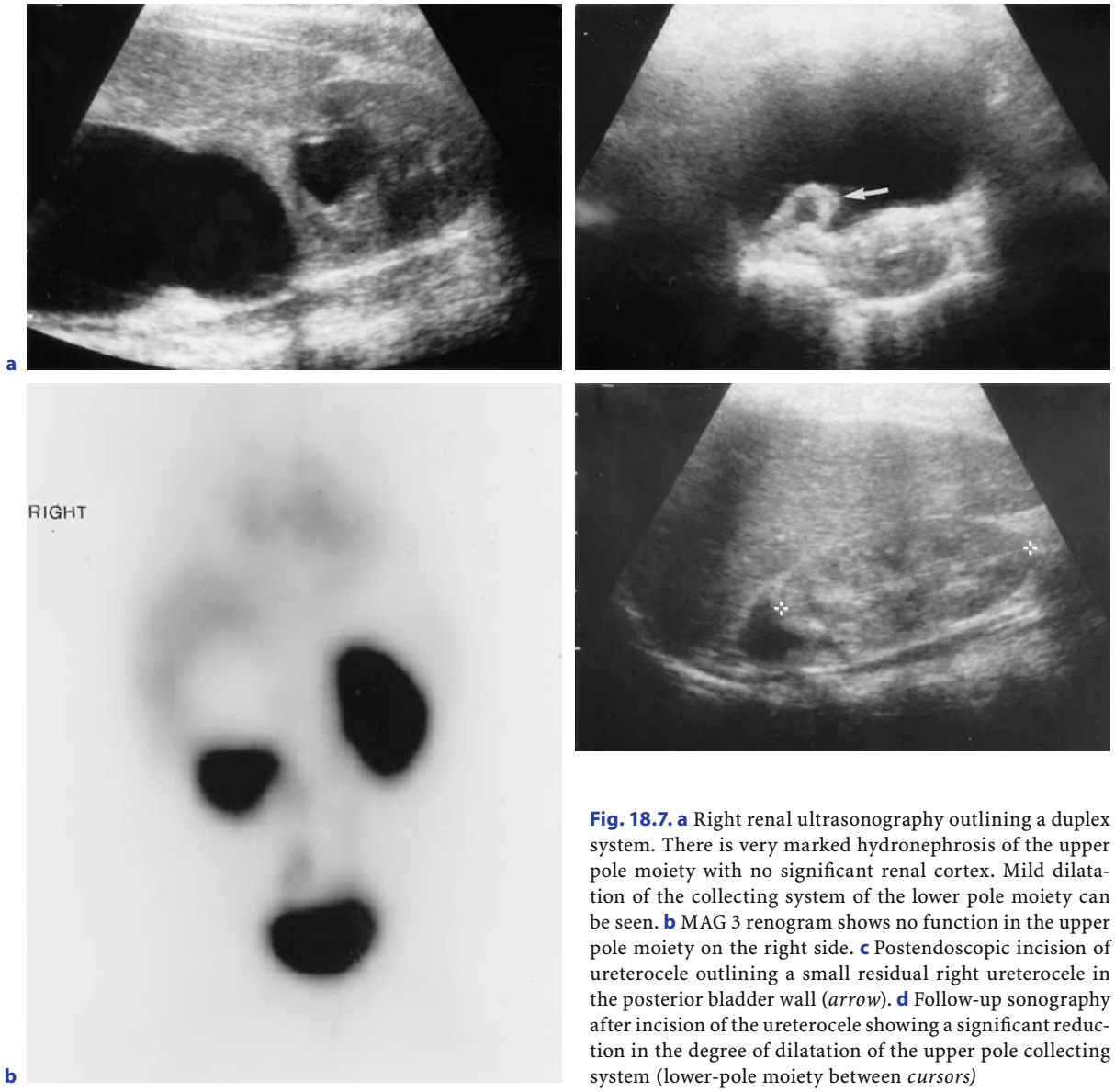
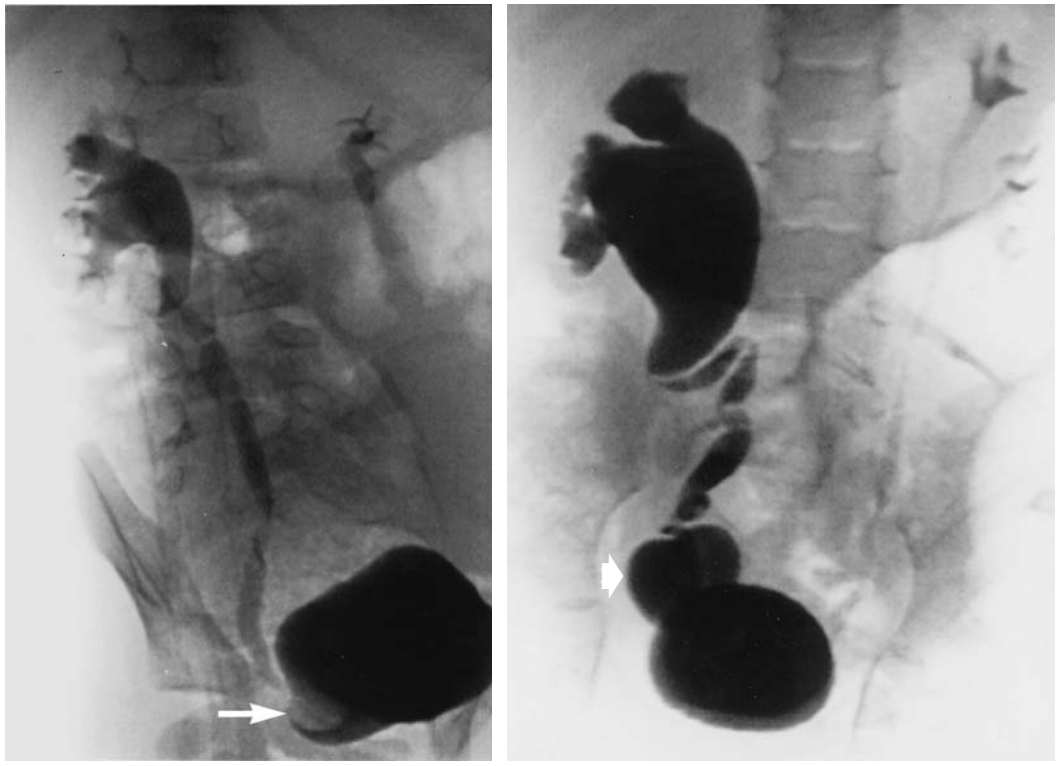


Fig. 18.7. a Right renal ultrasonography outlining a duplex system. There is very marked hydronephrosis of the upper pole moiety with no significant renal cortex. Mild dilatation of the collecting system of the lower pole moiety can be seen. **b** MAG 3 renogram shows no function in the upper pole moiety on the right side. **c** Postendoscopic incision of ureterocele outlining a small residual right ureterocele in the posterior bladder wall (*arrow*). **d** Follow-up sonography after incision of the ureterocele showing a significant reduction in the degree of dilatation of the upper pole collecting system (lower-pole moiety between *cursors)*

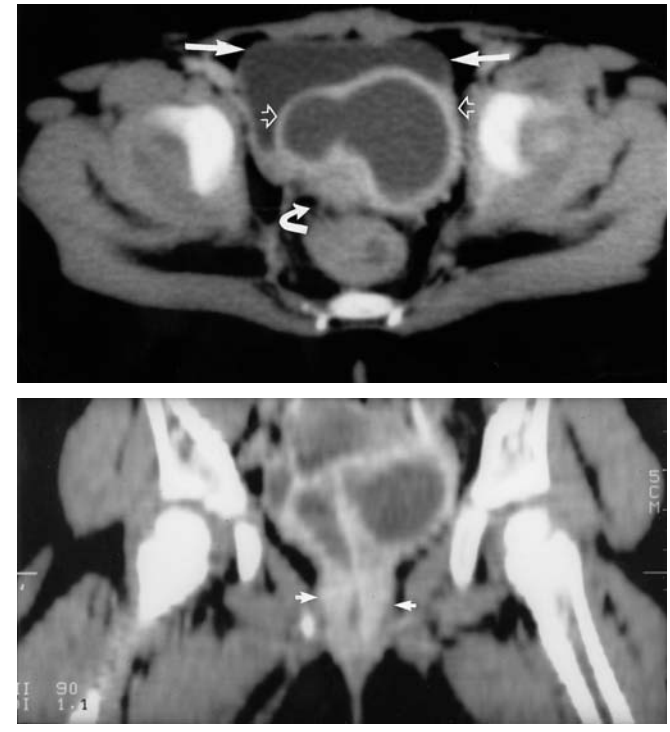
elostomy may be undertaken if there is an extrarenal pelvis or a dilated lower pole ureter. Some surgeons advocate a primary endoscopic incision of the ectopic ureterocele with follow-up investigations to see whether the upper pole will regain function. However, a secondary surgical procedure for persistent reflux is required in approximately 50% of these patients (Blyth et al. 1993). As the vasculature to the upper pole is often variable and anomalous, the blood supply to the lower pole may be damaged during upper-pole partial nephrectomy. It is also important that the entire upper-pole calyceal system is excised. This procedure, however, is not usually associated with significant blood loss.

Bladder dysfunction has been reported in approximately 6% of children with ureteroceles. The fact that patients treated with upper tract surgery alone have similar rates of incontinence to those who undergo additional lower tract surgery suggests that it is congenital in origin as opposed to surgically acquired (Holmes et al. 2002). Children who undergo bilateral ureterocele repair have been found to be at increased risk for postoperative voiding dysfunction (Sherman et al. 2003).



a b

Fig. 18.8a,b. Voiding cystourethrogram in a child with bilateral duplex systems. **a** There is significant reflux into the lower pole moiety of a right duplex system and a right ureterocele obstructing the upper pole moiety (*arrow*). **b** At the end of micturition there is prolapse of the ureterocele mimicking a bladder diverticulum (*arrowhead*)



a b

Fig. 18.9a,b. CT scan of the bladder after intravenous contrast administration. **a** There is a large ureterocele (*open arrowheads*) occupying the bladder (*white arrows*). There is significant enhancement of the ureterocele wall and loss of definition and "stranding" between the posterior bladder wall and rectum (*curved arrow*) in keeping with infective changes. **b** Reconstructed image outlining the ureterocele and thickening of the wall of the urethra in keeping with infection (*arrowheads*)

Conclusion

The many factors taken into account when planning treatment of ureteroceles are renal function, their intravesical or ectopic position, whether there is a single or duplex system, the degree of ureteric dilatation, the presence of ipsilateral or contralateral reflux and the degree of detrusor covering of the ureterocele.

18.4 Congenital Anomalies of the Bladder

Cloacal extrophy, bladder extrophy, and epispadias are developmental abnormalities of ranging severity, as a result of disruption of the formation and opposition of the pelvic bones, the cavitation of the pelvic organs, and the partitioning of the pelvic cavity (see also Chap. 9). Urinary tract diversion using an ileal conduit to treat this and other bladder abnormalities is now an obsolete procedure. However, children who have had this procedure require follow-up imaging studies. Yearly ultrasonography and occasionally IVU are necessary to detect dilatation due to obstruction and calculus disease (Fig. 18.10). Treatment now involves closure of the exstrophied bladder, bladder neck reconstruction, and epispadias repair. The upper tracts are usually normal in these infants and can be monitored using ultrasonography though multiple associated anomalies have been described. The main complication in these children after surgery is dehiscence of the wound due either to excess tension of the abdominal wall, infection, or bladder prolapse. Repeat closure with possible bladder augmentation is performed. A segment of ileum, colon, or stomach may be used. Rarely obstruction at the vesicoureteric junction occurs (Fig. 18.11). A technique of percutaneous bladder catheterization through an appendicovesicostomy has been developed for patients with chronic outlet obstruction (Mitrofanoff 1980). Close monitoring of the upper tracts using ultrasonography and possibly DMSA scintigraphy is necessary.

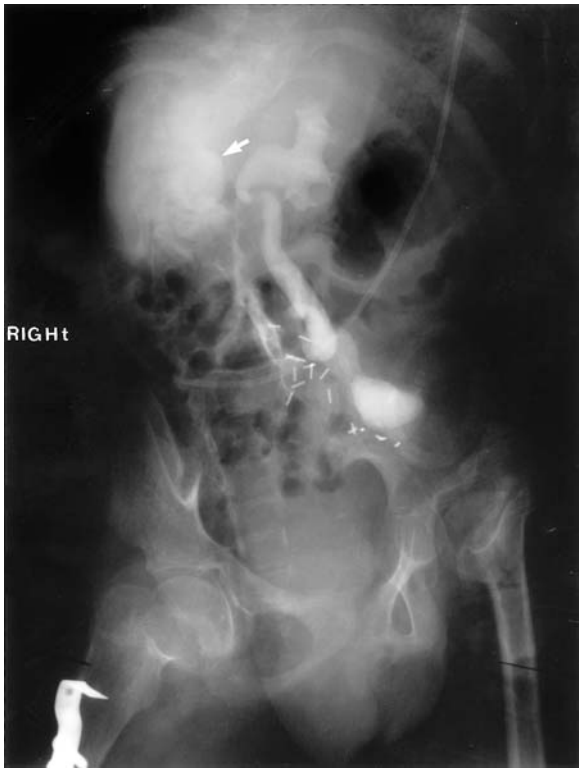
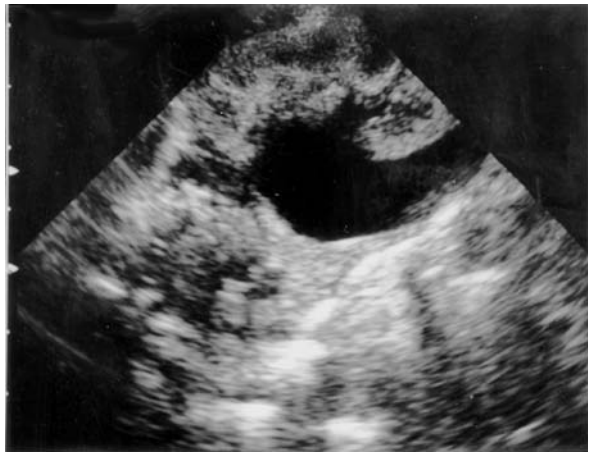


Fig. 18.10. IVU in a patient with urinary tract diversion using an ileal conduit. There is significant right hydronephrosis due to stone development at the pelviureteric junction (*arrowhead*)

Initial results with a complete primary extrophy repair procedure in a small number of patients have been reported (Lee et al. 2006). Magnetic resonance imaging of the pelvic floor in patients over 3 years of age who have undergone this procedure has demonstrated that symphyseal diastasis and iliac wing, puborectalis and ileococcygeus angles more closely approximate, but are still significantly different from those of controls. Patients with greater than 3 h continent intervals after complete primary extrophy repair have anatomic parameters more similar to those of age-matched controls (Gargallo et al. 2005).

18.5 Congenital Anomalies of the Urethra

The commonest congenital abnormality of the urethra is posterior urethral valves, which may result in the most severe renal disease in childhood (see also Sect. 6.2). This condition requires regular follow-up with imaging. Antenatal insertion of a double-J stent between the fetal bladder or dilated collecting system of the kidneys and the amniotic cavity under sonographic guidance allows decompression of the urinary tract. However, as this procedure



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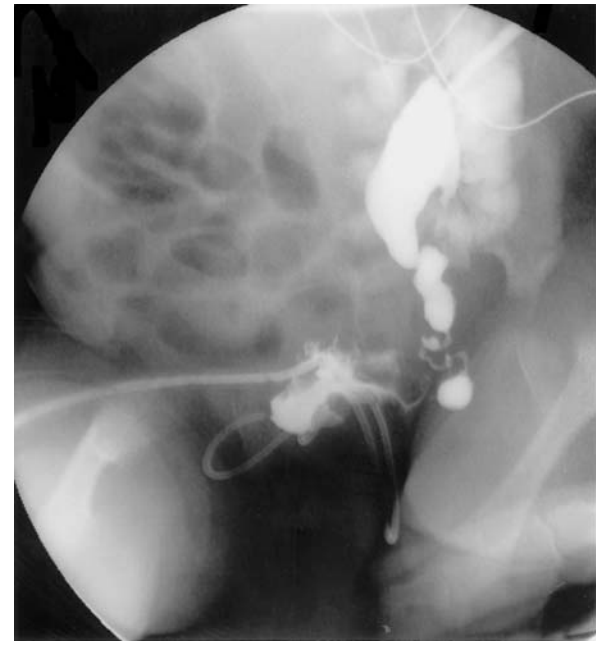
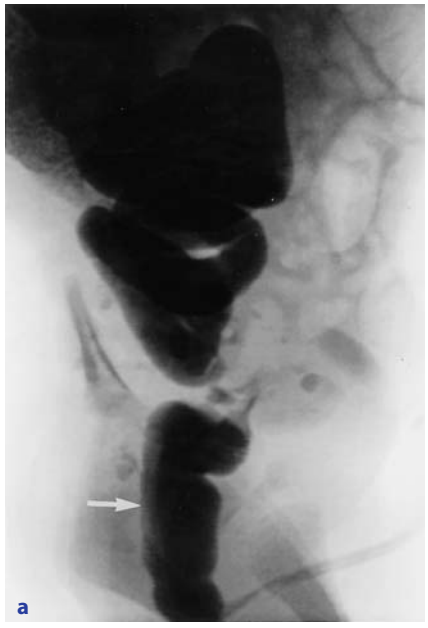


b

Fig. 18.11. a Repair of bladder extrophy in a patient with a single left kidney. The patient developed subsequent hydronephrosis of the single kidney following surgery. **b** This required temporary nephrostomy drainage for relief of obstruction. There is narrowing of the distal ureter that resolved spontaneously



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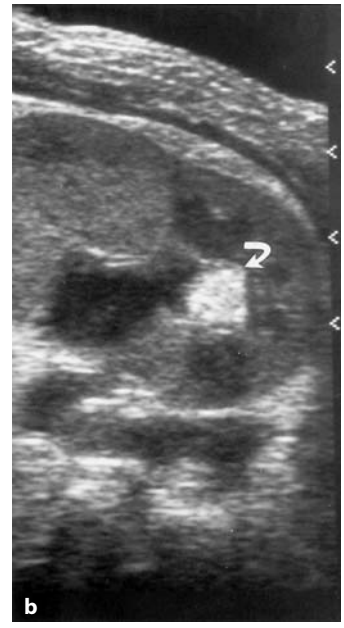

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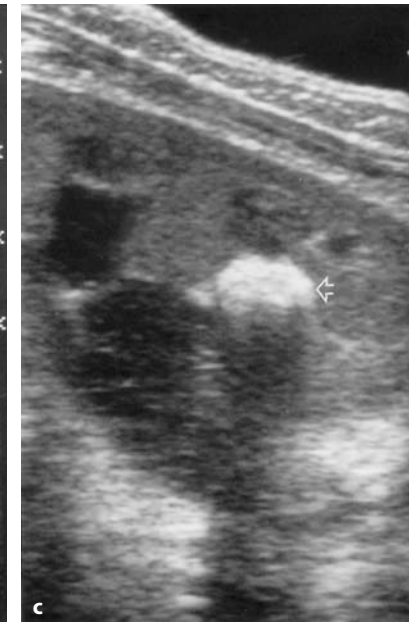


c

Fig. 18.12. a Infant with posterior urethral valves. There is dilatation of the posterior urethra (*arrow*) and marked reflux. **b** Patient developed echogenic area in the lower pole collecting system after valve surgery (*curved arrow*). **c** Stone developed at site of *Candida* ball 1 month after surgery (*open arrowhead*)

is performed rather late in pregnancy its benefit has not yet been demonstrated. More recently, laser perforation of posterior urethral valves has been performed using fetoscopy. After birth it is first essential to resuscitate the child when necessary, make urine drainage free, and destroy the valves. Urine drainage can be achieved by inserting a transurethral catheter or a suprapubic catheter. However, a transurethral catheter does not always allow complete drainage of the upper tracts because of the increased bladder-wall thickness and its poor compliance. Patients who have bilateral reflux,

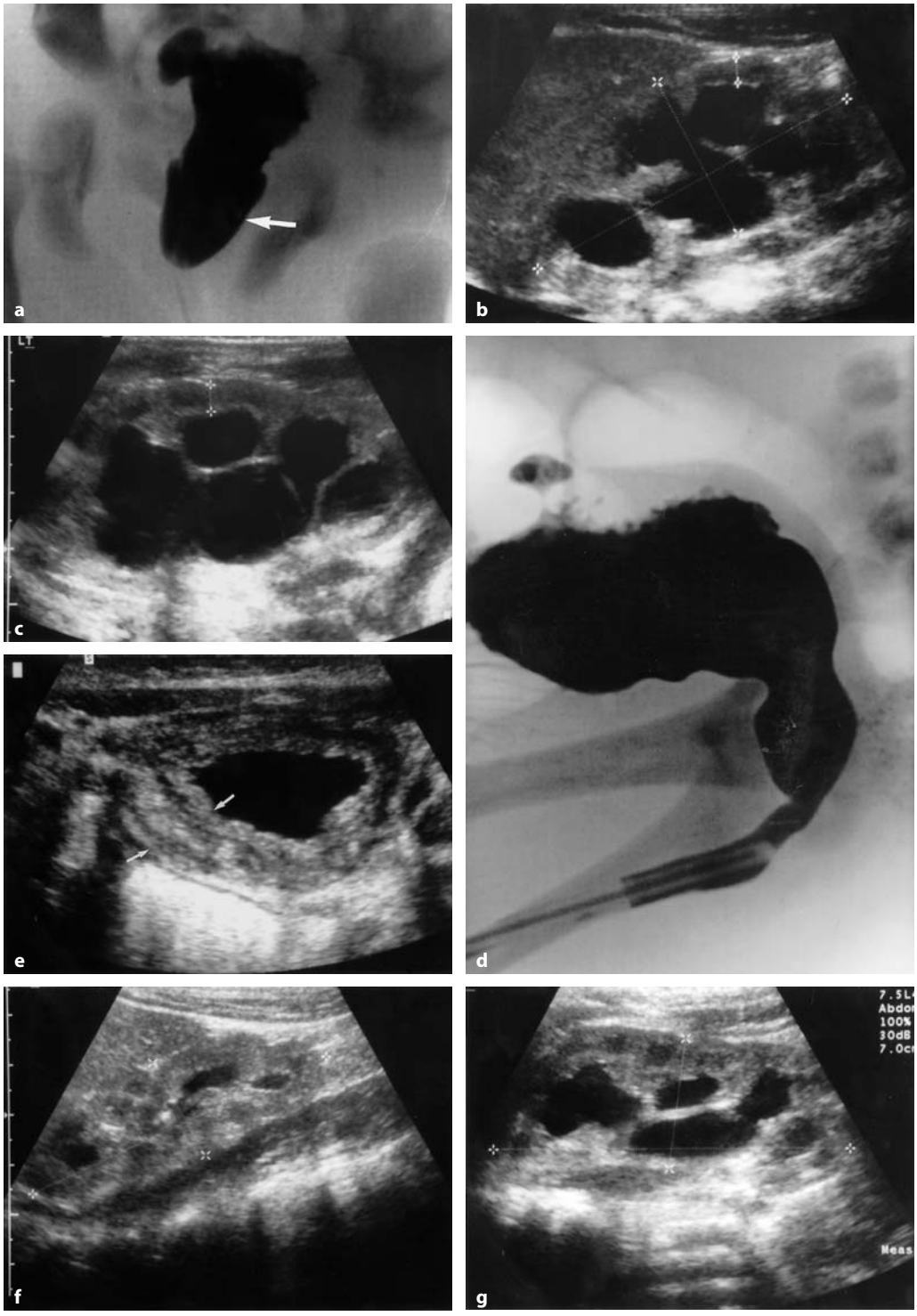
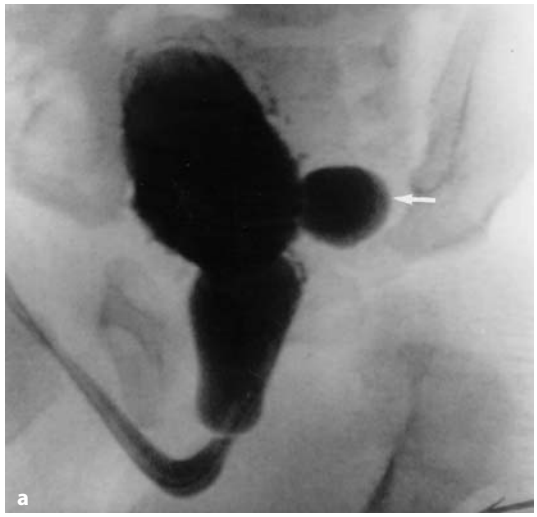
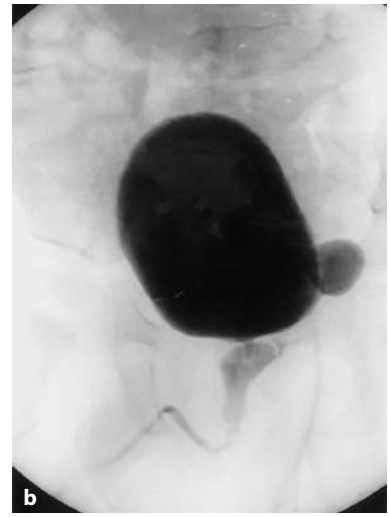
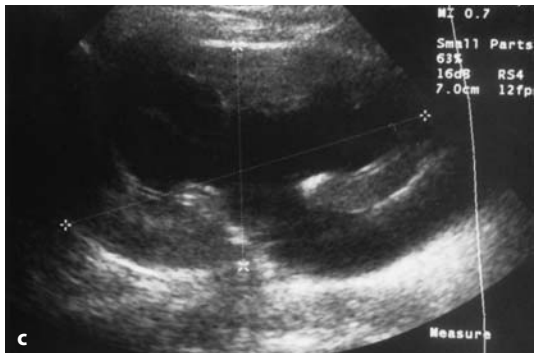
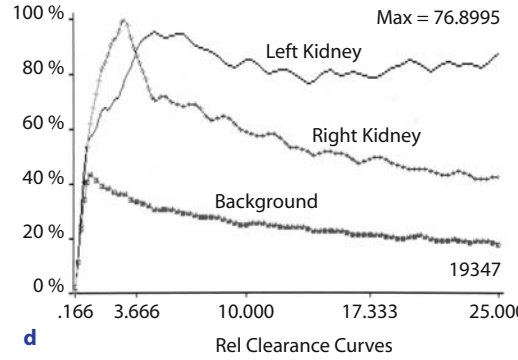


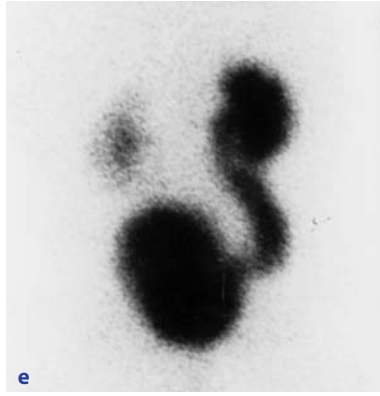
Fig. 18.13a–g. An infant with posterior urethral valves. **a** Marked dilatation of the posterior urethra (*white arrow*) with marked thickening of the bladder wall and a right bladder diverticulum. **b** Preoperative sonography of right kidney and (**c**) left kidney demonstrating marked bilateral hydronephrosis. **d** Voiding cystourethrogram at 10 days after valve destruction. The urethra is smaller in caliber, and there is good urine flow on voiding. There is still marked bladder-wall thickening with diverticulum formation. **e** Bladder sonogram 4 months after operation. There is still significant bladder-wall thickening (*arrows*). **f**,**g** Postoperative ultrasonography at 4 months of (**f**) right kidney and (**g**) left kidney shows significant improvement in the hydronephrosis

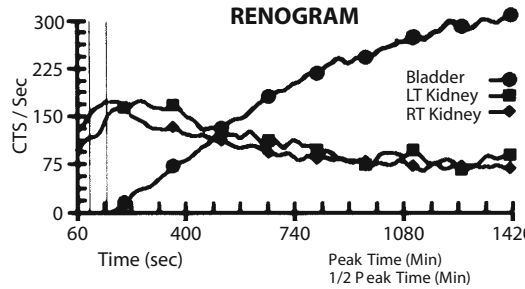












	Left	Right
Peak Time (Min)	: 270	195
1/2 Peak Time (Min)	: 555	465
Depth (cm)	: 2.92	2.94
Uptake (%)	: 42.85	57.15
GFR (ml/min)	: 19.59	26.12
Total GFR (ml/min)	: 45.71	
Normalized GFR (ml/min)	: 100.37	

f

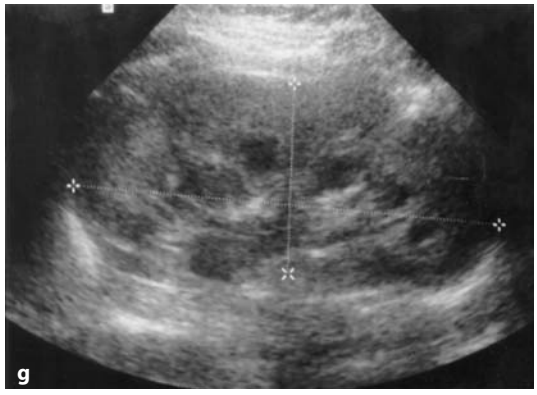


Fig. 18.14a–g. An infant with posterior urethral valves. **a** There is marked dilatation of the posterior urethra and significant bladder-wall thickening and a large left bladder diverticulum (*arrow*). **b** Five months after valve destruction. There is almost complete resolution of the dilatation of the posterior urethra, and the bladder wall has a much smoother outline. There is still a large left bladder diverticulum. **c** Ten months after surgery. Ultrasonography shows a significant left hydronephrosis and hydroureter. **d**,**e** Tc 99m DTPA scintigraphy confirms good uptake of the radiopharmaceutical on this left side with poor excretion down a dilated ureter. Voiding cystourethrogram was normal. These appearances are compatible with obstruction at the vesicoureteric junction. **f**,**g** Four years after surgery. Ultrasonography and renography demonstrate complete resolution of the obstruction without surgical intervention

severe ureter dilatation, poor renal function, and sonographic evidence of thin renal parenchyma with or without dysplasia are in an unfavorable group and may require vesicostomy. If uremia persists and the child is severely ill, percutaneous nephrostomy may be necessary. Valve destruction is usually achieved via retrograde endoscopy using an electrode, laser therapy, or occasionally by Fogarty balloon catheter ablation. Postobstructive diuresis or urinary tract infection can occur following relief of obstruction and instrumentation (Fig. 18.12). In most incidences there is a progressive improvement in the appearance of the bladder and the upper tracts after complete destruction of the valves, though it can take years for the dilatation to reduce. This progress is best monitored using ultrasonography (Fig. 18.13) and scintigraphy or possibly magnetic resonance urography (McMann et al. 2006). Vesicoureteric reflux monitored using a voiding cystourethrography study usually disappears if reasonable renal function is maintained. Dilatation of the posterior urethra also resolves with time (Fig. 18.14). However, unilateral reflux may act as a pop-off valve and may have a protective effect by reducing intravesical pressure. Urodynamic studies are required, therefore, before considering a nephroureterectomy or a ureteric reimplantation in such a patient. Reimplantation in a trabeculated bladder is often difficult and unsuccessful and apparently does not affect outcome (Speakman et al. 1987). Endoscopic treatment of reflux in these children is also difficult. Persistent dilatation of the upper tract without reflux may be related to a degree of obstruction at the vesicoureteric junction (Fig. 18.14). This obstruction may be intermittent or permanent. Bladder augmentation is rarely indicated. It can improve capacity and compliance and may relieve vesicoureteric obstruction. Incontinence is reported in up to 38% of boys after treatment of posterior urethral valves. Despite adequate relief of urethral obstruction, urodynamic abnormalities such as abnormal detrusor function are thought to be responsible for these symptoms. Growth problems, renal function deterioration, and end-stage renal disease can occur at any time during childhood, puberty, or even later. Therefore, all patients should have at least yearly imaging using sonography for assessment of upper-tract dilatation and drainage and residual bladder volume assessment. Renal functional imaging is also necessary using Tc-99m DMSA or MAG 3 scintigraphy.

Conclusion

After birth it is essential to resuscitate the child when necessary, make urine drainage free, and destroy the valves. Follow-up in all patients should include yearly imaging using sonography to assess upper tract dilatation, drainage, and residual bladder volume. Renal functional imaging is also necessary.

18.6 Prune Belly Syndrome

The hallmark findings of this condition include (see also Chap. 17):

- Partial lack of abdominal wall musculature
- Dilated upper urinary tracts and bladder
- Bilateral undescended testes

The degree of urinary tract involvement varies. Though the approaches to long-term management range from complete urinary tract reconstruction as a newborn and young infant to early permanent urinary diversion to observation with selective surgical intervention, the latter approach is currently the most popular. A minority of infants may have early problems such as recurrent urinary tract infections or raised urea and creatinine levels requiring urinary diversion. The easiest method, cutaneous vesicostomy, is adequate in most incidences. The majority of these patients reflux into their massively dilated ureters. Patients on prophylactic antibiotics who are free of infection usually have preservation of renal function. When reimplantation is required the lower ureter is resected, as the changes of marked decrease in smooth muscle and replacement of areas of the ureter by a hyaline material are more pronounced distally (Palmer and Tesluk 1974; Hanna et al. 1977). The upper ureter is tailored and reimplanted with or without a psoas hitch. These patients require careful monitoring for possible ureteric obstruction, which is a complication of reimplantation. It is no longer standard practice to perform reduction cystoplasty in these patients as it does not appear to alter their voiding pattern or residual urine volume (Kinahan et al. 1992). In some institutions incision of the membranous urethra has been employed in older patients. This procedure has been shown to improve voiding and reduce residual urine volume (Cukier 1977) and therefore

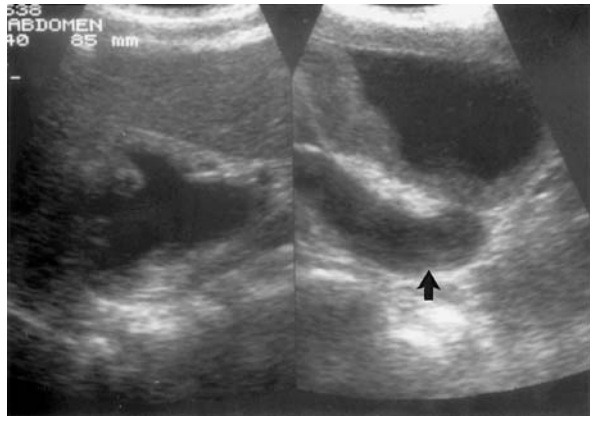
reduces the risk of bladder infection (Fig. 18.15). Urethral atresia is fatal unless associated with a patent urachus. In patients who survive, progressive urethral dilatation may be required (Passerini-Glazel et al. 1988). If this is not successful, standard urethroplasty techniques may be necessary. Megaurethra may also be an association and requires reconstruction. All conditions of the urethra are monitored using voiding cystourethrography. Patients who experience progressive renal function deterioration may require renal transplantation. Prior to this these patients should have voiding cystourethrograms and urodynamic studies. The complications of renal transplantation are discussed elsewhere.

Conclusion

In prune belly syndrome the degree of urinary tract involvement varies. Observation with selective surgical intervention is currently the most popular therapy. Patients require regular assessment using ultrasonography and radionuclide renal function studies.

18.7 Vesicoureteric Reflux

Management of vesicoureteric reflux should reduce renal tract infection to prevent renal damage. This is usually accomplished by a daily dose of prophylactic antibiotic therapy to maintain sterile urine. Reflux may resolve or improve in many incidences. Surgical correction of reflux may be required with higher grades of reflux (grades IV–V) when a child develops infections while on prophylactic antibiotic therapy, when new or progressive renal scarring develops, where long-term antibiotic use is not practical for medical or social reasons, or where severe reflux persists for years. The method of choice is ureteric reimplantation with elongation of the submucosal tunnel. Sonography demonstrates localized thickening of the bladder wall, and follow-up sonography is required early in the postoperative period to check the continued correct positioning of the ureterovesical stent, and following this, to monitor the ureter size (Fig. 18.16) and exclude the rare complication of stenosis of the distal ureter due to ischemia. Sub-



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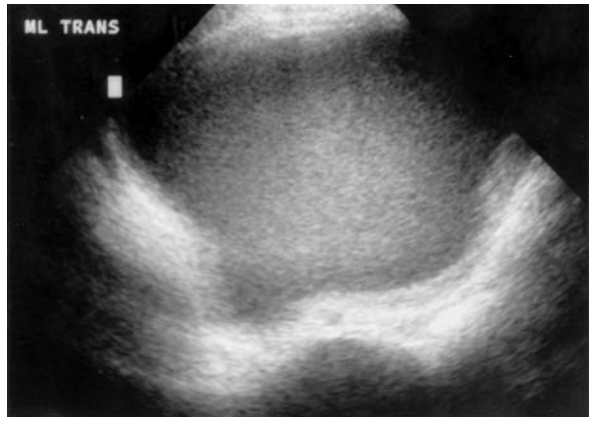

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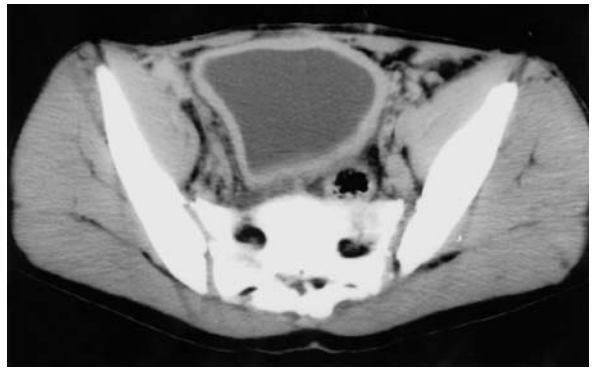
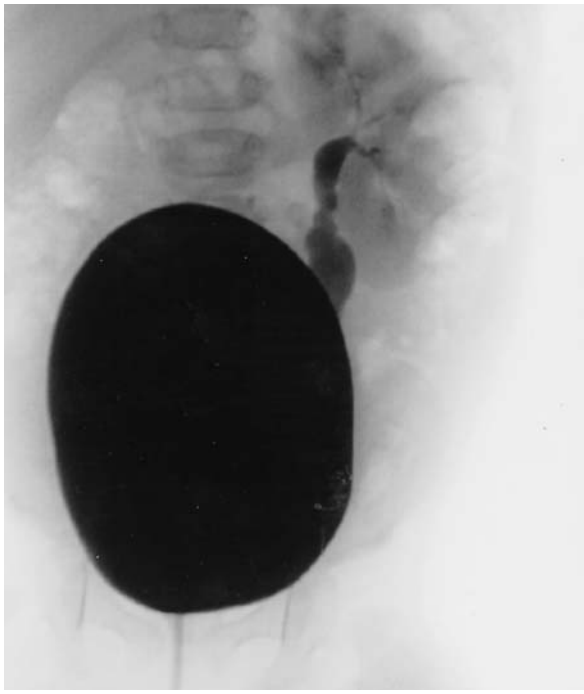


c

Fig. 18.15a–c. Boy with prune belly syndrome. **a** There is significant dilatation of the collecting systems and ureters (*arrow*). **b** Ultrasonography shows echogenic bladder content. **c** CT shows outlining of thickened bladder wall due to bladder infection as a result of poor emptying



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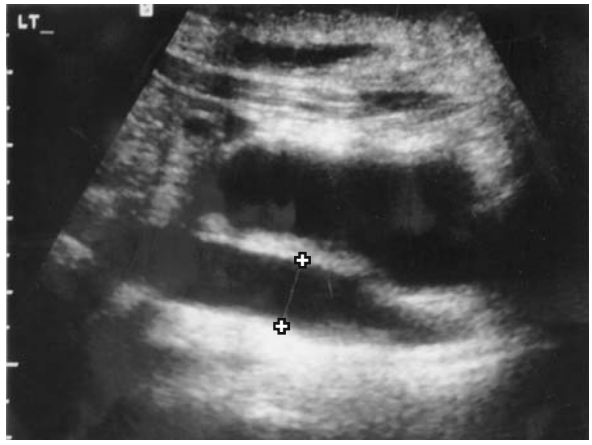

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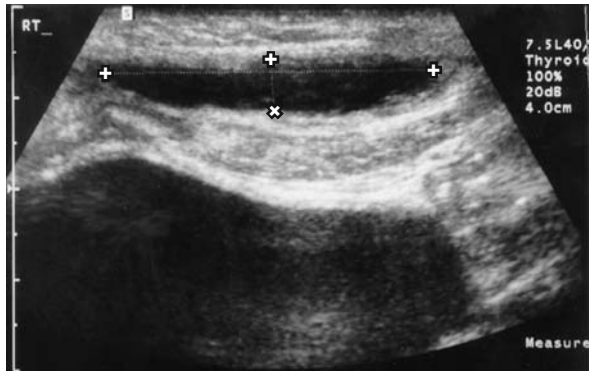


c

Fig. 18.16. a Patient with right multicystic kidney and left intrarenal reflux. **b** Ultrasonography shows development of ureter dilatation after surgery (*cursors*). **c** Patient also developed subcutaneous abscess at wound site (*cursors*)

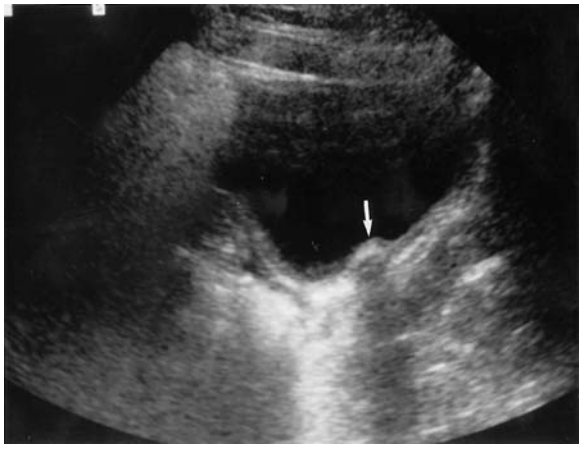


Fig. 18.17. Echogenic area with acoustic shadowing at Teflon injection site (*arrow*)

mucosal injection of Teflon is used in some centers, and its use remains controversial. Its results in preventing reflux are variable, and in the severe grades more than one injection may be required. In these incidences the repeated voiding cystourethrograms required to assess the results are extremely traumatic for the children and their parents. Following the injection, sonography shows an echogenic area with acoustic shadowing at the site of the injection (Fig. 18.17).

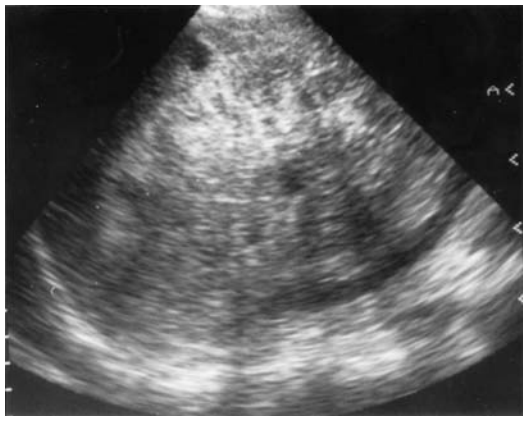
Conclusion

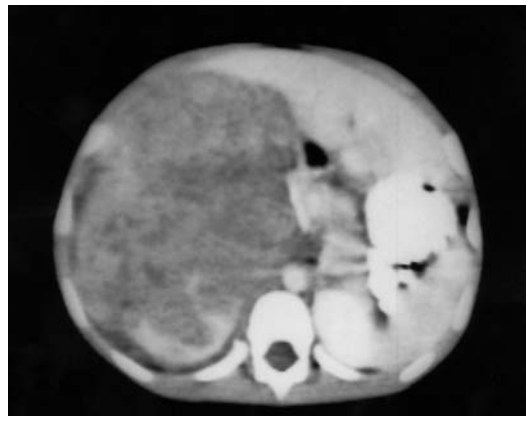
When surgery is required to treat vesicoureteric reflux the method of choice is ureteric reimplantation with elongation of the submucosal tunnel. Follow-up sonography is required to check ureteric size. Submucosal injection of Teflon is used in some centers.

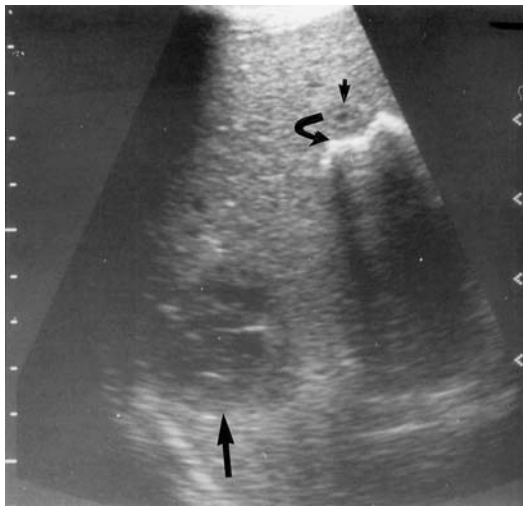
18.8 Oncological Surgery

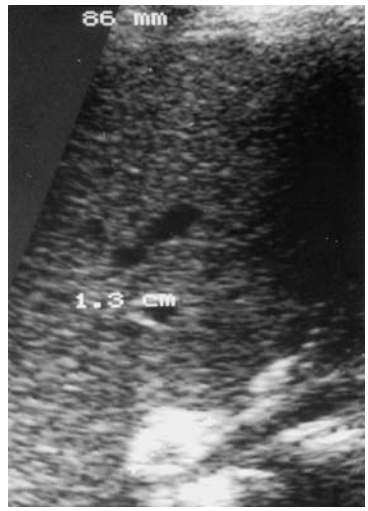
Surgical excision is still the cornerstone of therapy for Wilms' tumor, the most common malignant neoplasm of the urinary tract, and rhabdomyosarcoma, the most common soft-tissue sarcoma in childhood,

of which 15%–20% arise in the urinary tract. Meticulous surgical technique is necessary because of the risk of tumor spillage, particularly with surgery for Wilms' tumor. In patients with advanced Wilms' tumor disease and in patients with bilateral disease, the treatment involves percutaneous biopsy for diagnosis followed by chemotherapy before definitive surgery approximately 14 weeks after chemotherapy (Dykes et al. 1991; Weiner et al. 1998). Tumor can be present in adjacent organs in up to 17% of cases. Other authors used a similar regime that reduced tumor size and made it less vascular. In some incidences subsequent partial nephrectomy was possible. In these series there was no needle track seeding or tumor rupture (Greenberg et al. 1991; McLorie et al. 1991). However, controversy still exists as to the best approach to the management of these children with regards to neoadjuvant chemotherapy. In









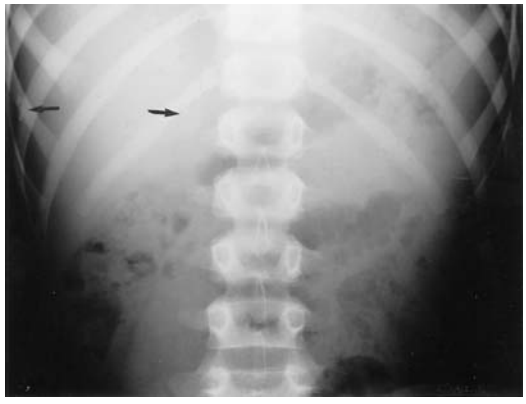


Fig. 18.18. a Ultrasonography and **b** CT scan shows a large mass arising from the right kidney. A Wilms' tumor was confirmed at biopsy. There were also tumor nodules present in the adjacent liver. **c** Follow-up ultrasonography at 6 weeks after chemotherapy shows a residual tumor nodule in the posterior aspect of the right lobe of the liver (*black arrow*). There is an area of increased echogenicity with some shadowing in a more anterior location in keeping with the development of calcification at the site of a second nodule (*curved arrow*) close to the gall bladder (*arrowhead*). **d** Follow-up ultrasonography at 2.5 years. There is an area of increased echogenicity (*between cursors*) in the inferior aspect of the right lobe of the liver, the site of a previous tumor nodule. **e** Calcification on plain radiography at two liver tumor nodule sites (*arrows*)

patients with a diagnosis of rhabdomyosarcoma, the treatment comprises various combinations of chemotherapy, radiotherapy, and surgical resection depending on the initial staging of the disease. This treatment protocol is determined by the Intergroup Rhabdomyosarcoma Study Group.

Surgical complications encountered in tumor surgery involving the genitourinary tract include small-bowel obstruction diagnosed using plain radiography and major hemorrhage for which ultrasonography and CT are useful. Follow-up imaging using ultrasonography and CT or MRI should be performed initially at 6 weeks and following this at 3-month intervals to assess response to chemotherapy and to plan the timing of surgery if required (Fig. 18.18). Following this, imaging, including chest radiography, is performed every 6 months on two occasions and then yearly as indicated, to check for tumor resolution or recurrence (Fig. 18.18).

Conclusion

Postoperative imaging in children following tumor surgery of the urinary tract is performed using ultrasonography and CT or MRI at time intervals dictated by the treatment protocol used.

18.9 Renal Stone Disease

In renal stone disease surgery is now reserved for cases that cannot be managed using extracorporeal shockwave lithotripsy (ESWL), particularly where stones are in a difficult location or where there is an underlying anatomic abnormality. Percutaneous renal surgery and lithotripsy are also occasionally used (Papanicolaou et al. 1986). Whatever the treatment, ultrasonography is used to monitor residual hydronephrosis, and radiography will monitor the disappearance of stone fragments from the ureter and bladder. Both are also necessary as follow-up investigations to exclude recurrence. CT scanning may be helpful in selected cases.

Conclusion

Whatever treatment is chosen for renal stone disease, ultrasonography and plain radiography are used to monitor outcome.

18.10 Conclusion

The surgical procedure undertaken to treat the various renal tract abnormalities may vary from surgeon to surgeon and may also depend on the severity of the conditions. These influence the complications and the outcome. Therefore, knowledge of the exact surgical procedure is necessary in most instances prior to postsurgical imaging, and close correlation with presurgical studies is mandatory.

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Renal Parenchymal Disease

19

Michael Riccabona, Christoph J. Mache, and Ekkehard Ring

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M. Riccabona, MD
Professor, Department of Radiology, Division of Paediatric Radiology, University of Graz, 8036 Graz, Austria
C. J. Mache, MD
E. Ring, MD, Professor
Department of Paediatrics, Division of General Paediatrics, University of Graz, 8036 Graz, Austria

19.1 Introduction

The renal parenchyma is divided into three main compartments:

- The cortex with glomeruli which create the primary ultrafiltrate; the juxtaglomerular apparatus, and the cortical proximal and distal tubules, which are responsible for processing the primary urine thereby maintaining body homeostasis.
- The medulla including the Henle loop performing salt and water reabsorption, involved in concentrating and diluting mechanisms, and medullary collecting ducts for final reabsorption draining the urine through the papilla into the renal collecting system.
- The interstitium, i.e., connective tissue and vasculature, of both compartments (cortex and medulla), including lymphatic tissue.

Renal parenchymal disease (RPD) is defined as a disease that involves one or more compartments of the renal parenchyma. Although different segments of the nephron, the interstitium, and the vasculature may be affected simultaneously or may become secondarily involved, RPD is generally classified into glomerular, tubular, interstitial, and vascular disease and will be discussed in this order. The causes for similar histological changes and similar imaging appearances of affected kidneys may vary; the same disease can manifest in different ways with a wide range of histology. Furthermore renal parenchyma may be affected by inherited diseases or may become secondarily involved in systemic disease such as metabolic disease, storage disease, infection (e.g., HIV), or sepsis, perfusional disturbances, autoimmune disease, and malignant disease (metastasis, leukaemic infiltration, etc.).

Some of the many causes for RPD are discussed and described in other chapters of this book, e.g.: infection and abscess (see Chap. 15), neonatal renal failure (see Chaps. 21, 23), cystic and dysplastic renal disease (see Chap. 10), nephrocalcinosis (see Chap. 20), chronic renal failure (see Chap. 21), changes in congenital urogenital malformations (including obstructive dysplasia, see Chaps. 4–9, 12, 17), traumatic changes (see Chap. 25), or malignant RPD (see Chap. 24). This chapter concentrates on the "classic entities" of RPD such as inherited nephropathy (e.g., Alport syndrome), glomerulonephritis (GN) and nephrotic syndrome (NS), RPD of vascular origin (e.g., haemolytic uraemic syndrome = HUS), and miscellaneous entities such as involvement in metabolic and autoimmune disease.

As well as describing the pathogenesis, main clinical symptoms, histology, and prognosis of the various diseases, this chapter aims to follow the clinical practice in a paediatric radiology department. We list the main findings on initial/primary imaging – generally ultrasound (US) – as established in paediatric radiology (Babcock 1989; Dietrich 1990; Gordon 2003; Hoyer 1996; Kettriz et al. 1996; Mettler and Guiberteau 1998; Riccabona et al. 2001, 2002, 2004, 2005 and 2006; Siegel 1991, 1999; Slovis 1989; Teele and Chare 1991; Toma 1991). Furthermore we try to correlate these US findings with the presenting clinical symptom(s) and the clinical query, and offer important differential diagnoses. We discuss the possibilities and indications for useful additional imaging including renal biopsy, and eventually describe the role of renal and extra-renal imaging during treatment or follow-up of patients with (chronic) RPD.

19.2 Clinical Presentation and Symptomatology

The presentation of renal disease is varied: symptoms may obviously point to the urinary tract, such as macrohaematuria, or–when the kidneys are affected as part of a systemic disease, such as systemic lupus erythematosus (SLE) or metabolic disorders–the initial presentation may be with other systemic manifestation of the disease. Although the aetiology (and the underlying cause, with different treatment and prognosis) may vary widely, the initial presenting features of RPD may be similar. However, serious renal illness may as well be asymptomatic or associated with non-specific symptoms, only coming to light as a consequence of routine examination or screening programs. Laboratory and clinical data can establish the definite diagnosis in only a proportion of cases. Additional imaging often remains inconclusive and histology is needed; certain presentations, symptoms and manifestations point to a varying list of differential diagnoses then initiating a specific diagnostic algorithm. The more frequently encountered modes of presentation of RPD are now discussed.

19.2.1 Haematuria

Isolated haematuria is a common finding in childhood and the outcome is benign in the vast majority of cases (Vehaskari et al. 1979). Occasionally, however, isolated haematuria may be an early sign of serious renal disease, e.g., Alport syndrome. Haematuria is classified as either microscopic haematuria with apparently clear urine, or macroscopic haematuria causing a reddish-brown urinary discoloration. The blood may originate from the kidneys or the urinary tract. The microscopic presence of urinary red cell deformity, urinary red cell casts, or proteinuria are characteristic markers of glomerular bleeding (Koehler et al. 1991). Medical history, clinical investigation, and distinction between glomerular and non-glomerular bleeding have a great impact on the diagnostic approach to a child with haematuria. Isolated recurrent or persistent microscopic haematuria is frequently related to idiopathic hypercalciuria, familial essential benign haematuria, minor forms of IgA nephropathy/Henoch-Schönlein nephritis, or acute postinfectious glomerulonephritis.

In these entities, the first orienting imaging is by ultrasound (US) including colour Doppler sonography (CDS), mainly to rule out nutcracker syndrome of the (retro-aortal) left renal vein or tumours that can also manifest with haematuria (Fig. 19.1) (also see Sect. 19.5). In post-renal macrohaematuria, particularly when painful or with colic, renal calculi must be considered and further radiological imaging may then be required additionally, such as abdominal plain film, IVU or CT (see Chap. 20).

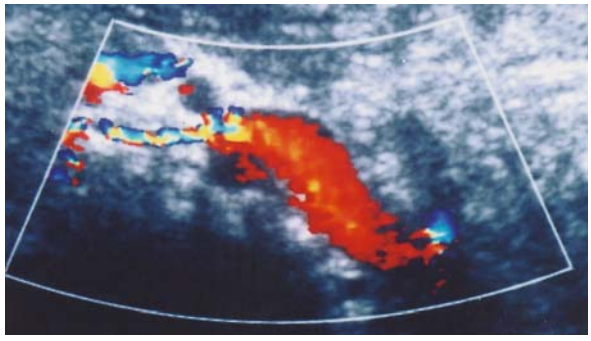
19.2.2 Proteinuria

Proteinuria is usually categorised according to the amount of urinary protein excretion as low-grade proteinuria (4–40 mg/m^2/h) or gross proteinuria (> 40 mg/m^2/h). Whereas low-grade proteinuria per se does not necessarily cause symptoms, gross proteinuria constitutes a hallmark of the nephrotic syndrome in many cases (see below). Asymptomatic isolated proteinuria is frequently an incidental transient finding in schoolchildren who do not have a progressive renal disease (Vehaskari and Rapola 1982). Orthostatic proteinuria is a frequent finding, defined as an abnormally high protein excretion in the upright posture, but not when recumbent, with usually good prognosis (Dodge et al. 1976). However, if asymptomatic proteinuria persists or is combined with other manifestations of renal disease like haematuria, elevated blood pressure, or renal failure, an underlying renal disease must be suspected. The diseases then to be considered are those usually presenting with a nephritic or nephrotic syndrome (see below). Initial imaging – if necessary at all – is restricted to US.

19.2.3 Acute Nephritic Syndrome

The acute nephritic syndrome includes haematuria, proteinuria, oliguria, and volume overload (Cameron 1979). Elevated serum creatinine levels are another common finding. This presentation is typical for acute postinfectious glomerulonephritis (GN) and rapidly progressive GN. Other forms of GN, such as membranoproliferative GN, lupus nephritis, and shunt nephritis may also manifest as an acute nephritic syndrome.

Again, initial imaging usually is restricted to US showing bilaterally enlarged kidneys with varying tissue changes such as increased parenchymal – particularly cortical – echogenicity or altered cortico-medullary differentiation, and mainly is used to rule out other underlying diseases (Fig. 19.2); however changes in size and echogenicity may go with functional improvement (Gershen et al. 1994).



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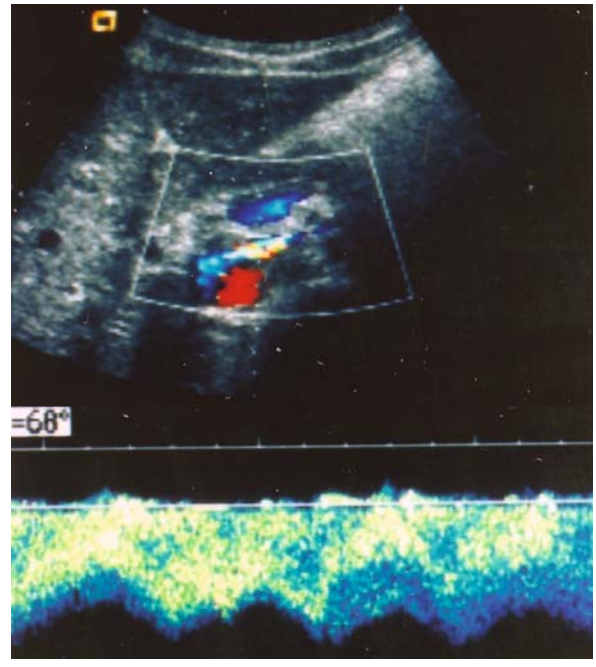

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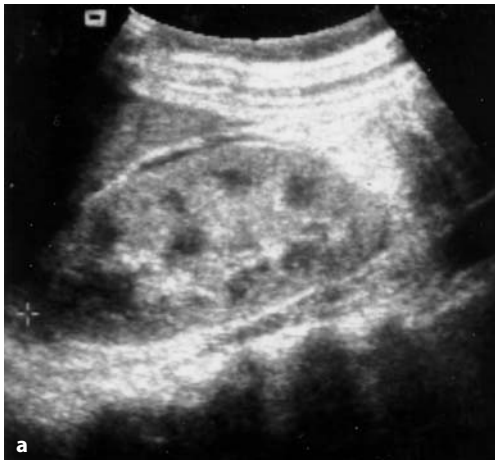
Fig. 19.1a,b. Ultrasound in pseudo-nutcracker-syndrome (= narrow crossing of left renal vein between the Aorta and the superior mesenteric artery). **a** Color Doppler sonography shows turbulent flow at the crossing of the left renal vein between the aorta and upper mesenteric artery. Note the marked change in diameter of the left renal vein. **b** Color Doppler sonography guided duplex Doppler evaluation at the side of the venous compression shows elevated flow velocity with arterialised pulsation in the left renal vein caused by propagation of aortal pulsations



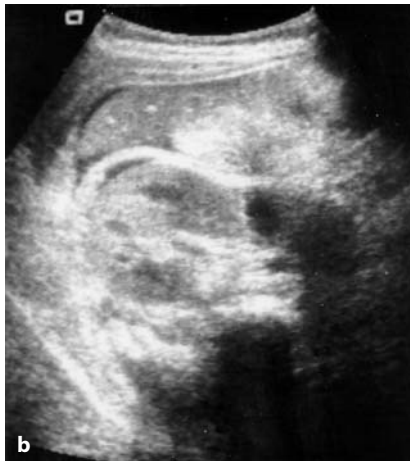


Fig. 19.2a,b. Sonographic findings in glomerulonephritis Longitudinal (**a**) and axial (**b**) section of the right kidney showing renal enlargement and increased cortical echogenicity (compared to the adjacent liver) with broadened cortex, relatively small medulla, and consequently accentuated corticomedullary differentiation in glomerulonephritis. Note the perirenal and perihepatic fluid accumulation

19.2.4 Nephrotic Syndrome

The nephrotic syndrome (NS) is defined by gross proteinuria, hypalbuminaemia, and oedema. Nephrotic children are prone to thrombembolic complications, infections, and intravascular volume depletion with the risk of acute renal failure. In childhood the most common variety is idiopathic NS, but it can occur in the course of many different glomerular diseases. Membranoproliferative GN, membranous glomerulopathy, and lupus nephritis are frequently presenting with NS. The congenital NS of the Finnish type and familial focal and segmental glomerulosclerosis are examples for inherited forms of NS (also see Chaps. 3, 21, 23).

US as the initial imaging modality usually shows enlarged kidneys with slightly increased parenchymal echogenicity. Alterations of cortico-medullary differentiation as well as the varying Doppler findings depend more on the activity of the disease and the actual renal function than on the specific underlying condition (see Sect. 19.5). If necessary, diagnosis is established histologically by sonographically guided renal biopsy (e.g., in recurrent disease, lack of response to treatment; see also Sect. 19.5).

19.2.5 Hypertension

Secondary hypertension in childhood is predominantly caused by renal or renovascular disease. The details as well as the necessary imaging, the various imaging options, and diagnostic algorithms, and possible interventional and therapeutic approaches are discussed in Chapter 22 and 26.

19.2.6 Tubular Dysfunction

There are three major tubular functions to be recognised: (1) salt and water balance, (2) potassium and acid/base homeostasis, and (3) calcium and phosphorus balance.

The renal tubule maintains extracellular fluid volume as well as electrolyte and acid-base balance by processing of the glomerular filtrate. Oliguria, defined as a urine volume <400 ml/24 h/1.73 m^2 body surface area (BSA), may represent the response to inadaequate renal perfusion, RPD (see also Chap. 10), or acute urinary tract obstruction (also see Chaps. 5, 12, 13, 17). Polyuria (urine volume >2,000 ml/24 h/1.73 m^2 BSA) and renal salt-wasting are common features of renal disease, in particular of obstructive nephropathy, juvenile nephronophthisis, chronic renal failure (see also Chaps. 21, 23), and congenital tubulopathies. Renal tubular acidosis can be a specific congenital disorder or an acquired symptom in tubulointerstitial disease and chronic renal failure. Disturbances of tubular calcium and phosphorus handling or decreased renal hydroxylation of vitamin D result in metabolic bone diseases like rickets, renal osteodystrophy, and poor statural growth.

US as the generally used initial imaging shows unspecific changes; nephrocalcinosis is seen in some diseases, may be detected quite early by high resolution US, and may help to narrow the list of differential diagnoses (Fig. 19.3). Additional imaging for skeletal pathology may be required in the initial diagnostic workup or during follow-up of these patients during treatment.

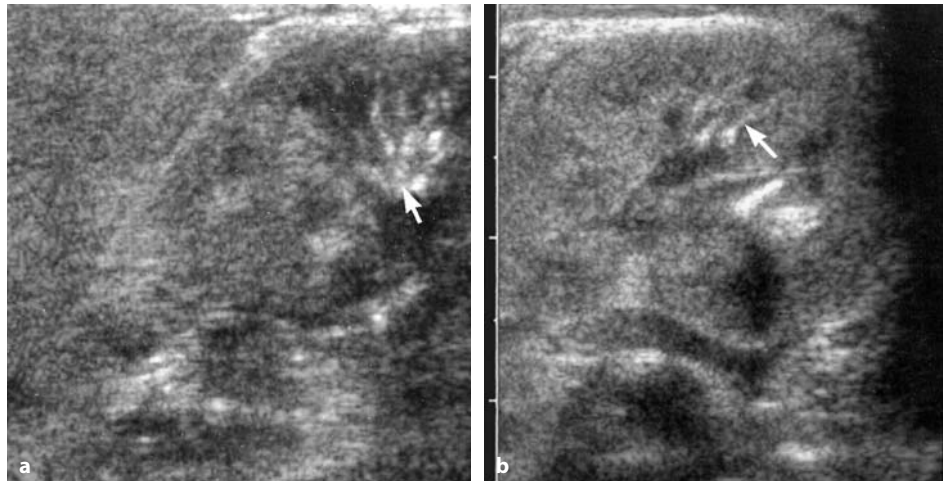


Fig. 19.3a,b. High-resolution ultrasound of a neonatal left kidney. Ultrasound demonstrates string-like areas of increased echogenicity (*arrow*) in the renal medulla demonstrating early changes of tubular calcification using a 15-MHz high-resolution linear transducer and image compounding. a longitudinal section. b axial section

19.2.7 Renal Failure

Acute renal failure (ARF) is defined as the sudden loss of renal function with or without oliguria, commonly due to acute tubular damage resulting from an ischemic/hypoxic or toxic insult. The decrease in glomerular filtration rate is an adaptive response to prevent massive losses of salt and water. Prerenal ARF results from renal hypoperfusion, often secondary to volume contraction. It implies that the kidneys are intrinsically normal and that renal function will normalise with restoration of renal perfusion. Intrinsic ARF due to acute tubular necrosis (ATN) may evolve from prolonged prerenal ARF or after a severe primary renal insult. Except for very severe injuries with the vasculature involved in microthrombi formation leading to cortical necrosis, the prognosis of ATN is good. Postrenal ARF (acute obstructive uropathy) may develop into acute bilateral obstructive uropathy due to acute pressure elevation and subsequent reduction of renal blood flow (see also Chap. 21). As a rule, the mechanisms of renal injury are complex. For example, in myoglobinuria ARF (crush kidney) may occur as a consequence of renal vasoconstriction, endogenous toxin-induced stress to tubular cells, and precipitation of the pigment in the tubular lumen resulting in obstruction. ARF results in azotaemia, acidosis, perturbation of electrolyte balance, and often fluid retention with hypertension. ARF in neonates, infants, children, and adolescents has many different and diverse causes (Table 19.1). Some causes of ARF such as cortical necrosis and renal vein thrombosis occur more commonly in neonates, whereas HUS is more common in young children, and rapidly progressive GN generally occurs in older children and adolescence.

Table 19.1. The most common causes of acute renal failure with regard to the major pathogenetic mechanisms: perirenal causes, intrinsic renal failure and postrenal etiology (modified from Andreoli 1999)

Prerenal failure
- Dehydratation
- Gastrointestinal losses
- Salt-wasting disease
- Third space losses (sepsis, trauma, and nephrotic syndrome)
- Congestive heart failure

Intrinsic renal failure
- Acute tubular necrosis
  - Prolonged (irreversible) prerenal failure
  - Ischemic/hypoxic
  - Drugs and contrast media
  - Toxins
- Urate nephropathy and tumour-lysis syndrome
- Tubulointerstitial nephritis
- Glomerulonephritis
- Vascular lesions
  - Haemolytic-uraemic syndrome (HUS)
  - Cortical necrosis
  - Renal artery thrombosis, renal vein thrombosis
  - Infectious causes

Obstructive uropathy (=post-renal)
- Obstruction in a solitary kidney
- Bilateral ureteral obstruction
- Urethral obstruction

Imaging again starts with US and is complemented by modern sonographic techniques such as Doppler, CDS, and amplitude coded CDS (aCDS),

rarely additional imaging such as MR or MR-angiography and isotope studies (with the typical pattern of delayed and flattened tracer uptake into the renal parenchyma by more or less impaired perfusion – depending on the underlying disease – and usually delayed and prolonged tracer transit into the collecting system and flattened/delayed tracer wash out curves from the renal pelvis) are used, particularly for follow-up or for confirmation or evaluation of equivocal US findings. The initial imaging in RF should address the following basic questions (also see Table 19.2):

Table 19.2. Differential diagnosis of sonographic renal changes (adapted from Perale 1992; Hoyer 1996). The typical sonomorphical appearances of various renal diseases with some hints for differential diagnosis are listed in 3 tables (Table 19.2a: normal parenchymal pattern, but different renal size; Table 19.2b: diffuse parenchymal abnormalities; Table 19.2c: focal renal parenchymal alterations). Some entities ▷▷

Table 19.2a. Differential diagnosis of sonographic renal changes: varying renal size with normal sonographic renal parenchymal pattern

A Normal renal size
- Normal kidney (5, 10)
- VUR (C)
- Non-cystic neonatal nephropathy
- Renal arterial thrombosis
- Trauma (7, 8, 10)
  - – Contusion
  - – Vascular interruption
- HUS* (5)
- CDG-Sy* (5, 6)
- Acute PN (B, 4, 7, 8)
- NS* (B)
- Acute GN* (B, 5)
- Nephroblastomatosis (B, 4, 7, 8, 9)
- Acute tubular necrosis* (5, 10)

B Increased renal size
- Compensatory hypertrophy
- In contralateral disease, e.g., hypo-/dysplasia, RNP, cystic disease, nephrectomy
- Obstructive uropathy, neoplasm, agenesis
- Uncomplicated duplication
- Organomegaly (9)
- Meckel syndrome
- Zellweger syndrome
- Beckwith-Wiedemann Sy,
- Crossed fused ectopia
- Horseshoe kidney (C)
- Acute PN (A, 4, 7, 8)
- NS* (A)
- Acute GN* (A, 5)
- Leukaemia (2, 5, 8)
- Nephroblastomatosis (A, 4, 7, 8, 9)

C Reduced renal size
- Simple hypoplasia
- RNP/VUR (A)
- Partial nephrectomy
- Ectopic kidney
- Supernumerary kidney
- Other hypo-dysplasia
  - – Non-cystic dysplasia (3)
  - – Oligomeganephronia
  - – In utero drug exposure and infections
- Horseshoe kidney (B)
- Chronic glomerular disease* (3, 10)

Table 19.2b. Differential diagnosis of sonographic renal changes: diffuse abnormality of sonographic renal parenchymal pattern

1 Large kidney with subcapsular hypoechoic rim
- ARPKD* (2, 9)
- (Finnish) congenital NS* (2)
- Acute cortical necrosis*
- Renal vein thrombosis (3, 5, 7, 10, 11)

2 Diffusely increased echogenicity: large
- ARPKD* (1, 9)
- ADPKD* (9)
- GCKD* (9)
- Congen. NS* (1)
- Bardet-Biedl syndrome* (9)
- Lesh-Nyhan syndrome
- Foetal hamartomatosis
- Urate NP* (6)
- Acute medullary necrosis*
- Candida infection (6, 7)
- Renal dysplasia (dilated urinary tract)
- Lymphangioma (intrarenal, mostly*)
- Acute lymphoblastic leukaemia

3 Diffusely increased echogenicity: small
- MCDKD (9)
- Non-cystic
- Hypodysplasia (C)
- Tamm Horsfall Sy (and TMHN, 6)*
- Renal atrophy
  - – Obstructive NP (5)
  - – Renal vein thrombosis (late, 1, 5, 7, 10, 11)
  - – Chronic glomerular KD (C, 10) *
  - – Chronic PN (7, 10)
  - – RASt
  - – Any chronic RPD
- Diffuse NC*
  - – Hyperparathyroidism (chronic) (6)
  - – Fanconi KD (9)
  - – Hypophosphataemic X-1 rickets (chronic)
  - – Cystinuria
  - – Oxalosis
- Acute lymphoblastic leukaemia

4 Diffuse hypoechogenicity
- Acute PN (A, B, 7, 8)
- Lymphoma (5, 7, 8, 10)
- Nephroblastomatosis (A, B, 7, 8, 9)

5 Increased cortical echogenicity
- Normal newborn (A, 10)
- Obstructive NP (B)
- Renal amyloidosis* (10)
- Diabetic NP*
- Myoglobinuria*
- Haemoglobinuria*
- HUS* (A)
- Acute:
  - – Renal vein thrombosis (1, 3, 7, 10, 11)
  - – Tubular necrosis* (A, 10)
  - – GN* (A, B)
- Interstitial nephritis*
- CDG syndrome* (A, 6)
- Glomerulosclerosis* (7)
- Hepoatorenal syndrome*
- Burkitt lymphoma (4, 7, 8, 10)
- Acute leukaemia (B, 2, 8)

6 Increased medullary echogenicity
- Medullary NC*
  - – Hypercalciuria
  - – Hypercalciaemia
  - – Williams syndrome
  - – Distal tubular acidosis
  - – Hyperparathyroidism (3)
  - – Bartter syndrome
  - – Cystinuria
  - – Xanthinuria
  - – Malignancies
  - – Drugs (Ca, ACTH, Vit.D, frusemide, etc.)
- Others*
  - – Sickle cell disease
  - – Tyrosinaemia
  - – Glycogenosis
  - – Multiple myeloma
  - – Urate NP (2)
  - – Shock, asphyxia
  - – Blood transfusion
  - – Candida infection (2, 5)
  - – TMHN* (3)
  - – CDG syndrome* (A, 5)
- Juv. nephronophthisis* (9, 10)
- MSKD* (9)
- Multiple angiomas (7)

a) renal size (enlarged = acute, small = chronic, but may be normal in early disease stage)
b) renal parenchymal alterations (may hint to a certain disease entity; Table 19.2)
c) dilatation of urinary tract (obstruction?, calculi? ≥ postrenal RF) (see also Sect. 19.3)
d) renal perfusion (aCDS and duplex Doppler for additional information on DD: normal vasculature or compromised perfusion?, homogeneous/diffuse disease or focal impairment?, RI?) (see also Sect. 19.5)
e) intravascular volume (size of inferior cava vein, hepatic veins, right atrium, etc.)? Extravascular

are listed in more than one column; the other locations are then indicated by letters (A–C in Table 19.2a) and numbers (1–6 in Table 19.2b; 7–11 in Table 19.2c). Note that these tables try to create a systematic approach using usual ("general") sonographic appearance as a guideline for differential diagnosis. However, occasional cases with atypical presentation "mimicking" other entities may well be encountered

Table 19.2c.
Differential diagnosis of sonographic renal changes:
focal abnormality and submersion of sonographic renal parenchymal pattern

7 Focal hyperechoic or complex abnormality
All entities of (6)
Intrarenal reflux in VUR
Juvenile xanthogranuloma
Elastic pseudoxanthoma*
Renal vein thrombosis (1, 3, 5, 10, 11)
Segmental infarct (8)
Acute segmental PN (lobar nephronia; A, B, 4, 8)
Chronic PN (including pseudotumoral glomerular sclerosis; 3, 7, 10)
(Micro)-cystic KDs (also see Chap. 10)
Abscess (8)
Candida infection (2, 6)
Trauma (A, 8, 10)
Neoplasm
– Benign (6, 9, 11) including angiomyolipoma
– Malignant (4, 5, 7, 8, 10, 11) including Wilms' tumour
Nephroblastomatosis (A, B, 4, 8, 9)

8 Focal hypoechic abnormality
Segmental infarct (7)
Acute focal PN (A, B, 4, 7)
Abscess (7)
Trauma (A, 7, 10)
Harmatomas
Lymphomas (4, 5, 7, 10)
Myolipoma (rare)
Nephroblastomatosis (A, B, 4, 7, 9)

9 Anechoic/cystic lesion
Cystic hypo-dysplasia
MCDKD (3)
ARPKD* (1, 2)
ADPKD* (2)
GCKD* (2)
MSKD* (6)
Cystic KDs (also see Chap. 10)
Juvenile nephronophthisis* (6, 10)
Multiple malformations syndrome*
– Tuberous sclerosis (7)
– Meckel sy (B)
– Jeune syndrome
– Zellweger syndrome (2)
– Hippel-Lindau syndrome
– Bardet-Biedel syndrome (2)
– Fanconi syndrome
– And many other syndromes
Cysts
– Simple cyst
– Complicated cysts
– Cystic end stage KD ("acquired cystic KD")*
– Hydatid cyst
– Multilocular cyst
Mesoblastic nephroma (7, 11)
Nephroblastomatosis (A, B, 4, 7, 8)
Cystic renal lymphangioma
Wilms' tumour (7, 11)

10 Focal reduction of parenchymal thickness
Normal kidney (A, 5)
– Lobar segmentation
– Lobulation
– Parenchymal junction line/ defect
Non-cystic congenital NP (A)
Juvenile nephronophthisis* (6, 9)
Renal amyloidosis* (5)
Chronic glomerular KD (*C, 3)
Chronic PN (3, 7)
Tuberculosis
Renal vein thrombosis (late; 1, 3, 5, 7, 11)
Late stage of acute neonatal tubular necrosis* (A, 5)
Trauma (A, 7, 8)
Treated lymphoma (4, 5, 7, 8)

11 Submersion of parenchymal pattern
Renal vein thrombosis (1, 3, 5, 7, 10)
Xanthogranulomatous pyelonephritis
Neoplasm
– Malignant (7, 9)
– Mesoblastic nephroma (7, 8, 9)

*	= bilateral
NS	= nephrotic syndrome
Sy	= syndrome
KD	= kidney disease
chron	= chronic
PN	= pyelonephritis
GN	= glomerulonephritis
PN	= pyelonephritis
HUS	= haemolytic uraemic syndrome
RNP	= reflux nephropathy
VUR	= vesicoureteral reflux
CDG-Sy	= carbohydrate-deficient glycoprotein syndrome
NP	= nephropathy
GCKD	= glomerulocystic kidney disease
TMHN	= transient medullar hyperechogenicity of the newborn
MSKD	= medullary sponge kidney disease
NC	= nephrocalcinosis
RASt	= renal artery stenosis
MCDKD	= multicystic dysplastic kidney disease

fluid collections (ascites, pleural and pericardial effuion, etc.)?
f) Do the information from items a–e allow a narrowing of the DD or differentiation acute versus chronic RF and/or RPD (Table 19.2)?

A congenital or acquired renal disease leading to a substantial reduction of functioning nephrons results in chronic renal failure (CRF). A progressive decline of renal function ensues and CRF ultimately leads to end-stage renal failure. As renal function deteriorates, various clinical symptoms emerge. As detailed in Chapter 21, acidosis, growth failure, renal osteodystrophy, hypertension, and anaemia are common manifestations and indicate more extensive and also extra-renal imaging particularly during follow-up.

19.3 Primary Imaging Management

In general patients with clinical symptoms and laboratory findings suspicious of renal disease are initially sent to US as the primary imaging modality, mostly before the final diagnosis is established. The role of this initial study is to rule out other diseases like obstructive or refluxive uropathy, acute obstruction, nutcracker syndrome, and renal tumours (that all might cause, e.g., haematuria), cystic renal disease, and renal dysplasia (that might present with hypertension, proteinuria, tubular symptoms, or even haematuria, e.g., in case of a medullary sponge kidney or nephrocalcinosis, see also Chaps 10, 20), or other pre-existing urinary tract malformations. The typical pattern of transient renal medullary hyperechogenicity in neonates represents a well-known neonatal physiological transient condition that may aggravate under certain circumstances such as long-term Frusemide application or antibiotic treatment, indometacin administration, hyperviscosity, or dehydration (Avni et al. 1983; Howlett et al. 1977; Riebel et al. 1993; Schulz et al. 1991; Nakamura et al. 1999; Slovis et al. 1993; Starinsky et al. 1994). We shall not discuss this entity here, as this is described in the respective chapters.

Furthermore the clinician may expect additional information for differential diagnosis and disease status as provided by renal size, e.g., acute versus chronic disease and renal parenchymal echogenicity/sonomorphology (Table 19.2), or by renal perfusion (see Sect. 19.5). One of the key findings for most RPD is bilateral renal involvement; sometimes one may observe secondary extra-renal findings such as ascites and pleural effusion (Fig. 19.2). The combined information on renal size, bilateral or unilateral involvement, structural pattern, and clinical data may point out the differential diagnosis (Toma 1991; Piaggio et al. 1999). Generally, cortical hyperechogenicity (compared to the adjacent liver or spleen) with consecutively increased cortico-medullary differentiation in an enlarged kidney corresponds with acute glomerular disease. Reduction in size as well as a more or less inhomogeneously increased echogenicity with reduced cortico-medullary differentiation hint towards chronic RPD, particularly with both glomerular and tubulo-interstitial involvement (Fredericks et al. 1989; Perale 1988, 1992). Loss of cortico-medullary differentiation with normal cortical echogenicity may hint towards medullary disease, particularly in cases with medullary or papillary hyperechogenicity and consecutively reversed echogenicity pattern as seen in hypercalciuria, nephrocalcinosis, nephrotoxicity of some drugs (e.g., chemotherapy), cystinosis, and oxalosis. Dilatation and differentiation of the collecting urinary system depend on renal function – in polyuric renal failure the renal pelvis can be prominent, in poor functioning units the renal pelvis may collapse and thus be invisible for US. Knowledge of hydration and diuresis is essential for adequate interpretation of particularly slight calyceal and pelvic dilatation, as even in severe acute obstruction only little distension may be seen. Furthermore – in some diseases – sonographic changes may precede clinical recurrence (HUS, IgA nephropathy), and the severity of changes (e.g., degree of hyperechogenicity of the renal cortex) may correlate with the severity of the disease (Rosenfield and Siegel 1981; Hricak et al. 1982). Advanced sonography such as high-resolution imaging or Doppler evaluations may still offer more potential for differential diagnosis and may provide valuable information during the course of the disease (see Sect. 19.5.1). Some centres use standardised diagnostic flow charts to evaluate typical clinical presentations; however they are more commonly applied to other entities such as congenital urinary tract malformations than to RPD.

Other modalities such as intravenous urography (IVU), CT, or MRI are rarely used in the initial assessment, as they partially are expensive, invasive, not generally available, bare the risk of contrast toxicity, and yet are not specific to date (Dietrich 1990; Kettriz et al. 1996; Siegel 1999). Depending on the patient's

history and the initial US finding (e.g., dilated collecting system with enlarged ureter, increased echogenicity of renal parenchyma, decreased renal size), voiding cysto-urethrography (VCU) may be indicated to find or to rule out vesico-ureteral reflux (VUR) associated with RPD. In suspected obstructive RPD/uropathy dynamic isotope studies may be performed and may show a flattened dynamic curve with delayed tracer uptake as well as prolonged tracer washout and diffusely speckled tracer rarefaction over the renal parenchyma (Mettler and Guiberteau 1998).

Seldom are renal parenchymal abnormalities consistent with RPD picked up as an incidental finding on a US, CT or MRI study performed because of a different query, such as interstitial (septic) renal involvement and parainfectious GN in a septic patient, or RPD in a dystrophic child. Contrast-enhanced CT studies may demonstrate delayed and prolonged parenchymal enhancement with reduced cortico-medullary differentiation of enlarged kidneys in acute GN. In general radiopaque intravenous contrast as administered for IVU or CT should be avoided in RPD with renal functional impairment; if these studies are performed, good hydration as well as diuretic measures are compulsory to prevent possible contrast nephropathy with renal damage such as papillary necrosis or even renal failure (Erley and Bader 2000; Morcos 1998; Murphy et al. 2000).

Conclusion

Clinical manifestation of RPD is unspecific, and symptoms vary. Primary imaging in RPD is generally accomplished by US, helps in the initial differential diagnosis, but mainly rules out other disease entities. IVU and contrast-enhanced CT should be avoided to prevent contrast nephropathy in cases with compromised renal function.

19.4 Specific Entities

19.4.1 Glomerular Disease

19.4.1.1 Congenital and Inherited Glomerular Disease

Alport syndrome is a genetically heterogeneous, frequently X-linked dominant transmitted form of hereditary nephritis (Smeets et al. 1996). Mutations of genes encoding for type IV collagen subunits are responsible for the disease. Type IV collagen constitutes a major component of the glomerular basement membrane (GBM). The characteristic lesions of the GBM, like irregular thickening, thinning, multilammelation and splitting are best demonstrated by ultrastructural studies. Affected males present with microscopic or macroscopic haematuria, later with proteinuria, hypertension and progressive renal failure. In the juvenile type end-stage renal failure occurs around the age of 20 years (Kashtan 2000). Important extrarenal symptoms are progressive bilateral hearing loss, ocular defects like anterior lenticonus and macular lesions, and occasionally diffuse oesophageal or vulvar leiomyomatosis. In rare cases transplanted males develop anti-GBM crescentic nephritis due to anti-GBM antibodies recognising type IV collagen epitopes (Rutgers et al. 2000). In affected females microhaematuria is a typical finding and progressive renal failure seldom ensues (Jais et al. 2000). Diagnosis is established on clinical criteria, skin biopsy with immuno-histochemical identification of type IV collagen defects, renal biopsy with ultrastructural studies, or mutation analysis (Flinter et al. 1988; van der Loop et al. 1999).

Familial essential benign haematuria (FEBH) is characterised by the familial occurrence of persistent, usually microscopic haematuria without progression to renal failure and extrarenal manifestations (Gauthier et al. 1989). Diffuse attenuation of the GBM (thin basement membrane nephropathy) is the typical ultrastructural finding, but renal biopsy is mostly unnecessary.

In both entities imaging studies are normal or uncharacteristic. US is used in the primary assessment and for renal biopsy; during follow-up radiology may additionally serve in imaging of potential complications such as leiomyomatosis.

Genetically determined glomerular diseases may present with a NS. The congenital nephrotic syndrome of the Finnish type (CNF) is an autosomal recessive disease with massive proteinuria starting in utero. The gene responsible for CNF codes for nephrin, a protein involved in the maintainance of the glomerular filtration size-selective area (see Chaps. 3, 10, Bratton et al. 1990). Denys-Drash syndrome and Frasier syndrome are related diseases caused by mutations in the WT1 gene. WT1 gene mutations have been described in early onset nephrotic syndrome progressing to end-stage renal failure, gonadal dysgenesis and male pseudo-hermaphroditism,

Wilms' tumor, isolated diffuse mesangial sclerosis, and focal and segmental glomerulosclerosis (Little and Wells 1997; Jeanpierre et al. 1998; Barbaux et al. 1997; Denamur et al. 1999). These sequalae point out the role of imaging in dealing with these patients; furthermore one has to consider these entities in patients with unilateral Wilms' tumour and contralateral renal abnormalities and/or gonadal alterations. Familial forms of idiopathic nephrotic syndrome with focal and segmental glomerulosclerosis with an autosomal dominant or recessive mode of inheritance have been linked to several genes on chromosomes 1, 11, and 17 (Winn et al. 1999; Bopute et al. 2000; Kaplan et al. 2000) (see also Sect.19.3).

Other hereditary diseases with glomerular involvement, like nail patella syndrome, collagen type III glomerulopathy, Fabry disease, and Biedl-Bardet syndrome, are very rare and beyond the scope of this chapter.

19.4.1.2 Acute Postinfectious Glomerulonephritis

This entity is one of the classical immuno-complex-mediated renal diseases following a febrile infection of the upper airways or of the skin. Group A ß-haemolytic streptococci are the most common associated organisms, but infections with other types of streptococci, staphylococci, viruses, and parasites were also found as etiologic factors. Clinical manifestation with an acute nephritic syndrome is the rule, but there is a wide spectrum including a subclinical and a rapidly progressive course with severe acute renal failure. Laboratory values typically show low levels of C3 complement returning to normal after 6 to 8 weeks; the antistreptolysin titer is elevated in cases associated with streptococcal infections. Differential diagnoses with low levels of C3 complement as a leading feature are membranoproliferative GN and S LE. As these parameters usually are diagnostic, (renal) imaging plays a rather unimportant role, is restricted to US (including CDS), and shows findings just as in any type of GN (Fig. 19.2), but never is diagnostic. Therapy is supportive in most cases and outcome is excellent even in cases with prolonged microscopic haematuria.

19.4.1.3 Rapidly Progressive Glomerulonephritis

This clinical nomenclature defines a variety of severe glomerular diseases histologically defined by proliferation within Bowman's space and formation of crescents ("crescentic nephritis"). Clinical presentation is an acute nephritic/nephrotic syndrome with pronounced oliguric renal failure, hypertension, and signs of volume overload. Underlying diseases include nearly all primary renal or systemic diseases with possible renal manifestation including IgA nephropathy, Henoch-Schönlein purpura, membranoproliferative nephritis, S LE, Wegener's granulomatosis, and polyarteritis nodosa. The classical disease with crescentic nephritis and pulmonary haemorrhage is Goodpasture's syndrome (Kluth and Rees 1999) caused by auto-antibodies against the glomerular and alveolar basement membranes (GBM), but haemoptysis is not restricted to this specific disease.

Any patient presenting with nephritis and pulmonary haemorrhage may be in a nephrological emergency situation acutely requiring renal biopsy for correct diagnosis, as US and all other imaging are non-diagnostic. Additionally, (HR)CT of the lung may be performed for differential diagnosis of the pulmonary manifestation; renal granulomas ("pseudotumors", e.g., in Wegener's granulomatosis, see also Chaps. 10, 24, and Sect. 19.5.3) must not be mistaken for renal neoplasm. Otherwise, US may not show much, but bilaterally increased renal size and some increase of the cortical echogenicity, and Doppler indices usually are normal (see also Sect. 19.5.); only a halo sign (= reduced peripheral/cortical perfusion demonstrated as a lack of colour on aCDS in the periphery of the renal parenchyma, creating a halo-like impression) may be seen in patients with severe GN (Hoyer et al. 1999) (Fig. 19.4).

Treatment includes pulses with methyl-prednisolone, application of cytotoxic agents, and plasma exchanges in anti-GBM disease. The prognosis of crescentic nephritis in general is poor, but can be ameliorated by immediate diagnosis and therapy. Even during therapy imaging plays a marginal role, except for monitoring biopsy, renal size, and eventually in the pre-transplantation workup.

19.4.1.4 IgA Nephropathy and Henoch-Schönlein Nephritis

IgA nephropathy (IgAN), originally described by Berger and Hinglais in 1968, nowadays seems to be the most common glomerulopathy worldwide. Initially regarded as a benign disorder, IgAN is a major cause of end-stage renal failure observed in 20%–34% of adults and in 10% of affected children.

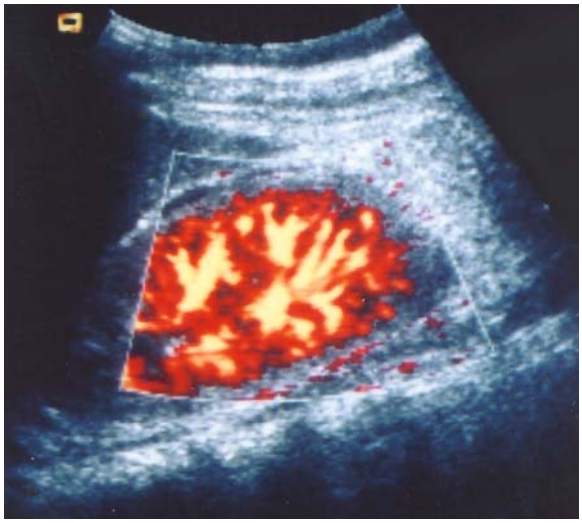


Fig. 19.4. Amplitude-coded color Doppler sonography in glomerulonephritis ("halo"-sign"). Amplitude-coded color Doppler sonography demonstrates a small cortical peripheral rim- or halo-like layer with no color signals, indicating peripherally reduced flow (in spite of normal RI values) in a patient with glomerulonephritis

The pathogenesis is not yet completely understood. There seems to be a basic abnormality of IgA1 eventually combined with a less efficient hepatic clearance of IgA1 polymers leading to mesangial deposition of circulating IgA immuno-complexes, proliferation of mesangial cells, increase of mesangial matrix, and progressive obstruction of glomerular capillary lumen (Allen et al. 1997; Davin and Weening 1999; Hunley and Kon 1999). Patients predominantly present with painless gross haematuria and a normal renal function during upper respiratory infections; isolated microscopic haematuria is the next frequent finding. Persistent proteinuria, nephrotic syndrome, and acute nephritic presentation with acute renal failure are rare, but indicate a worse course of the disease. Although clinically suspected in many cases, definite diagnosis can only be made by demonstration of mesangial deposition of IgA in a renal biopsy specimen.

Thus imaging again is non-diagnostic and only used to rule out other diseases or to monitor renal changes during the course of the disease, where relapses may be predicted by US changes. Therapy of patients with risk factors for a progressive course of the disease include administration of corticosteroids, ACE inhibitors, cytotoxic agents, and of omega-3-polyunsaturated fatty acids contained in fish oil (Pozzi et al. 1999; Yoshikawa et al. 1999).

Henoch-Schoenlein purpura (HSP) is a systemic vasculitis affecting the skin, joints, gut, and kidneys. Nephritis in HSP (HSPN) and IgAN seem to be related diseases. Both have mesangial deposition of IgA as the dominating feature in renal biopsy specimens and thus can be discussed in combination. Clinical presentation is typical; renal manifestation is present in up to 80% of patients mostly with isolated haematuria. Presentation with acute nephritic syndrome and renal failure or with nephrotic syndrome is rare, but indicates a progressive course of the disease.

US may show unspecific changes, may even be normal, and probably reflects more the severity of the disease than the individual entity. Renal biopsy is indicated in cases presenting with acute nephritic/nephrotic syndrome suggesting a rapid progressive nephritis and if significant proteinuria persists for more than 3 months. No other imaging is used for diagnosis, but may well be indicated for monitoring the patients during treatment (see Sect. 19.5.4). In cases with severe or prolonged disease therapy is indicated similar to therapy of IgAN (Niaudet and Habib 1998). A severe progressive course may lead to end-stage renal disease despite adequate therapy. Both diseases (IgAN and HSPN) may show recurrence after renal transplantation.

19.4.1.5 Idiopathic Nephrotic Syndrome

The idiopathic nephrotic syndrome (INS) is defined by the combination of a usually severe nephrotic syndrome with non-specific histological abnormalities including minimal changes (MC), focal and segmental glomerulosclerosis (FSGS), or diffuse mesangial proliferation (DMP) (Chesney 1999). The glomeruli typically show a fusion of epithelial cell foot processes on electron microscopy. Patients with INS are mostly categorised on the basis of their response to steroid therapy as steroid-responsive or steroid-resistant. Steroid-responsive patients may have a single relapse, occasional relapses or become steroid-dependent. About 10% of the patients with INS are steroid-resistant. These patients more commonly have haematuria, the histological appearance of FSGS or DMS, and progress more often to chronic renal failure. They are particularly prone to disease-related complications, such as acute renal failure due to hypovolemia, infections, thrombosis, hypertension, and growth failure. Apart from symptomatic treatment and conventional steroid protocols,

methylprednisolone pulse therapy, cyclosporine A, cytotoxic agents, and plasmapheresis are used in steroid-resistant INS (Niaudet and Habib 1994; Tune and Mendoza 1997). Nevertheless, steroid-resistant INS accounts for more than 10% of children who progress to end-stage renal failure, and their risk of recurrent INS following transplantation with subsequent graft failure is considerably increased.

Imaging is generally restricted to US that demonstrates bilaterally increased renal volume and unspecific diffuse changes of the parenchyma with usually increased echogenicity specifically of the cortex, as well as ascites and pleural effusion. The sonographic changes correspond with the clinical course and sonographic normalisation may even precede clinical improvement. In persisting disease renal biopsy is performed.

19.4.1.6 Membranoproliferative Glomerulonephritis and Membranous Glomerulopathy

Membranoproliferative GN (MPGN) and membranous glomerulopathy (MGN) are chronic glomerular diseases with typical findings on renal biopsy specimen and a questionable prognosis in many cases.

Patients with MPGN (three subtypes recognised) can present acutely and are undistinguishable from patients with acute postinfectious GN, but fail to have quick resolution of disease. Especially persistent low levels of C3 complement – frequently caused by the presence of C3 nephritic factor (C3NeF) – point to MPGN. Other patients may have asymptomatic microhaematuria and proteinuria detected by chance. The prognosis is unfavourable in cases with acute nephritic/nephrotic syndrome. Therapeutic measures include corticosteroids, cytotoxic agents, and ACE inhibitors. MPGN lesions can be found secondary to systemic immunological diseases (e.g., SLE, Henoch-Schönlein purpura) or in chronic infectious diseases like viral hepatitis, HIV, or chronically infected ventriculoatrial shunts ("shunt nephritis", Arze et al. 1983). The latter condition is treatable by prompt antimicrobial therapy and shunt revision with resolution of MPGN in many cases.

MGN may be primary or secondary to other conditions (e.g., hepatitis B, malaria, congenital syphilis, SLE, drugs, and neoplasms). The latter cases predominate in children (Cameron 1990). Clinical presentation is with NS and microhaematuria or with asymptomatic proteinuria in the majority of cases. NS usually is steroid-resistant. As diagnosis is made by renal biopsy, there is no specific role for further imaging – however US and CDS studies are usually performed initially and during follow-up. No definite approach to therapy is available for primary MGN. Patients with asymptomatic proteinuria frequently achieve spontaneous remission without any therapy; approximately 20% of mostly nephrotic children develop chronic renal failure. Secondary MGN may resolve after therapy of the associated condition.

19.4.2 Vascular and Tubulo-interstitial Disease

19.4.2.1 Vasculitis/Systemic Vasculitis Syndromes

Vasculitis occurs in different diseases and syndromes in childhood. It is the predominant manifestation in certain rare disorders, and the pathogenetic mechanisms involved may be immune complexes, autoantibodies, cell adhesion molecules, or miscellaneous factors. Following, some specific childhood vasculitis syndromes are addressed.

Polyarteritis nodosa (PAN) is a necrotizing vasculitis of the medium-sized arteries with aneurysmal nodule formation. Patients manifest clinically with fever, malaise, musculoskeletal symptoms, cutaneous lesions and nodules, or peripheral neuropathy (Ozen et al. 1992; Jennette et al. 1994). Systemic disease involves the kidneys in about half of the patients, initially often with haematuria and hypertension. Biopsy tissue, especially from skin lesions, muscles, or nerves can be diagnostically helpful. Renal biopsy usually provides no additional information and may even be dangerous in aneurysma formation (Curran et al. 1967). Induction therapy includes steroids and cytotoxic agents; however kidney involvement still remains a major cause of morbidity and mortality in PAN.

US including (a)CDS serves as the initial imaging tool and includes other abdominal organs and vessels. Renal (and hepatic as well as cerebral) (MR-) angiography is recommended and frequently shows arterial aneurysms, segmental narrowing, variation in vascular caliber, and infarctions (McLain et al. 1972). Ischaemia and infarctions may as well be visible as patchy areas of decreased isotope uptake on DMSA scanning (Dillon 1998).

Microscopic polyarteritis is a small-vessel vasculitis and differs from PAN by the presence of extensive glomerular involvement in form of a focal necrotising and crescentic (glomerulo-) nephritis (Savage et al. 1985). The clinical presentation is similar to PAN, however renal involvement as a rapidly progressive GN soon predominates the clinical picture. There is also an association with lung disease, including pulmonary haemorrhage. In microscopic polyarteritis angiography usually does not add to the diagnosis. Renal biopsy is frequently performed, but may fail to demonstrate characteristic histopathological lesions. Despite aggressive treatment the outcome may be poor.

Wegener's granulomatosis is a necrotising granulomatous vasculitis of the upper and lower respiratory tract. GN, at times with a rapidly progressive course, occurs in a proportion of children (Singer et al. 1990; Rottem et al. 1993). Radiology, including CT and MRI, of paranasal sinus and chest contributes to the diagnosis, whereas renal US only shows non-specific tissue alterations. However, histological evaluation of affected tissue from the respiratory tract or kidneys is often needed. Furthermore, the disease may present as a renal pseudotumor on initial scans ("renal granuloma") or may develop secondary bladder and/or prostatic disease (cystitis, cancer, etc.) due to treatment with cyclophosphamide (Verswijvel et al. 2000; Talar-Williams et al. 1996) and therefore indicate regular imaging follow-up.

Giant cell arteritis (Takayasu's disease) is an inflammatory vasculitis of the large arteries, especially affecting the aorta and its major branches (D'Souza et al. 1998). Doppler US of the kidney, but also of other organs and vessels (sometimes additional transcranial CDS), echocardiography, and (MR) angiography are essential for diagnosis, therapeutic decisions, and prognostic.

19.4.2.2 Haemolytic-Uraemic Syndromes

The haemolytic uraemic syndromes (HUSs) are a heterogeneous group of similar entities with variable expression and severity. Renovascular endothelial cell injury is central to the pathogenesis, leading to platelet activation and intravascular coagulation, haemolytic anaemia with fragmented erythrocytes, thrombocytopenia, and renal failure.

Shiga toxin (Stx)-associated HUS, the typical form of HUS, occurs mainly in childhood and represents the most common cause of acute renal failure in this age group (Repetto 1997). Stx HUS is caused by infection with enterohaemorrhagic strains of *Escherichia coli* or *Shigella dysenteriae* (Rondeau and Peraldi 1996) (Fig. 19.5a). The release of Stx by these bacteria is responsible for renal endothelial cell injury in genetically susceptible children. The typical histopathological changes are thrombotic microangiopathy with endothelial damage and microthrombi as well as focal glomerular lesions. Stx HUS is characterised by the sudden onset of haemolytic anaemia, thrombocytopenia, and acute renal failure, mostly after a prodromal phase of acute enterocolitis with often bloody diarrhoea. Extrarenal involvement is common in Stx HUS (Siegler 1994). Neurological symptoms, including seizures, coma, stroke, or brainstem involvement are seen in up to one third of patients. Pancreatitis occurs in about 20% of cases. Although pancreatic involvement is often subclinical, permanent insulin-dependent diabetes mellitus may ensue. In Stx HUS, comprehensive supportive therapy is essential. Optimal fluid and electrolyte management, adequate dialysis if necessary, cautious administration of blood transfusion, and avoidance of antibiotics are important (Kaplan et al. 1998; Wong et al. 2000). Despite dramatic improvement in the acute mortality rate, a proportion of patients develops renal long-term sequelae and should be evaluated regularly for many years.

The atypical HUS forms a heterogeneous group (Neuhaus et al. 1997; Fitzpatrick et al. 1993). Hereditary factors, e.g., complement deficiencies, are responsible for familial HUS (Noris et al. 1999); systemic conditions, such as SLE, lupus anticoagulant syndrome, cancer, GN, and pregnancy as well as exposure to toxins or potential toxins, such as cyclosporine A, tacrolimus, OKT 3, mitomycin, and radiation, may be involved in atypical HUS. In idiopathic HUS all known causes for HUS are excluded. The predominant histopathological lesion in idiopathic HUS is arteriolar, thus differing from Stx HUS. The onset of idiopathic HUS is typically insidious, and the course is often progressive. Some patients may run a relapsing or remitting course. The treatment of idiopathic HUS follows the same principles as those of Stx HUS. Plasmapheresis may be beneficial in some patients. As compared to Stx HUS, there are more frequent chronic sequelae, an increased incidence of end-stage renal failure, and a higher mortality rate (Siegler et al. 1996). The risk of recurrent HUS following renal transplantation is increased.

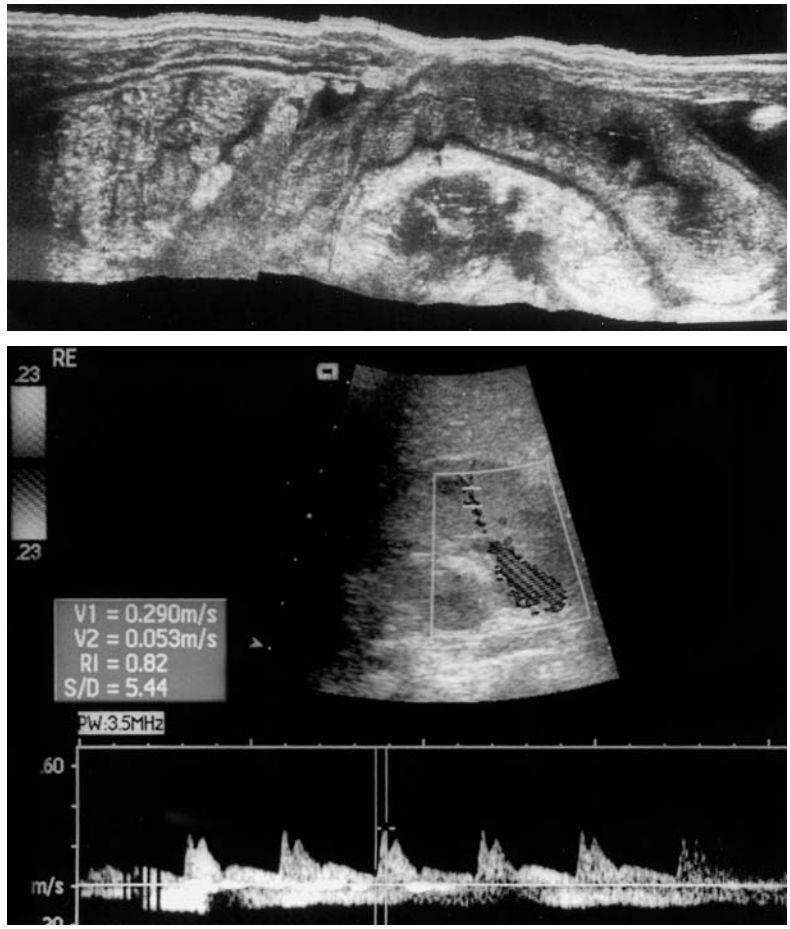


Fig. 19.5a,b. Sonography in haemolytic uremic syndrome (HUS). **a** Severe thickening of the bowel wall caused by severe E. coli enteritis (extended view sonography with tissue harmonic imaging). **b** Alteration of renal parenchymal echogenicity in HUS, with duplex Doppler sonography showing elevated RI (RI = 0,82) due to reduced diastolic flow velocity and increased renal vascular resistance

Thrombotic thrombocytopenic purpura-haemolytic uraemic syndrome (TTP-HUS) is defined by the classical pentad of clinical features: (1) thrombocytopenia, (2) microangiopathic haemolytic anaemia, (3) neurological symptoms and signs, (4) renal functional abnormalities, and (5) fever (Amorosi and Ultmann 1966). Deficiencies of von Willebrand factor (vWF)-cleaving protease activity have recently been demonstrated in patients with TTP-HUS (Furlan et al. 1998; Tsai and Lian 1998). The vWF-cleaving protease usually degrades unusually large vWF (ULvWF) multimers into their normal size range. In case of protease deficiency ULvWFs accumulate and attach to platelets, thereby promoting platelet activation and clotting. Deficiencies of the vWF-cleaving protease activity have been demonstrated in familial TTP-HUS and – due to IgG antibodies with protease inhibitor activity – in non-familial TTP-HUS. These findings explain why with the routine use of therapeutic plasma exchange – by removing autoantibodies and restoring protease activity – TTP-HUS has changed from a fatal to a curable illness (Kwaan and Soff 1997).

Imaging usually starts with abdominal and renal US (including Doppler investigations). Depending on the underlying entity and the severity of the disease, it may show more or less enlarged kidneys with increased parenchymal echogenicity as well as extrarenal changes of the bowel wall and ascites (Fig. 19.5b); alterations in renal perfusion are depicted as reduced vasculature on (a)CDS and increased RI (Garel et al. 1983; Hoyer 1998; Patriquin et al. 1989; Platt et al. 1991; Riccabona 2000). These Doppler findings may be valuable for predicting relapses or improvement and may even serve for prognostic considerations (Scholbach 1999). CT, MRI, and isotope studies are rarely used, although new reports on MRI evaluation of renal blood flow and perfusion may emphasise the future possible role of other imaging modalities in the initial differential diagnosis, the prognosis, as well as for following up these patients (Vallee et al. 2000).

19.4.2.3 Tubulo-Interstitial Nephritis

Acute tubulo-interstitial nephritis (TIN) is an inflammatory disorder affecting the renal tubules and the interstitial space. Glomeruli and vessels may be affected secondarily. Acute TIN is found in immunologic disorders associated with GN such as IgAN, S LE, or in renal allograft rejection. Immune-mediated TIN, infection-mediated TIN, and idiopathic forms are further causes. Drug hypersensitivity is one of the main causes of immune-mediated TIN. A variety of antibiotics, nonsteroidal anti-inflammatory drugs, anticonvulsants, diuretics, and other drugs such as cyclosporine A are involved. Infection-mediated TIN can be divided in cases with direct infection of the renal parenchyma (infectious agents identified in the interstitium such as cytomegalovirus, hantaviruses, or bacteria causing pyelonephritis) and in reactive (sterile) TIN. Sterile TIN is found associated with various infectious agents like Streptococci, Legionella, Yersinia, EBV-virus, Hepatitis B virus, or HIV virus. Idiopathic TIN can be associated with uveitis (Vohra et al. 1999). Clinical presentation is non-specific with fatigue, weight loss, and emesis in most cases; fever may be present. Laboratory investigations show acute mostly polyuric renal failure, signs of tubular dysfunction, sterile leukocyturia, microhaematuria, and mild proteinuria.

The contribution of radiology is restricted to US showing marked enlargement of the kidneys and a more or less diffuse cortical hyperechogenicity (Hiraoka et al. 1996). Normalisation of kidney size seems to parallel improvement of renal function; Doppler findings are unspecific and reflect primarily systemic changes and functional improvement. However, renal interstitial disease may be associated with elevated RI value. Treatment of TIN mostly is supportive. Corticosteroids may be required in severe cases, but prognosis is usually excellent.

19.4.2.4 Tubular Disorders

Numerous disorders can affect one or more of the renal tubular functions, and most of them are inherited diseases. Diagnosis is made by clinical, laboratory, and genetic evaluation. There is little contribution of diagnostic imaging for primary diagnosis, but during the course of the disease US is of value to show secondary parenchymal lesions or to detect side effects of therapy, as most tubulopathies important for imaging lead to nephrocalcinosis and/or urolithiasis (see Chap. 20). It is beyond the scope of this chapter to discuss all possible renal tubular disorders, but we shall briefly name a few important entities (Table 19.3).

Cystinuria may serve as an example of a hereditary aminoaciduria leading to urolithiasis. Bartter's syndrome and distal renal tubular acidosis (d-RTA) are disorders mostly characterised by nephrocalcinosis. The severe polyuria of nephrogenic diabetes insipidus may cause impressive dilatation of the upper urinary tract similar to urinary obstruction

Table 19.3. Renal tubular disorders. **Systematic approach to most recognised tubulopathies.**

Aminoacidurias and renal glycosuria
• Classic cystinuria
• Isolated cystinuria
• Hyperdibasic aminoaciduria
• Lysinuric protein intolerance
• Hartnup disease
• Methioninuria
• Histidinuria
• Iminoglycinuria
• Isolated glycinuria
• Dicarboxylic aminoaciduria
• Renal glycosuria type A, B, and O
Disorders of electrolyte regulation
• X-linked hypophosphataemic rickets
• Idiopathic hypercalciuria
• Familial hypocalciuric hypercalcemia
• Bartter syndromes
• Gitelman syndome
• Familial hypomagnesemia-hypercalciuria
• Dent disease
• Liddle syndrome
• Hyporeninemic hypoaldosteronism
• Pseudohypoaldosteronisms
Disorders of acid-base and water regulation
• Renal tubular acidosis (RTA)
– Distal (type 1)
– Proximal (type 2)
– Hyperkalaemic (type 4)
• Nephrogenic diabetes insipidus
Fanconi syndrome
• Cystinosis
• Galactosemia
• Hereditary fructose intolerance
• Tyrosinemia
• Wilson disease
• Lowe syndrome
Fanconi-Bickel syndrome and idiopathic

("pseudo-obstructive" pattern). X-linked hypophosphatemic rickets (XLH), caused by a mutation of the PHEX gene, is characterised by renal phosphate loss, hypophosphataemia, rickets, and short stature (Drezner 2000). Untreated XLH causes no renal parenchymal lesion. The recommended therapy with calcitriol and phosphate supplementation may lead to nephrocalcinosis; therefore – aside from monitoring laboratory values – repeated skeletal radiographs are necessary to show adequacy of therapy concerning rickets. Renal US is recommended at regular intervals for early detection of nephrocalcinosis as a harmful side effect of therapy.

19.4.3 Renal Parenchymal Involvement in Systemic Disease

19.4.3.1 Systemic Lupus Erythematosus

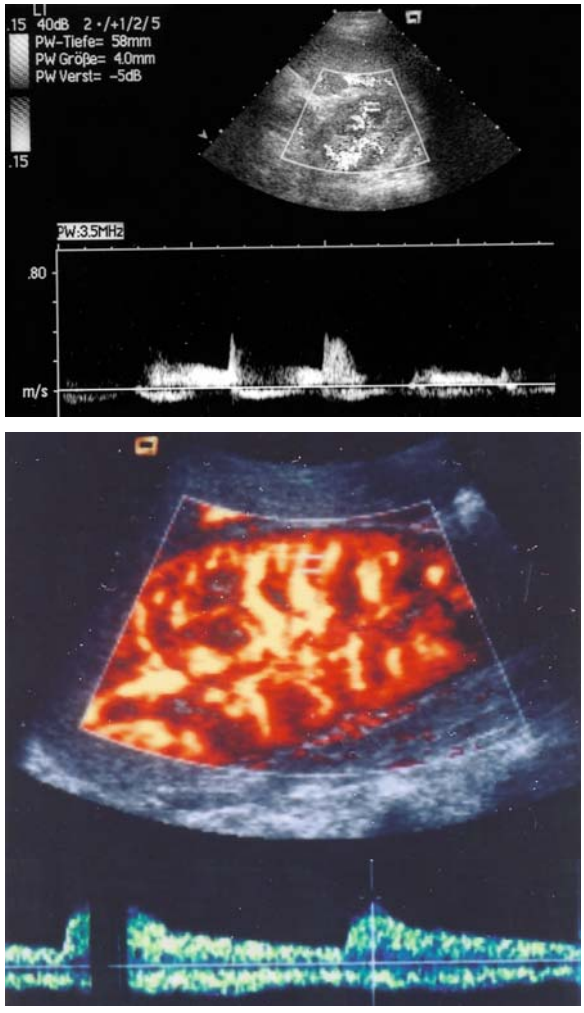
In systemic lupus erythematodes (SLE) a generalised autoimmunity is present with autoantibodies directed against a variety of cell components. Renal manifestation is present in nearly two-thirds of children. The dominant feature of lupus nephritis is proteinuria, frequently leading to a nephrotic syndrome. Microhaematuria, hypertension, and reduced renal function are variably present. Renal biopsy is crucial in all children with SLE who have abnormal urine findings and/or reduced renal function, because of its impact on initial treatment and prognosis. A hallmark of lupus nephritis is its variability, between patients, within biopsies, and even within glomeruli. Lupus nephritis is categorised as class I–VI according to the 1995 WHO classification, ranging from normal glomeruli to advanced sclerosing GN (Cameron 1999). Tubulo-interstitial or vascular disease may also be present. Since SLE is a systemic disease, a wide range of extrarenal manifestations, including non-specific complaints such as fever, weight loss, and malaise may be present. The central nervous system, lungs, musculoskeletal system, skin, heart, or gastrointestinal tract may be affected. Some patients with lupus nephritis have antiphospholipid antibodies which have been associated particularly with renal arterial, venous, and glomerular capillary thrombosis, valvular heart disease, and cerebral thrombosis (Asherson et al. 1996). Haematologic manifestations, hypocomplementaemia, and immunosuppressive therapy contribute to the increased frequency of infections in SLE, which represent a major cause of disability and death.

Treatment of lupus nephritis mainly depends on the histopathologialc findings and activity scoring (Bansal and Beto 1997). Especially corticosteroids, cytotoxic agents, azathioprin, and mycophenolat-mofetil have significantly improved the prognosis of lupus nephritis, and today there is little difference in renal outcome between different WHO classes of nephritis in properly treated patients (Cameron 1999). However, complications of SLE and its treatment, such as sepsis, end-stage renal failure, avascular bone necrosis, thrombosis, and – in the long-term – accelerated atherogenesis, myocardial infarctions, and neoplasia are still seen in a proportion of cases.

Renal imaging usually is performed by US. Depending on the state and severity of the disease the kidneys may look normal or appear as in GN; in severe renal involvement one may observe rarefaction of vasculature on aCDS with elevated RI values in duplex Doppler (Fig. 19.6). Improvement and normalisation of Doppler findings correlate with clinical improvement. Renal biopsy is mandatory for evaluation of the degree of renal involvement. Extrarenal imaging may be necessary in severe extrarenal manifestation, such as MR and CT in cerebral involvement, or echocardiography and cardiac MR in valvular heart disease.

19.4.3.2 Sickle Cell Nephropathy

Sickle cell disease is an inherited haemoglobinopathy with various renal manifestations leading to renal failure in 5 to 18% of the patients at a median age of 23 years (Saborio and Scheinman 1999). Low O_2 tension in the renal microvasculature as well as hypertonicity and low pH of the renal medulla promote deformation of the sickled cells. The increased blood viscosity, functional venous engorgement, and interstitial oedema predispose the kidneys to ischaemia and infarction. Segmental scarring, interstitial fibrosis, dilatation of veins and capillaries, and renal papillary necrosis are the result. The increased renal cortical blood flow leads to hyperfiltration and glomerular hypertrophy with progressive glomerulosclerosis and a declining renal function. The clinical findings are characterised by polyuria, proteinuria, nephrotic syndrome,



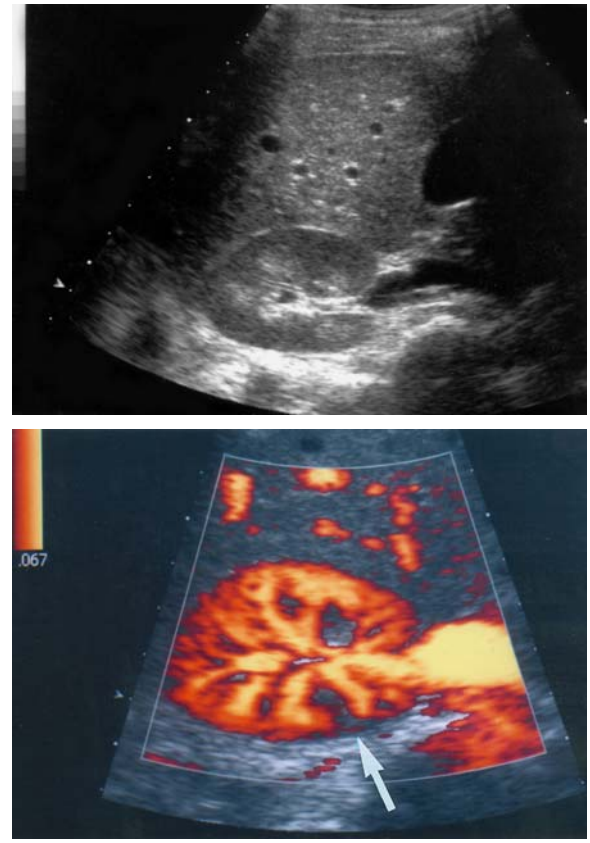
a

b

Fig. 19.6a,b. Sonographic findings in lupus nephritis. **a** Unspecific changes of the renal parenchyma with reduced vasculature on color Doppler sonography and increased RI (peripheral RI = 0,75) on duplex Doppler in acute severe lupus nephritis. **b** Normalization of renal vasculature on amplitude-coded color Doppler sonography with improvement of peripheral RI during treatment (prior to clinical normalization)

and various degrees of haematuria. Proteinuria may start early in life and seems to be associated with severity and progression of nephropathy (Wigfall et al. 2000). Episodes of macrohaematuria are self-limited in most situations, but may be dramatic and prolonged. Rupture of vessels may be the reason for severe haematuria, with the left kidney four times more frequently involved; furthermore renal papillary necrosis may often be discovered in patients with macrohaematuria. Renal medullary carcinoma is an aggressive neoplasm associated with sickle cell disease and may also present with haematuria and flank pain, with the right kidney involved more often (Davis et al. 1995).

When looking at these renal and extrarenal complications the role of imaging becomes evident. The task of paediatric radiology is not the initial diagnosis, but rather the reliable monitoring, yet as non-invasively as possible, to detect any of these sequelae. So radiological investigations include US and (a)CDS as basic investigations to show alterations of the renal perfusion (including screening for renal infarctions, Figure 19.7; or transcranial CDS for cerebral complications, etc.) and to exclude other causes of haematuria such as urolithiasis. Increased echogenicity of renal pyramids in the absence of hypercalciuria is suggestive of sickle cell nephropathy. US may help to detect papillary necrosis, or show renal medullary



a

b

Fig. 19.7a,b. Renal sonography in sickle cell disease. **a** Increased echogenicity of the medulla with consecutively inverted corticomedullary differentiation. In the absence of hypercalciuria, this pattern is typical for sickle cell nephropathy. **b** Amplitude-coded color Doppler sonography of the right kidney (*cross section*) shows a segmental parenchymal area without colour signals (*arrow*), consistent with a renal infarction in sickle cell disease

carcinoma, that usually exhibits a lobulated pattern of the tumour, located within the renal medulla, with areas of necrosis and haemorrhage and satellite nodules in the renal cortex (Davidson et al. 1995). These entities definitely must be confirmed and evaluated by CT or MRI. DMSA scans, CT, or MRI can be of value in special situations such as renal infarction or scarring as well as extra-renal sequelae of the disease (e.g., auto-splenectomy, cerebral infarction, vascular aneurysm and bleeding, etc.). Uncontrolled severe renal bleeding may require angiography and selective embolisation.

Treatment of sickle cell nephropathy is directed to prevent vaso-occlusive crises and to manage renal complications adequately. As a prophylactic measure, altitudes above 2,500 m without oxygen supply should be avoided as well as heavy exercise and fluid deprivation. Bed rest is recommended in gross haematuria, sometimes combined with intravenous fluids and diuretics. ACE inhibitors eventually can diminish proteinuria and ameliorate the progressive course of nephropathy. Renal transplantation seems to be a viable option for adolescents with end-stage renal disease (Warady and Sullivan 1998).

19.4.3.3 Miscellaneous Other Systemic Diseases with Renal Involvement

Renal sarcoidosis is a granulomatous disease of unknown aetiology, with multiorgan involvement (Newman et al. 1997). Renal involvement is mainly attributed to granulomatous interstitial infiltration and hypercalcaemia/hypercalciuria (Casella and Allon 1993). In children proteinuria, leukocyturia, haematuria, concentration defects, and renal failure are the prominent features (Milman et al. 1998). Sonographic appearances are unspecific; other imaging is used to assess not only renal granulomas and pseudotumours, but also manifestations in other body compartments (Herman et al. 1997). Steroid therapy, eventually with methotrexate, may prevent end-stage renal failure (Coutant et al. 1999).

Hereditary amyloidosis encompasses a group of rare autosomal dominant disorders associated with deposition of protein fibrils in beta-pleated sheet configuration. Familial Mediterranean fever (FMF) is an autosomal recessive disease occurring in patients of Mediterranean descent. FMF manifests clinically with recurrent attacks of fever and abdominal pain as well as arthritis. In FMF, renal amyloidosis may present with a nephropathy that progress through proteinuria and nephrotic syndrome to renal failure unless cholchicine is administered in time (Zemer et al. 1986). Since amyloidosis is a systemic disease, other organs such as the thyroid gland may be involved as well (Mache et al. 1993). Renal amyloidosis may also be an important complication of chronic disease or persisting infection. US shows a varying degree of diffusely increased echogenicity in bilaterally enlarged kidneys, the other findings (CDS, duplex Doppler, isotope studies) depend on the disease status and actual renal function.

19.4.3.4 Renal Manifestations of Metabolic Disorders

A variety of metabolic disorders may affect the kidneys. The basic metabolic abnormality – eventually with a toxic metabolic product – can cause tubular dysfunction and tissue changes. Other disorders primarily lead to glomerular damage with hyperfiltration, glomerular hypertrophy, and progressive glomerulosclerosis. Metabolic disorders frequently do not present as primary renal diseases, but show involvement of the central nervous system, the liver, and the haematopoetic system. Most renal lesions are not specific for any metabolic disease. Nevertheless, the changes may be pronounced like the enlarged, hyperechoic kidneys sometimes with additional nephrocalcinosis found in hereditary tyrosinaemia (Forget et al. 1999). Another example are the CDG syndromes (= carbohydrate-deficient glycoprotein Sy), a group of inherited, multisystemic metabolic diseases with heterogeneous presentation often showing kidney involvement with hyperechoic cortex or medulla and poor cortico-medullary differentiation at normal renal size (Hertz-Pannier et al. 2000). One disorder with deleterious effects for the kidneys is primary hyperoxaluria type I which manifests as nephrocalcinosis and/or urolithisasis (see Chap. 20).

Diabetic nephropathy (DN) is the most important single disorder leading to chronic renal failure during adulthood with a peak incidence after 15 to 20 years of insulin-dependent diabetes. A variety of factors contribute to progression from silent DN with microalbuminuria to overt DN with proteinuria, hypertension, and declining renal function. Glomerular hypertrophy/hypertension with hyperfiltration is an early pathophysiolgical marker for progression. Functional markers seem to correlate well with an increase of kidney volume on ultrasound evaluation

(Cummings et al. 1998; Lawson et al. 1996). Thus US could give valuable information for long-term monitoring of DN that is mainly used in adults, but there is no indication for further renal radiological investigation. Good metabolic control and early therapy with ACE inhibitors are essential therapeutic measures to prevent overt DN (Casani et al. 2000).

Glycogen storage diseases (GSD) represent several enzymatic defects of glucose metabolism with GSD type I as a main type for renal involvement. The metabolic dearrangement leads to hepatic storage of glycogen, hypoglycaemia, lactic acidaemia, hyperlipidaemia, and growth failure. Overt renal disease is similar to DN with proteinuria and progressive renal dysfunction eventually leading to end-stage renal failure. This can be prevented by optimal dietary therapy. US can demonstrate hepatic and renal enlargement with unspecific diffuse alteration of the parenchymal echogenicity and texture. Furthermore imaging with US, CT, and/or MRI is used during follow-up, as focal hepatic lesions usually representing hepatic adenomas may undergo carcinomatous transformation, a serious long-term complication (Wolfsdorf and Crigler 1999).

Methylmalonic acidemia is an inborn error of metabolism leading to renal tubular dysfunction and to progressive renal failure in many cases. Renal disease seems to be caused by toxic products of metabolism and can be ameliorated by good metabolic control. Renal US is not specific. Further imaging may be required according to chronic renal failure or after transplantation, as combined liver-kidney transplantation is a promising therapeutic option (also see Chap. 21) (van't Hoff et al. 1999).

19.4.3.4.1 Cystinosis

Nephropathic cystinosis is an autosomal recessive inherited disorder resulting from a defective lysosomal transport of cystine. The cystinosis gene has been mapped to chromosome 17p13 (Town et al. 1998). Biochemically, the disorder is characterised by intracellular accumulation of cystine in the kidneys and nearly all other organs like the bone marrow, leukocytes, the thyroid gland and the cornea, but the renal symptoms predominate. Affected patients present during infancy with vomiting, dehydration, polydipsia, polyuria, failure to thrive, and sometimes with rickets. Laboratory investigations show the typical signs of proximal tubular dysfunction (Fanconi syndrome) lsuch as acidosis, potassium wasting, hypophosphataemia, glucosuria, and generalised aminoaciduria. Diagnosis is made by demonstration of cystine crystals within the bone marrow and by demonstration of elevated cystine content in leukocytes. Treatment includes proper correction of electrolyte and fluid disturbances and administration of the drug cysteamine reducing the intracellular content of cystine. Nevertheless, progression to end-stage renal failure can just be delayed, but not prevented nowadays. Renal transplantation is possible, but cannot prevent accumulation of cystine in other organs eventually leading to hypothyroidism, cardiac failure, and cerebral complications.

Radiological investigations contribute little to the primary diagnostic approach. Echogenicity may not be specifically increased on renal US; skeletal radiography can show rickets. Repeated US can contribute to monitoring therapy and – by detection of early changes of renal parenchymal/medullar echogenicity and cortico-medullary differentiation – help to prevent severe nephrocalcinosis (Saalem et al. 1995; Theodoropoulos et al. 1995). Further renal and extra-renal imaging is needed in chronic renal failure and after transplantation (see also Chap. 21). Cystinosis encephalopathy is a long-term problem in patients reaching adulthood after renal transplantation. Cerebral atrophy and cystine deposition – especially in the basal ganglia – are the predominant findings. CT and MRI can contribute significantly to diagnosis and follow-up (Broyer et al. 1996).

Conclusion

RPD represents a vast variety of entities differentiated only by clinical, laboratory, histologic, and genetic findings. US including (a)CDS as initial imaging usually is unspecific, but contributes to the differential diagnosis and to monitoring. Imaging furthermore helps in renal biopsy, in evaluation of associated extrarenal disease, and in detection of complications during the course of the disease.

19.5 Advanced Imaging

19.5.1 Advanced Sonography and Doppler Sonography

Modern sonographic techniques have widened the sonographic diagnostic potential in paediatric nephrourology (Riccabona et al. 2001, 2002, 2004, 2005, 2006). High resolution transducers allow for better tissue differentiation and depiction of tiny structures, helpful to early visualisation of subtle renal parenchymal changes (e.g., tiny cysts, dilated tubules, small or tubular calcifications, etc.) (Fig. 19.3). (Tissue) harmonic imaging (HI) improves delineation of cysts and of the collecting urinary system; it furthermore enhances tissue differentiation and particularly improves visualisation of cortico-medullary differentiation (Choudhry et al. 2000; Desser et al. 1999; Girard et al. 2000). Contrast-enhanced HI or new contrast-specific imaging techniques may further improve tissue evaluation by enabling dynamic studies of contrast inflow, uptake, and wash-out; however these technique have not jet been evaluated extensively for application in paediatric RPD (Burke et al. 2000; Claudon et al. 1999; Girard et al. 2000). Duplex Doppler and (a)CDS are applied to visualise vasculature and evaluate flow as well as flow pattern. In general, diseases limited to the glomeruli do – relatively regardless of the severity of the disease – not affect the RI significantly, or may even decrease RI (particularly inflammatory disease), whereas tubulo-interstitial and vascular diseases may increase RI (Hoyer 1998; Piaggo et al. 1999; Platt et al. 1991; Platt et al. 1997; Siegel 1995; Taylor 1994; Vade et al. 1993). However, all these findings still are affected by many other factors and by renal function and therefore are just another part in the puzzle of the differential diagnosis. aCDS improves visualisation of peripheral/cortical renal vasculature/perfusion that may help to evaluate focal disease or diffuse alteration with reduced renal perfusion (Babcock et al. 1996; Bude et al. 1994; Gainza 1995; Preidler et al. 1996; Riccabona et al. 1997; Riccabona et al. 2000; Riccabona et al. 2001; Rubin et al. 1994; Scholbach 1999) (Figs. 19.4, 19.7). The combination of these modalities enables a non-invasive diagnosis of various perfusional disturbances, as some examples may demonstrate:

- Renal vein thrombosis may be an essential differential diagnosis in neonatal RPD (also see Chap. 23). In renal vein thrombosis arterial RI of the enlarged kidney with increased echogenicity is increased due to congestive changes, with better identification of this entity using high frequency transducers (Wright et al. 1996). The central renal vein may still be patent in early stages of peripheral renal vein thrombosis, or may show flow disturbances such as increased flow velocity and spectral broadening in partially thrombosed veins. In central renal vein thrombosis, no venous flow can be visualised. CDS can demonstrate regression of thrombosis and improvement of arterial perfusional waveforms during thrombolytic treatment much earlier than clinical improvement or regression of gray scale findings (Hoyer 1998). Remnants after renal vein thrombosis may be difficult to diagnose sonographically and may require additional imaging such as MR and (MR) angiography.
- In (pseudo-) nutcracker syndrome the left renal vein is compressed. This leads to venous congestion of the left kidney creating intermittent haematuria and pain. The left kidney consecutively is asymmetrically enlarged; the left renal vein shows a marked change in diameter at the pre- or retro-aortal crossing, with elevated flow velocity, turbulent flow, and arterialised pulsatility of the flow pattern due to propagation of the pulsation of the abdominal aorta [and superior mesenteric artery in pseudo-nutcracker syndrome (Scholbach 1999)] (Fig. 19.1).
- In inflammatory RPD (e.g., GN) the parenchyma of the more or less enlarged kidney usually shows an altered cortico-medullary differentiation with varying changes of parenchymal echogenicity. In early stages or mild disease perfusion patterns are normal, or RI may be decreased due to increased diastolic flow velocity. In severe disease with compromised renal function RI increases and eventually even systolic flow velocities may decrease (Figs. 19.5, 19.6). These findings reflect a complex system: various renal compartments may be affected in different diseases such as vasculitis, inflammation, oedema, or interstitial fibrosis. Doppler findings are furthermore influenced by extra-renal factors such as heart rate and function, medication, or blood concentration, and therefore may vary and are not specific (Gill et al. 1994; Knapp et al. 1995; Kuzmic et al. 2000; Mostbeck et al. 1991).

- In HUS, severe GN, and acute obstruction, RI is increased due to high renal parenchymal or vascular resistance (Garel et al. 1983; Patriquin et al. 1989; Platt et al. 1990, 1991; Riccabona et al. 1993). RI changes correlate well with the course of the disease and may be used as a prognostic factor. Differentiation of single event or recurrent disease in HUS with poorly differentiated, hyperechogenic kidneys may be supported by flow volume measurements that demonstrate reduced renal perfusion in patients with bad prognosis and poor outcome (Scholbach 1999).
- Evaluation of the amount of renal perfusion and assessment of flow profiles may be helpful for studying acute and chronic renal failure. Phenomena such as the cortical halo, diffuse/focal vessel rarefaction on aCDS, increased RI values, reduced flow velocities, or atypical venous flow profiles in cardiac/congestive renal failure are as unspecific as those changes observed in renal transplants (also see Chap. 21) (Figs. 19.4–19.6). However, they may help in the differential diagnosis and hint towards a certain disease entity (Hoyer et al. 1999; Platt et al. 1991; Riccabona et al. 1997). They may furthermore serve as an additional valuable parameter for follow-up, as normalisation of these sonographic findings may precede clinical improvement.
- Focal renal infarction, e.g., in sickle cell disease or in vascular disorders that sometimes also cause hypertension, as well as other focal renal disease can be detected using (a)CDS, in some cases even supported by administration of intravenous echo-enhancing agents (Riccabona et al. 2000) (Fig. 19.7). Other focal renal parenchymal changes such as papillary calcinosis or renal calcifications may be picked up by CDS using the "twinkling artifact" as a diagnostic tool (Cehfouh et al. 1998; Rahmouni et al. 1996). Thus equivocal echogenic spots on grey scale US without definite shadowing may be differentiated, reducing the need for ionising imaging in some patients and helping to narrow down the list of differential diagnoses (e.g., papillary necrosis, dysplastic calcifications, and nephrocalcinosis; see also Chap. 20).

All these modern sonographic modalities may also be incorporated in the initial imaging. This depends on local circumstances, diagnostic algorithms, and the individual facilities, equipment and staff. The more complex this modality becomes, the more specific investigations need high-end equipment and sonographers who are skilled and experienced in properly handling this task in the paediatric population – therefore often these modern sonographic modalities are only used at specialised referral centres, such as contrast enhanced voiding ultrasonography (ce-VUS), which is increasingly used and promoted for VUR detection in some countries and centers (Riccabona et al. 2008, see Table 19.4, see also Chap. 1.1).

Table 19.4. Procedural guideline: contrast-enhanced voiding urosonography (ce-VUS) (from Riccabona et al. 2007)

No diet restriction or enema, urine analysis …

↓ Accepted indications: VUR-follow-up, girls, family screening, bedside

↓ Catheterism: feeding tube, 4-8 french, or suprapubic puncture anaesthetic lubricant or coated plaste

↓ Latex precaution: neuro tube defect, bladder exstrophy

Standard US of bladder & kidneys (supine, ± prone)

↓ Bladder filling with NaCl (only from plastic containers)

US contrast medium, e.g., Levovist® – 300 mg/ml, 5%–10% of bladder volume slow, US-monitoring, potentially fractional administration

Peri-/ post-contrast US of bladder & kidneys

↓ US modalities: fundamental, HI, CDS, dedicated contrast imaging alternate scans of right & left side during & after filling

During + after voiding: US of bladder & kidneys supine ± prone, sitting or standing

VUR diagnosis: echogenic micro-bubbles in ureters or renal pelves

CDS = colour Doppler sonography,
aCDS = power Doppler,
ce-VUS = contrast-enhanced voiding urosonography,
HI = Harmonic Imaging,
US = ultrasound,
VUR = vesico-ureteral reflux

19.5.2 Renal Biopsy

As discussed above, histological classification of RPD remains essential for therapeutic and prognostic assessment as well as for monitoring complications during treatment of RPD (e.g., cyclospo-

rine A toxicity). Therefore renal biopsy still is an essential tool in paediatric nephrology (Cohen et al. 1989). After the introduction of–usually sonographically–guided renal biopsy the incidence of complications during and after the procedure has been reduced. Nevertheless, there still exists a considerable risk for possible complications such as intrarenal, perirenal, abdominal (in transplanted kidneys), and urinary tract bleeding (especially dangerous if a clot threatens to congest the urinary collecting system) as well as post-biopsy arteriovenous fistula (AVF) with its implicated potential sequelae (Diaz and Donadio 1975; Dodge et al. 1962; Karafin et al. 1970; Merkes et al. 1993; Pälvensalo et al. 1984; Proesman et al. 1982; Riccabona and Ring 1995; Riccabona et al. 1998; Zeis et al. 1976). Various contraindications for percutaneous needle biopsy have to be considered: coagulopathies, uncontrolled hypertension, and severe hydronephrosis as absolute contraindications. Relative contraindications are abscesses, large cysts, sever pyelonephritis, tumours, some variants of abnormal vascular supply, and single, ectopic, or horseshoe kidneys. In these situations "open", surgical renal biopsy allows a safe procedure and viewing of the kidney with specific selection of certain areas of interest. It furthermore avoids spread of malignant cells or infection.

Sonographically guided renal biopsy is performed in prone position, with a percutaneous dorsal access to the lower pole of the left kidney, often using a needle guide; for renal transplants an anterior access in supine position is used (Fig. 19.8). One to three specimens are obtained under systemic analgo-sedation and ECG and pulsoxymetric monitoring using a 16–20 gauge core biopsy needle with real time visualisation of the needle and the major vessels during the procedure. The adequacy of the sample can be evaluated immediately by visual inspection or by microscopy. Small red dots (representing the glomeruli) should be present in the sample. The sample size is particularly important in FSGS, SLE, and crescentic nephritis.

Post-biopsy evaluation of possible complications is recommended. Sonography is usually performed immediately after the procedure, after 4 to 8 h, and 24 h after the intervention, as well as on demand (e.g., clinical deterioration of the patient or clinical symptoms of bleeding, etc.). Some degree of subcapsular or perirenal haematoma is considered "physiological"; more extensive haemorrhage needs proper immobilisation and monitoring of the patient, as well as treatment if symptomatic (Fig. 19.9). CDS should be applied to detect post-biopsy AVF, as these need an altered post-biopsy regime (anti-hypertensive medication, drugs that do not affect competence of renal vascular regulation, prolonged immobilisation and careful mobilisation, clinical monitoring). CDS findings should always be confirmed by duplex Doppler evaluation that demonstrate shunt flow at the AVF as well as various flow changes of the feeding and draining vessel, such as decreased arterial RI and arterialised flow pattern in the draining vein with higher flow velocities (Middleton et al. 1989; Riccabona et al. 1998) (Fig. 19.9). Usually these AVFs are asymptomatic and diminish spontaneously. However, some persist and may become symptomatic with macrohaematuria and hypertension. Uncontrolled bleeding and symptomatic AVF usually then indicate catheter angiography with embolisation; acute clotting with urinary tract obstruction may require percutaneous drainage (see Chap. 26). In patients with equivocal sonographic findings CT or MR angiography should be performed to establish the definite diagnosis. CT-guided renal biopsy should be avoided in childhood for radiation issues except for selected

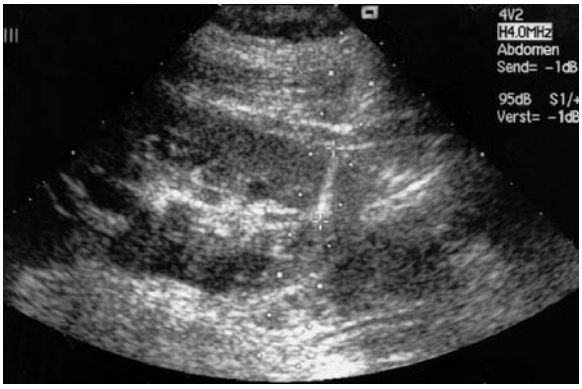


Fig. 19.8. Sonographically guided renal biopsy using the needle guide attached to the transducer: the dotted lines show the path of the needle and help to guide the biopsy needle (18 gauge core cut needle, performed with a biopsy gun) for safe puncture as well as retrieval of sufficient specimen material. The image is retrospectively taken from the cine-loop analysis of the needle movement during biopsy (useful for documentation and analysis of the procedure): The callipers mark the length of the intraparenchymal needle track (1.7 cm)

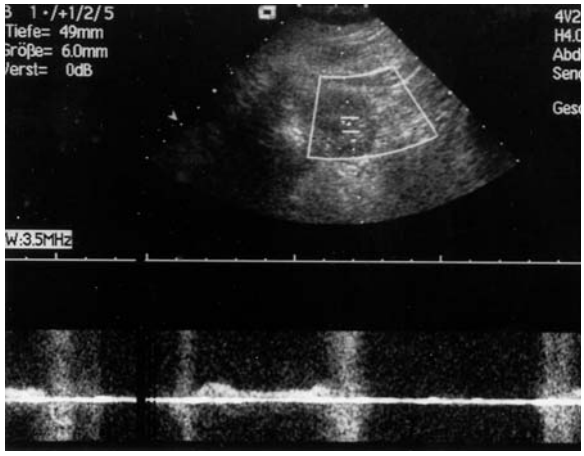


Fig. 19.9. Imaging of complications after renal biopsy. Color Doppler sonography depicted an area with atypical colour signals and color aliasing suspicious for an arteriovenous fistula. Duplex Doppler sonography trace confirms the shunt flow of a post biopsy arteriovenous fistula

cases with insufficient sonographic visualisation of the kidney or with specific (multi-)focal pathology not adequately picked up on US.

19.5.3 Role of Other Imaging Modalities

Plain film (for renal calculi and nephrocalcinosis), IVU (e.g., for diagnosis of medullary sponge kidney, otherwise today replaced by MRI – if available), contrast-enhanced CT, and isotope studies are rarely used for the diagnosis or differential diagnosis of RPD, except for nephropathy secondary to urinary tract malformations or infections. However, imaging findings such as enlarged kidneys, flattened take-up and wash-out curves on isotope studies, delayed contrast enhancement with vague cortico-medullary differentiation on CT, or calcifications may be noticed in some patients as an incidental finding. These must be properly recognised to initiate further diagnostic workup. MRI is not used in RPD to date; however, there might be a future role for advanced MR techniques (e.g., perfusion or diffusion imaging, BOLD techniques, new and/or intracellular contrast agents such as USPIO and spectroscopy) in differentiating various entities or quantifying vital renal tissue, thus perhaps reducing the need for renal biopsies in some diseases.

19.5.4 Imaging of Complications and Imaging in Motoring Chronic Disease

19.5.4.1 Monitoring in Renal Complications

Renal complications are rare except for deterioration during the course of the disease. However, de novo disease may evolve such as tumour in end stage kidneys or complications such as increasing calcifications in tubular disorders with obstructive calculi and renal colic may occur. Infection may occur, renal artery stenosis may develop in vasculitis, or a post-biopsy AVM may be present. Depending on the individual query these entities have to be evaluated and considered. This necessitates at least a minimal imaging follow-up strategy that should be adapted to the individual situation. In general, regular US is sufficient; some queries necessitate scintigraphy (relative renal function, scars, etc.), MRI (tumour, infarction, etc.), MR angiography (major renal vessel anomaly), or catheter angiography (peripheral RASt, PTA, AVF embolisation, etc.). Furthermore, as RPD may lead to end-stage renal failure and to renal transplantation, imaging (US and particularly VCU) is important to assess the urinary bladder situation, as this will be a prerequisite for successful future treatment (see Chap. 21).

19.5.4.2 Imaging of Extra-Renal Complications/ Manifestations and Treatment-Induced Changes

Depending on the underlying disease, various extra-renal complications may occur; involvement of other organs, primarily or secondary to therapy, may be present. These changes may influence patient management, prognosis, outcome and quality of life. Therefore they have to be considered when treating these patients and following them during the course of their disease. The most important aspects are skeletal changes during corticosteroid therapy or as a manifestation of the ongoing disease (e.g., osteoporosis, avascular necrosis, extrarenal clcifications and hyperostosis, etc.) evaluated by plain film and MRI (Fig. 19.10). Rarely CT is used for differential diagnosis in a suspicious lesion to define the entity (Table 19.5). Furthermore, associated changes in systemic or syndromal disease must be evaluated appropriately necessitating a wide range of imaging in the individual case. The detailed description

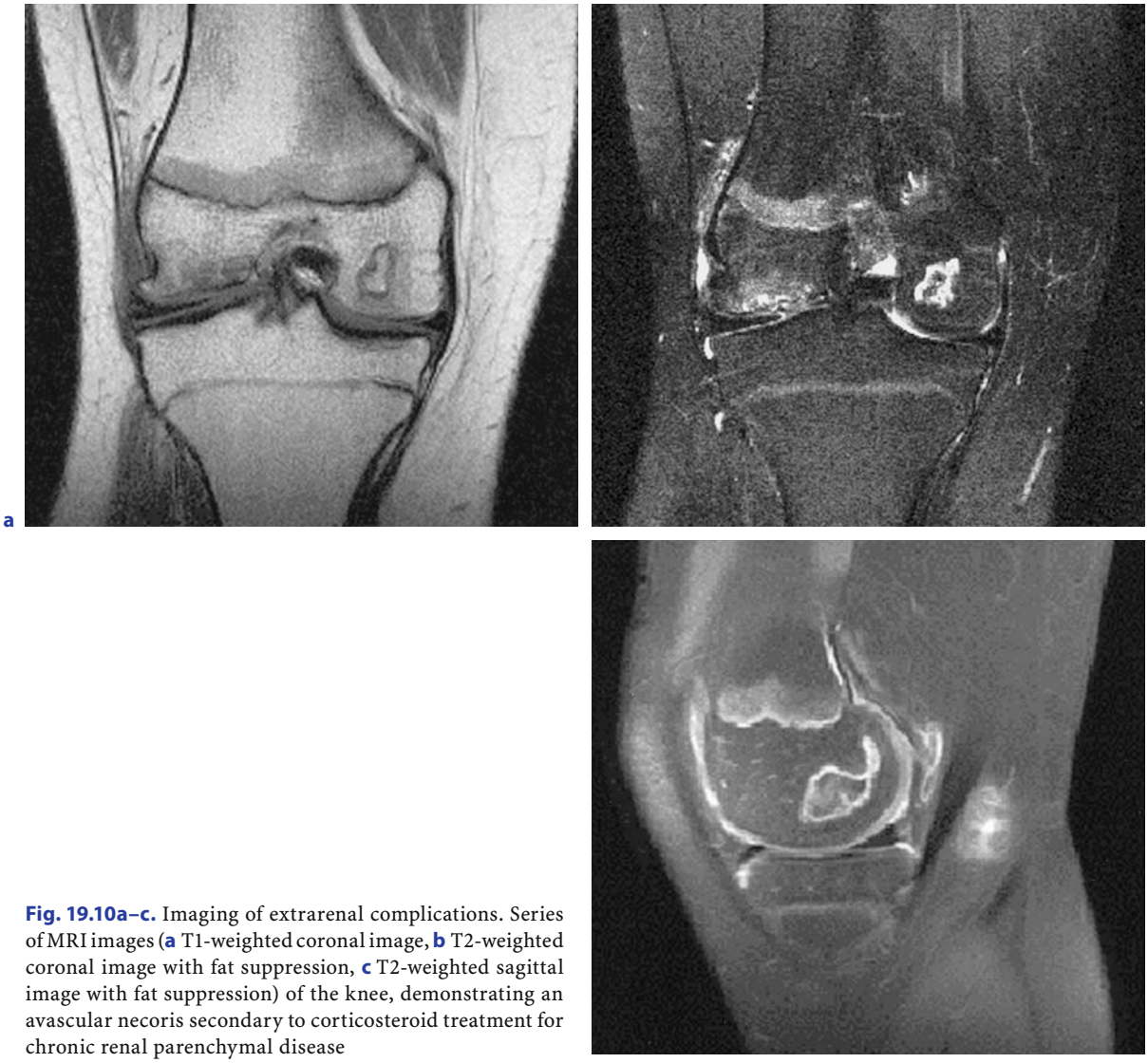


Fig. 19.10a–c. Imaging of extrarenal complications. Series of MRI images (**a** T1-weighted coronal image, **b** T2-weighted coronal image with fat suppression, **c** T2-weighted sagittal image with fat suppression) of the knee, demonstrating an avascular necoris secondary to corticosteroid treatment for chronic renal parenchymal disease

Table 19.5. Imaging of extrarenal complications and manifestation in renal parenchymal disease. This table gives a short overview of the various imaging methods used for imaging of extrarenal changes and complications arising during treatment or as a complication during the course of the disease with regard to the affected compartment or organ and the clinical query

Skeletal anomaly (including hyperostosis, calcifications, etc.)	=> Plain film
Renal osteodystrophy (osteoporosis, etc.)	=> Plain film DEXA, CT (osteodensitometry)
Avascular necrosis (bone)	=> Plain film, MRI, scintigraphy
Cardiac disease (valvular disease, effusion, myocardial hypertrophy, associated malformation, etc.)	=> Echocardiography, chest film, cardiac MR
Vascular anomalies (AVM, aneurysm, vasculitis, etc.)	=> US, MR/catheter angiography
Malignant transformation (e.g., liver adenomas) and other extrarenal manifestation of a systemic disease (e.g., Goodpasture syndrome, etc.)	=> US, CT/MRI
CNS involvement (e.g., infarction in sickle cell disease, cranial haemorrhage, central venous thrombosis)	=> MR, CT, transtemporal CDS

and discussion of all these findings and the various modalities used for imaging cannot be included in this chapter due to space restrictions.

Conclusion

Advanced imaging consists mainly of US focusing on modern sonographic techniques. However, diagnosis is often established only by histology necessitating sonographically guided renal biopsy. For imaging of various complications, US may be complemented by CT, MRI, and plain film, in particular for extrarenal changes related to RPD or medical treatment.

19.6 Conclusions

A variety of histologically different RPDs and pathogenitically different entities with varying prognosis and therapy may clinically present in a similar way. Here imaging is needed, may help in the differential diagnosis or – as often is the primary task – can rule out other disease such as malignancy, obstructive uropathy, or congenital conditions. Other diseases such as vascular disorders may be depicted; this ability to help to define the diagnosis gives particularly US an essential role in the early diagnostic workup of patients with clinically suspected RPD. However, even modern imaging modalities like harmonic imaging, aCDS, echo-enhanced US, or MRI to date cannot properly define the individual underlying entity; thus renal biopsy remains necessary. Here again imaging helps to monitor the procedure and to reduce or to detect complications. Furthermore, imaging is helpful for monitoring the disease process, not only with regard to renal changes, but also to extra-renal associated pathology. Thus imaging can play a significant role for the clinician dealing with RPD, although these renal diseases do not represent a major imaging domain and in general cannot precisely be diagnosed or reliably be ruled out by imaging.

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Urolithiasis and Nephrocalcinosis

20

Gabriele Benz-Bohm and Bernd Hoppe

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G. Benz-Bohm, MD, Professor
Birresborner Strasse 40, 50935 Cologne, Germany
formerly
Department of Radiology, Division of Pediatric Radiology, University of Cologne, Kerpenerstrasse 62, 50924 Cologne, Germany
B. Hoppe, MD
Professor, Department of Pediatrics, Division of Pediatric Nephrology, University of Cologne, Kerpenerstrasse 62, 50924 Cologne, Germany

20.1 Definition

Urolithiasis and nephrocalcinosis (NC) are the two types of calcification associated with the urinary tract. Urolithiasis is macroscopic calcification in the urinary collecting system. Urinary stones are composed of crystal agglomerations, sometimes mixed with proteins. Stones are formed on the renal papillae by retention of lithogenic particles, either by obstruction or by adherence to damaged renal epithelium (Bruwer 1979; Laufer and Boichis 1989). This takes place when urine is supersaturated with regard to stone-promoting factors, e.g., increased calcium or oxalate excretion, or because the inhibitor activity is reduced, e.g., low citrate excretion (Karlowicz and Adelman 1995; Verkoelen et al. 1998). Nephrocalcinosis is microscopic calcification in the tubules, tubular epithelium, or interstitial tissue of the kidney. It is classified according to the anatomic area involved. Medullary NC is differentiated from cortical NC and diffuse NC. In a variety of diseases urolithiasis and NC occur together (Hoppe et al. 2007).

20.2 Incidence

Urolithiasis in children has a wide geographic variation, being more frequent in the Far and Middle East (< 1% of children) and less common in North America and Europe (1–5 per 10,000 children). Within the United States, urolithiasis is more common in the southeast, where it may be found in 1 in 1,000 to 1 in 7,600 hospital discharges (Stapleton 1996).

Boys are affected more often than girls, particularly in the younger age group (Bruziere and

Roubach 1981). Although stones used to be most common during the first 5 years of life, there is now a more equal age distribution (Brühl et al. 1987), at times even with a strong preponderance in children over 10 years old (Hoppe et al. 2007). In contrast to the infectious stones, which are mostly found in infants and young children, the incidence of calcium stones increases from the age of 5 years. In contrast to adults, uric acid stones are very rare in childhood, at least in the Western world: Western Europe 1%, Eastern Europe and the Middle East 5%–10% (Table 20.1) (Basaklar and Kale 1991; Brühl et al. 1987). Primary bladder stones used to be very frequent, but have almost disappeared in the Western world (Ashworth 1990). Stones are less frequently seen in black children. There is a family history in more than one-third of cases (Danpure 2000).

The incidence of NC is not yet known, but it is very common in metabolic disorders in which it can be seen as frequently as urolithiasis, e.g., in primary hyperoxaluria (Latta and Brodehl 1990), or where it is even the single form of crystal agglomeration and deposition, e.g., in Bartter's syndrome (Buckalew 1989; Karlowicz and Adelman 1998). Preterm infants in particular seem to be prone to NC, which was said to be due to a higher excretion of lithogenic factors, but now seems more and more to be caused by an extremely low urine inhibitory activity by hypocitraturia (Fig. 20.1). The incidence reported, however, differs drastically between 10% and 65% with a level of 15% in our premature infants (Hufnagle et al.1982, Jacinto et al. 1988, Schell-Feith et al. 2000, Sikora et al. 2003, Sonntag and Schaub 1997).

More than 10% of patients have bilateral stones (Bruziere and Roubach 1981). However, this percentage may decrease with earlier diagnosis.

Table 20.1. Renal stone analysis in infants and children in Germany with infrared spectroscopy (From Brühl et al. 1987). Stones are listed in order of decreasing radiopacity

Stones	Girls *n*=350	Boys *n*=500
Calcium oxalate	63.4%	58.2%
Weddellite (monohydrate)	27.7%	29.2%
Whewellite (dihydrate)	35.7%	29.0%
Infectious	24.6%	29.0%
Struvite	12.9%	15.0%
Carbonate-apatite	9.7%	12.8%
Ammonium hydrogenurate	2.0%	1.2%
Other phosphate stones		
Brushite	1.7%	3.2%
Cystine	0.3%	1.2%
Uric acid	1.4%	2.2%
Uric acid dihydrate	0.3%	0.6%
Proteins	1.4%	1.6%
Artifacts	6.9%	4.0%

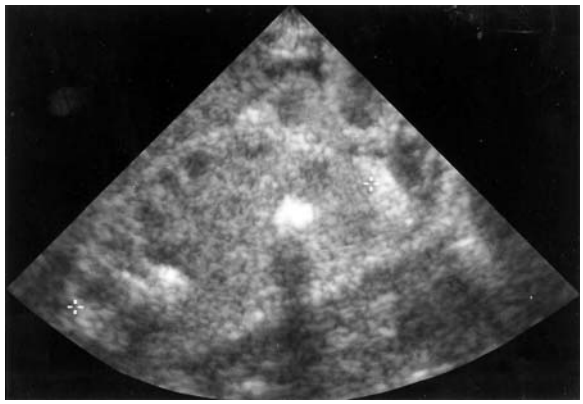


Fig. 20.1. A 3-day-old premature boy with feto-fetal transfusion syndrome, hypercalciuria and hypocitraturia. Sonogram of right kidney showing nephrolithiasis and nephrocalcinosis

20.3 Clinical Findings

The most common symptoms of urolithiasis are abdominal pain, sometimes clearly identifiable as colicky pain, urinary tract infection, gross or microscopic nonglomerular hematuria and, more rarely, flank tenderness or urinary retention. Diagnosis is easily missed if stones are not specifically looked for. Small stones may not be detectable even when their presence is strongly suggested. Recurrent urinary tract infections or unexplained sterile pyuria, secondary to noninfectious stones, may provide a clue.

In contrast to patients with urolithiasis, the clinical presentation of NC is often asymptomatic especially during infancy. Renal colic has been suspected in some infants with NC and urolithiasis, but is difficult to prove. Renal ultrasound screening may detect NC in high-risk infants or as part of the diagnostic

evaluation of urinary tract infection. Common clinical signs are gross or microscopic hematuria, acute increases in blood pressure and urinary tract infection. Sterile leukocyturia may also be the first sign of NC (Hoppe et al. 2007; Karlowicz and Adelman 1995).

20.4 Diagnostic Imaging

High-resolution ultrasonography (US) is the optimal imaging method for detecting and monitoring NC. The routine use of US in premature infants and in children at risk of developing NC has resulted in a large increase in the number of conditions reported to be associated with NC (Table 20.2) (Hernanz-Schulman 1991; Jéquier and Kaplan 1991; Nayir et al. 1995; Shultz et al. 1991). It has also been increasingly recognized that urolithiasis and NC can coexist in the same patient (Alon 1997; Karlowicz and Adelman 1995) (Figs. 20.2–20.4).

The sonographic diagnosis of medullary NC can be suggested only when increased echogenicity is localized in the area of the renal medulla. Normally the pyramids are anechoic relative to the cortex. In general the severity of NC can be reliably interpreted with an US grading scale (Table 20.3, Fig. 20.4) (Dick et al. 1999).

The brightest renal medullary pyramids probably result from interstitial calcium deposition. Patriquin and Robitaille (1986) correlated the sonographic development of medullary NC with four patterns in vivo with Anderson-Carr's postmortem pathologic study, which described the progression of intrarenal stone formation (Bruwer 1979). In contrast to the interstitial calcium deposition, intratubular calcifications are more common in neonatal NC (Katz et al. 1994).

The varying responses of experimental NC reflect the complex and multifactorial etiology of NC best. There are two distinct forms of experimental NC in rats: diffuse, but predominantly corticomedullary following sodium phosphate, and predominantly cortical following calcium glucomide (Fourman 1959). Phosphate-induced NC in rabbits occurs maximally at the corticomedullary junction, but also frequently in the cortex, seldom in the medulla. NC was not permanent or stable, but improved on return to a normal diet (Cramer et al. 1998b).

Table 20.2. Common causes of nephrocalcinosis and differential diagnosis

Nephrocalcinosis	Common causes
Medullary	Adrenal insufficiency
	Bartter's syndrome (Fig. 20.13)
	Bone metastases
	Cushing syndrome
	Hypercalciuria
	Hyperoxaluria
	Hyperparathyroidism
	Hyper-, hypothyroidism
	Idiopathic hypercalcemia
	Lipoid necrosis (Fig. 20.10)
	Lesch-Nyhan syndrome (Fig. 20.14)
	Lowe's syndrome
	Malignant neoplasm
	Medication: furosemide, dexamethasone
	Medullary sponge kidney (Fig. 20.12)
	Nutrition: long time parenteral nutrition, ascorbic acid supplementation
	dRTA (Fig. 20.4)
	Tyrosinemia
	Sarcoidosis and other granulomatous diseases
	Sickle cell disease
	Vitamin D, A intoxication (Fig. 20.11)
	William's syndrome, Wilson's disease
Cortical	Chronic hypercalcemia
	Lipoid necrosis
	Ethylene glycol intoxication
	Primary hyperoxaluria
	Sickle cell disease
Differential diagnosis	Acute cortical necrosis
	Alport syndrome
	Chronic glomerulonephritis
	Kidney transplant rejection
	Pyelonephritis
	Renal tuberculosis
	Renal vein thrombosis (Fig. 20.16) (Lam and Warren 1980)
	Tamm-Horsefall depositions (Fig. 20.15)

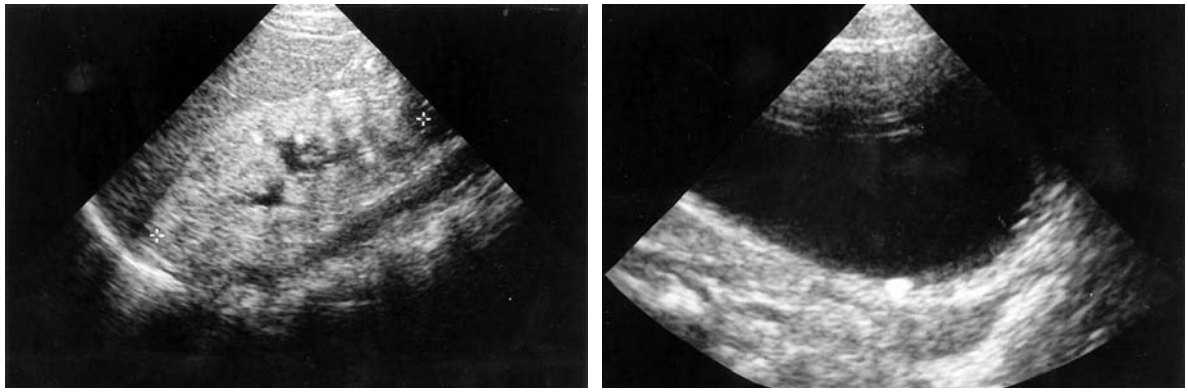


Fig. 20.2a,b. A 10-month-old girl with primary hyperoxaluria type I. **a** Sonogram of right kidney showing diffuse nephrocalcinosis. **b** Sonogram of bladder showing a small stone

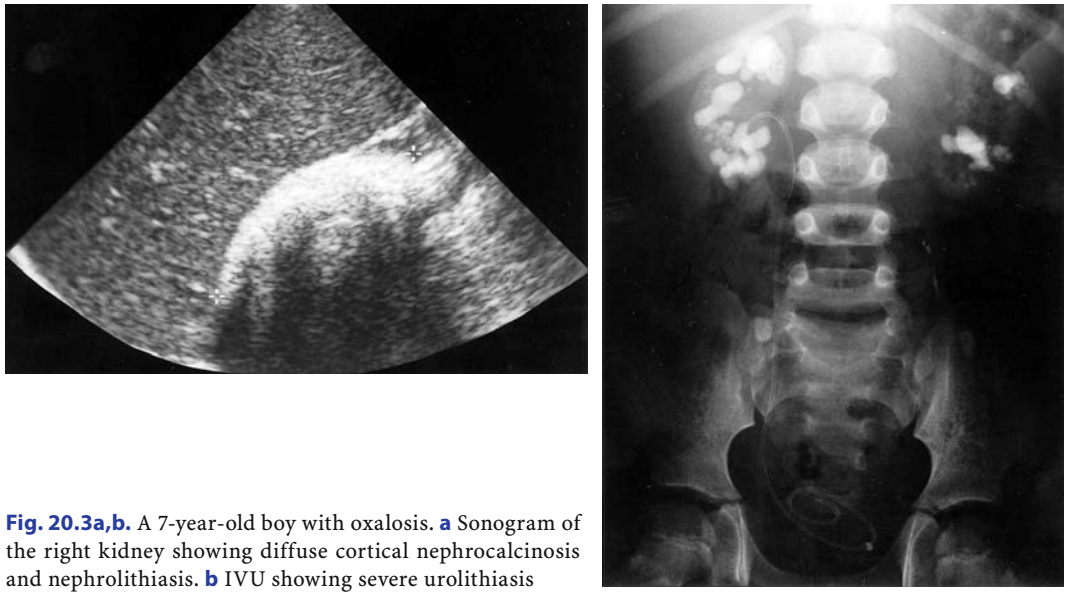


Fig. 20.3a,b. A 7-year-old boy with oxalosis. **a** Sonogram of the right kidney showing diffuse cortical nephrocalcinosis and nephrolithiasis. **b** IVU showing severe urolithiasis

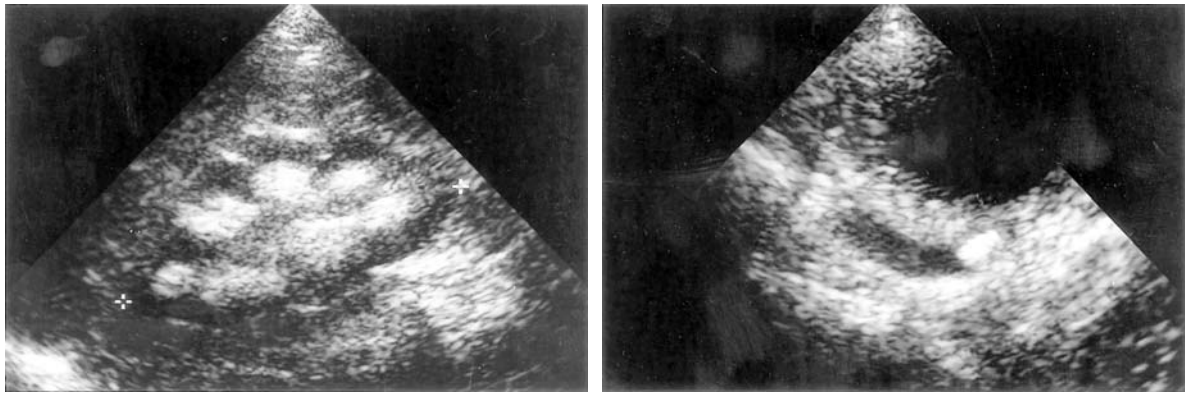


Fig. 20.4a,b. A 4-year-old boy with incomplete RTA and hyperoxaluria. **a** Sonogram of right kidney showing medullary nephrocalcinosis grade III (Dick et al. 1999). **b** Sonogram of bladder showing an ureteral stone on the right immediately before the ureterovesical junction

Table 20.3. Nephrocalcinosis grading scale (from Dick et al. 1999)

Grade I	Mild increase in echogenicity around the border of the medullary pyramids
Grade II	Mild diffuse increase in echogenicity of the entire medullary pyramids
Grade III	Greater, more homogeneous increase in the echogenicity of the entire medullary pyramid

Cases of asymmetric NC are described in children with hypercalcemia as being due either to unilateral renal vein thrombosis or unilateral hydronephrosis (Navarro et al. 1998).

Only the association of echogenic pyramids with posterior acoustic shadow is visible on abdominal X-ray. Macroscopic aggregates of calcification seem to be necessary for this (Glazer et al. 1982).

The echogenicity of the renal cortex in neonates is increased (Haller et al. 1982). Therefore detection of cortical NC may be difficult. However, cortical NC develops within a few weeks of acute renal cortical necrosis, after which time it may be evident radiographically as a rim of cortical calcification (Leonidas et al. 1971). Diffuse cortical NC by primary hyperoxaluria is most evident both by US and X-ray (Fig. 20.3) (Akhan et al. 1995; Cremin et al. 1982).

The correlation of US, CT, pathology, and renal function of experimental NC in rabbits demonstrated a better sensitivity for US (96%–64%), but a better specificity for CT (96%–85%) (Cramer et al. 1998a).

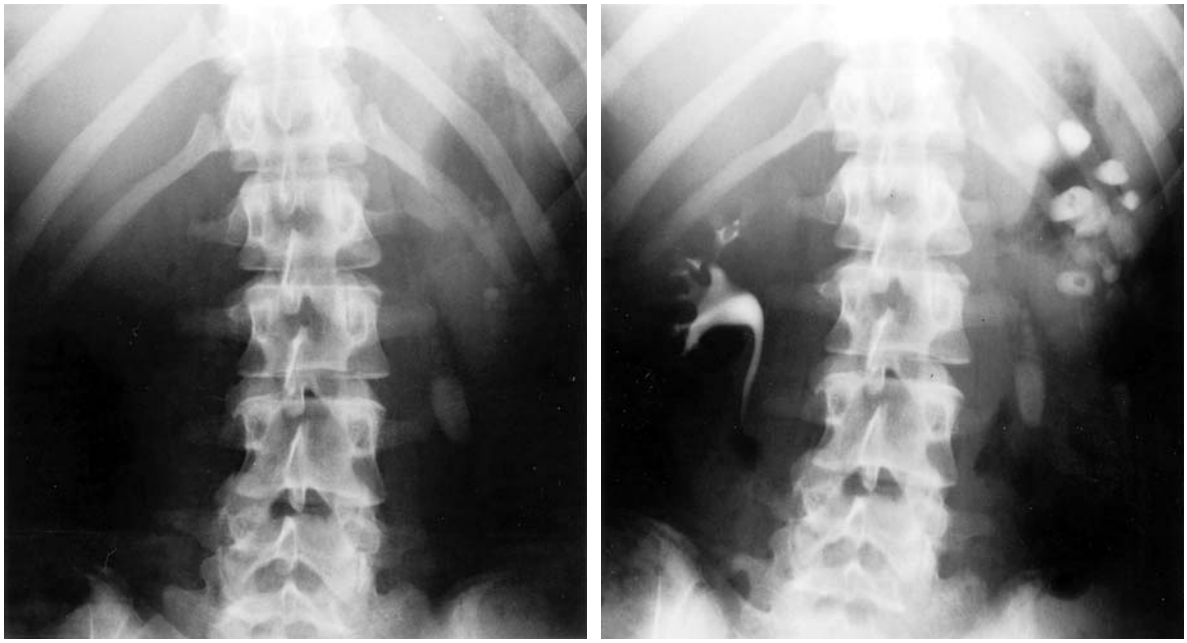
Most urinary tract calculi are visible in X-ray examination as a result of their calcium content (Table 20.1). Calcium oxalate stones may occur in either a pure monohydrate or dihydrate form. Pure calcium phosphate stones and calcium oxalate monohydrate stones are the densest calculi for their small size. Calcium oxalate dihydrate stones may be spiculated or mamillated and are somewhat less dense than other pure stones of equivalent size.

Struvite stones composed of magnesium ammonium phosphate are of low radiopacity in their pure form. This material frequently forms a complex with calcium phosphate, which provides increased radiopacity and may produce a laminated radiographic appearance in the staghorn stone.

Cystin stones may develop as small stones or also assume a staghorn configuration. Because of their sulfur content, they are less opaque than calcium stones. The density is typically homogeneous, similar to that of ground glass (Fig. 20.5) (Dyer and Zagoria 1992; Dyer et al. 1998).

Table 20.4. Diagnostic procedure in urolithiasis/nephrocalcinosis

Patient's history	Familial stone disposition
	Stone recurrence
Stone localization	US, abdominal X-ray,
	Low-dose CT
Lab	Electrolytes, uric acid, creatinine, urea, Mg, PO4, plasma oxalate, acid base status, AP
Urine	Culture, sediment
	24 h urine ⇒ promotors and inhibitors
Renal function	Clearance
Diet	Daily fluid intake ⇓, meat ⇑, milk ⇑⇑
Drugs	Diuretics, ACTH
	Vitamin D, A, C overdose
	Allopurinol
	Chemotherapy
Inherited metabolic disorders	Cystinuria
	Primary hyperoxaluria
	Xanthinuria
	2,8-Dihydroxyadeninuria
	dRTA
	Dent's disease
	Lesch-Nyhan syndrome
	Wilson's disease
	Bartter's syndrome
	William's syndrome
	Lowe's syndrome
Chronic diseases	Malabsorption syndromes (e.g., cystic fibrosis)
	Steatorrhea
	Celiac disease
	Short bowel syndrome
Immobilization	Hypercalciuria
Stone analyses	Infrared spectroscopy,
	X-ray diffraction
Differential diagnosis	E.g., appendicitis



a b

Fig. 20.5a,b. A 17-year-old girl with cystinuria. **a** Abdominal plain radiograph showing urolithiasis on the left. **b** IVU showing hydronephrosis on the left due to urolithiasis

Most stones are found in the renal pelvis and/or calyces, the ureter (Figs. 20.3–20.6), and the bladder; they are rarely found in the urethra. The most common ureteral calcification is a stone that has migrated from the kidney. Stones typically become impacted at points of anatomic narrowing in the urinary tract and may be difficult to detect when they overlie bony structures such as the sacrum. To detect a ureteral stone by US may be difficult, but a concomitant hydroureter or hydronephrosis due to a ureteral stone might lead to diagnosis. In general high-resolution US in combination with abdominal X-ray is mostly sufficient for diagnosis. Intravenous urography (IVU) is seldom necessary, except before extracorporeal shock wave lithotripsy (ESWL).

The comparison between non-contrast-enhanced CT and IVU in adults suspected of a ureteric obstruction by stone demonstrated that non-contrast-enhanced CT is more effective than IVU in precisely identifying ureteric stones (Smith et al. 1995). Spiral CT underscores the concept that the "radiolucent calculus" is a thing of the past-virtually all urinary calculi are visible on CT (Mindell and Cochran 1994). Because of the sedation and the radiation dose, spiral CT is very seldom used for detecting urinary tract stones in children, and then only in late childhood as low-dose CT (Fig. 20.7) (Kluner et al. 2006; Poletti et al. 2007).

Conclusion

High-resolution US is the best method for detecting and monitoring nephrocalcinosis. Low-dose CT may be necessary to detect urolithiasis, but only in late childhood.

20.5 Etiology

Urine is a supersaturated solution that may change its concentration very drastically within a short time. It is therefore not surprising that stone formation or the development of NC may take place when the delicate interplay between promoters (e.g., calcium, oxalate, and uric acid) and inhibitors (e.g., citrate, magnesium, and glycosaminoglycans) is disturbed (Evan 2005; Karlowicz and Adelman 1995; Ryall 1996).

A low urine volume and/or fluctuations in the urinary pH both lead to changes in the solubility product and can therefore predispose to stone formation and stone growth (Coe et al. 1992). A urinary pH of less than 6.0 will increase the risk of uric acid and calcium oxalate stones, whereas a urinary

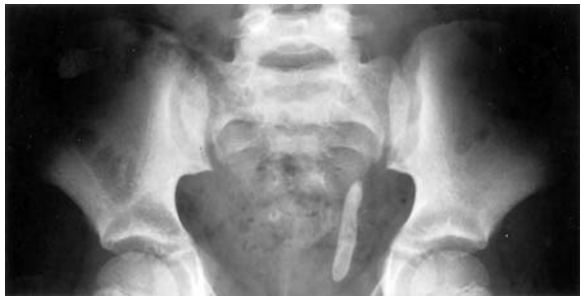


Fig. 20.6. An 8-year-old boy with primary hyperparathyroidism, hypercalciuria, and urinary tract infection. Abdominal plain radiograph showing a huge ureteral stone on the left immediately before the ureterovesical junction

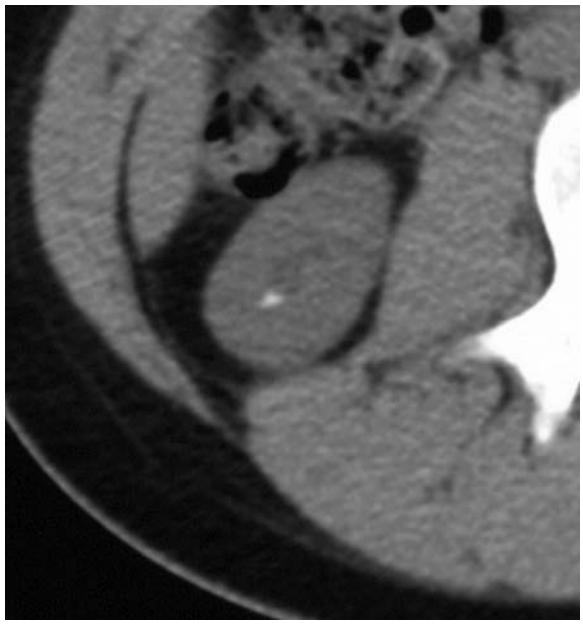


Fig. 20.7. Low-dose CT in nephrolithiasis, not diagnosed by US. A 14-year-old girl

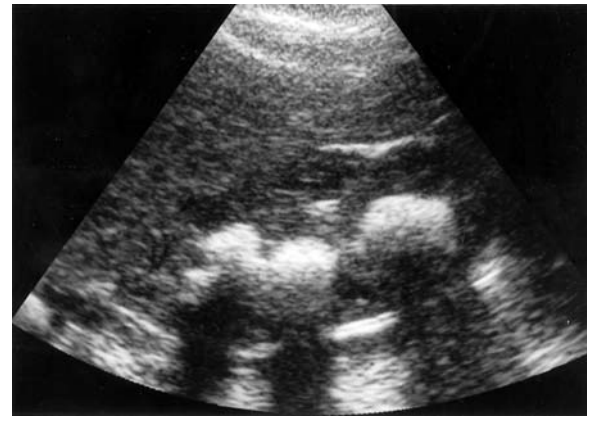


Fig. 20.8. A 5-month-old boy with recurrent urinary infection (*Proteus mirabilis*). Sonogram of the right kidney showing multiple stones (struvite 70%, carbonate-apatite 30%)

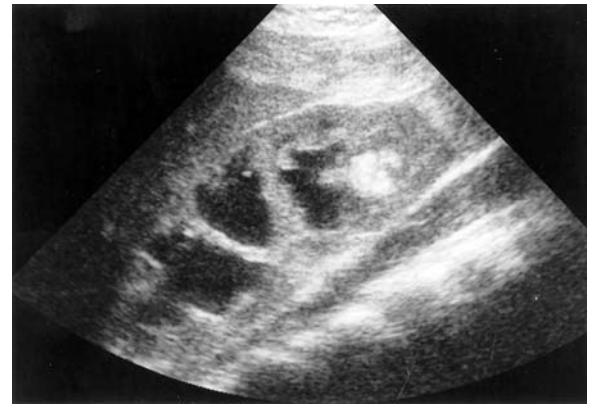


Fig. 20.9. A 3-month-old boy with ureteropelvic junction obstruction. Sonogram of right kidney showing hydronephrosis and nephrocalcinosis

pH greater than 7.4 increases the chances of calcium phosphate precipitation.

An infectious (Fig. 20.8) or metabolic cause for stone formation is detected in the majority of pediatric patients (Hoppe et al.2007). All children with urolithiasis should therefore undergo careful examination (Table 20.4). Anatomical anomalies are often found to be the reason for stone disease. Renal calculi then develop due to disturbances in urine transport, because of urine stasis or flow changes (Fig. 20.9) (Burton et al. 1995).

The stone composition is important for interpretation and for hints of the possible etiology. The results of stone analysis depend on the origin of the children examined and the country where they are living (Table 20.1).

20.5.1 Promoters

20.5.1.1 Hypercalciuria

Hypercalciuria is one of the most frequent conditions in urolithiasis and NC (Table 20.5; Fig. 20.1). There is no sharp limit between normal (up to 0.1 mmol, 4 mg/kg per day) (Ghazali and Barratt 1974; de Santo et al. 1992) and abnormal, except for very

Table 20.5. Metabolic disturbances associated with urolithiasis/nephrocalcinosis

Hypercalciuria	
Normocalcemic hypercalciuria	Idiopathic hypercalciuria
	dRTA
	Diuretics-furosemide
	Bartter's syndrome
	Wilson's disease, Lowe's syndrome
Hypercalcemic hypercalciuria	Primary hyperparathyroidism
	Immobilization
	Hyperthyroidism
	Hypothyroidism
	Cushing syndrome–ACTH therapy
	Adrenal insufficiency
	Hypervitaminosis D, A
	Idiopathic hypercalcemia of childhood
Hyperoxaluria	
	Primary hyperoxaluria type I, II, (III)
	Secondary hyperoxaluria
	Malabsorption syndromes
	Lack of intestinal Oxalobacter formigenes
	Short-bowel syndrome
	Dietary
Cystinuria	
	Type I, II
Hyperuricosuria	
	Inborn errors of metabolism
	Lesch-Nyhan syndrome
	Glycogen-storage diseases type I, III, V, VII
Overproduction in:	Leukemia
	Non-Hodgkin's lymphoma
	High-protein diet
Hypocitraturia	
	dRTA
	Idiopathic
	Treatment related (e.g., calcineurin inhibitors)

high excretions (> 0.2 mmol/kg per day). Whether such children will form stones or develop NC also depends on other factors, e.g., urine volume, pH, and the concentration of the other urinary constituents, primarily of oxalate and citrate (Hesse et al. 1986; Hoppe et al. 1997).

Primary-idiopathic-hypercalciuria is the most common cause of calcium-containing stones (Coe et al. 1992). It has traditionally been divided into renal and absorptive subtypes (Stapleton 1983). Theoretically, in patients with an empty stomach, urinary calcium excretion is elevated in the former, renal, but normal in the latter, absorptive, subtype. Many pediatric patients, however, cannot easily be classified.

Finally, there is a rare, but extremely severe form of idiopathic hypercalciuria leading to progressive NC and renal failure: X-linked hypercalciuric nephropathy with tubular proteinuria, also called Dent's disease (Lloyd et al. 1996).

Medullary NC and calcium phosphate stones are common in patients with distal renal tubular acidosis (dRTA) (Fig. 20.4) (Buckalew 1989; Gückel et al. 1989). A high urinary pH, hypercalciuria, and hypocitraturia contribute to these findings (Hamm 1990). In the complete form of dRTA the urine pH cannot be lowered to less than 6.1 after an acid loading test (Hesse and Vahlensieck 1986).

Medullary NC with hyperechogenic cortex has recently been described in children with tyrosinemia. This rare disease, occurring in 1:100,000 live births, is often combined with an impaired renal function: aminoaciduria, hypercalciuria, tubular acidosis (Forget et al. 1999).

There are several clinical entities leading to hypercalcemia with secondary hypercalciuria (Breslau 1994). Primary hyperparathyroidism, although the most frequent cause of hypercalcemic hypercalciuria in adults, is very rare in children (Fig. 20.6) (Damiani et al. 1998). NC and nephrolithiasis due to subcutaneous fat necrosis with hypercalcemia are described in neonates (Fig. 20.10) (Gu et al. 1995). Hypervitaminosis D due to administration of multivitamin preparations including vitamin D (Fig. 20.11), or due to vitamin D added to milk preparations, can induce hypercalcemia and hypercalciuria (Davies 1989; Jacobus et al. 1992). An excessive daily intake of vitamin A, > 10,000 units, may also lead to hypercalcemia and can induce hypercalciuria (Ragavan et al. 1982). Immobilization for as little as 4 weeks will lead to a reduction of bone calcium and bone mass of about 15%–20% accompanied by hypercalciuria (Zanchetta et al. 1996).

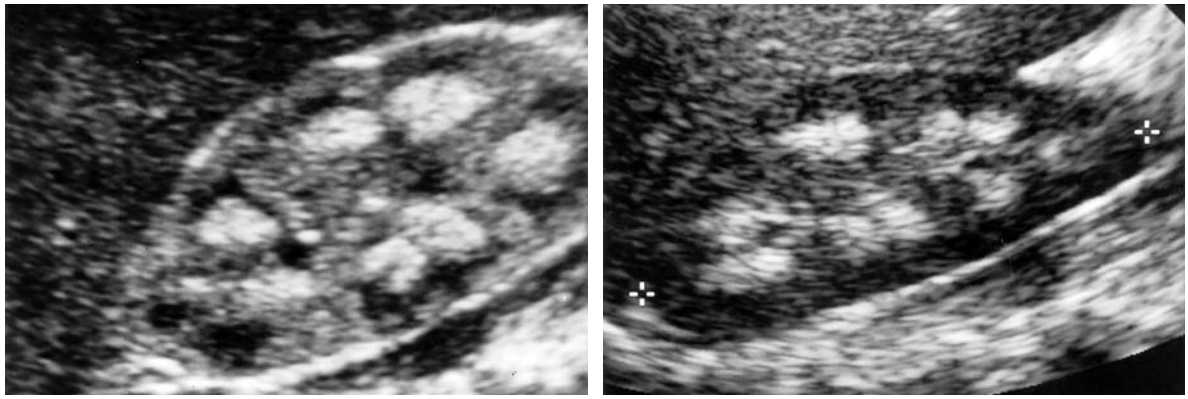


Fig. 20.10a,b. Boy with subcutaneous fat necrosis. **a** Sonogram of right kidney at 2 months. **b** Sonogram of right kidney at 2 years, still showing medullary nephrocalcinosis

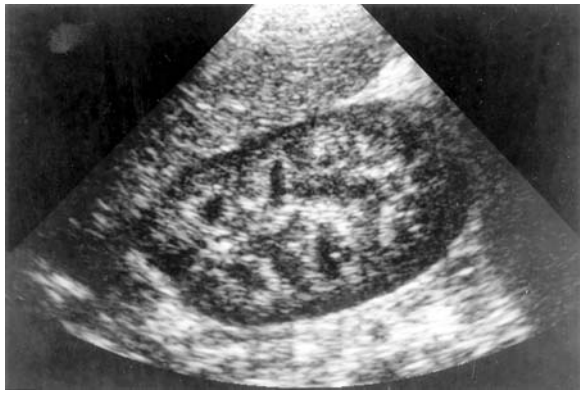


Fig. 20.11. A 3-year-old girl with opsismodysplasia under vitamin D and phosphate therapy. Sonogram of right kidney showing mild increase in echogenicity around the border of the medullary pyramids, grade I (Dick et al. 1999)

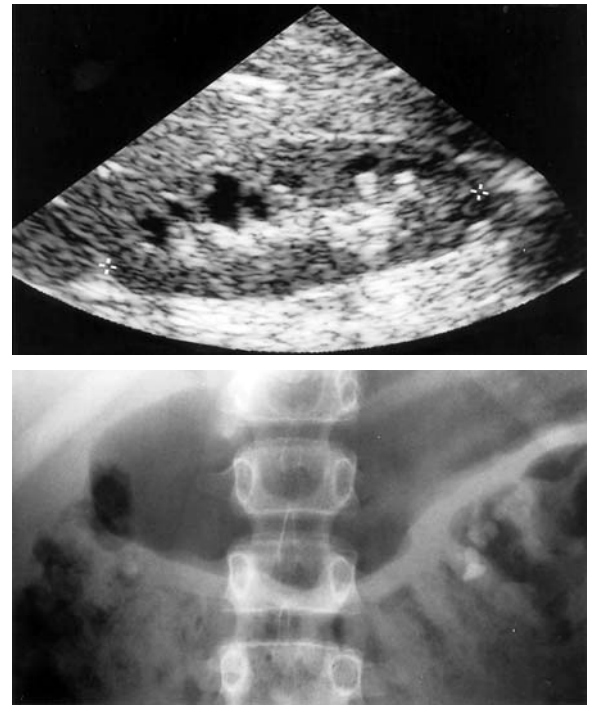


Fig. 20.12a,b. An 11-year-old boy with medullary sponge kidney and hypercalciuria. **a** Sonogram of right kidney showing dilated collecting ducts and nephrocalcinosis. **b** Abdominal X-ray showing renal stones on both sides

Long-term administration of furosemide (Downing et al. 1991; Libenson et al. 1999; Myracle et al. 1986; Pope et al. 1996) or dexamethasone and ACTH (Rausch et al. 1984) can lead to hypercalciuria, NC, or stone disease (Alon et al. 1994; Hufnagle et al. 1982; Kamitsuka and Peloquin 1991). Hypercalciuria is also found in children with medullary sponge kidney (Fig. 20.12) and in several syndromes, either linked to the pathogenesis Bartter's syndrome (Gückel et al. 1989), William's syndrome (Cote et al. 1989) or due to renal tubular damage (Wilson's disease, Lowe's syndrome) (Hoppe et al. 1993b; Sliman et al. 1995). Patients with Bartter's syndrome develop NC, but no stones (Table 20.2, Fig. 20.13). Further conditions include hyper- and hypothyroidism, Cushing syndrome, adrenal insufficiency and metastatic malignant bone disease (Coe et al. 1992; Laufer and Boichis 1989), long-term assistant ventilation (acid base changes) and long-term parenteral nutrition, e.g., in very low birth weight infants (Campfield and Braden 1989; Hoppe et al. 1993a; Pfitzer et al. 1998; Sikora et al. 2003).

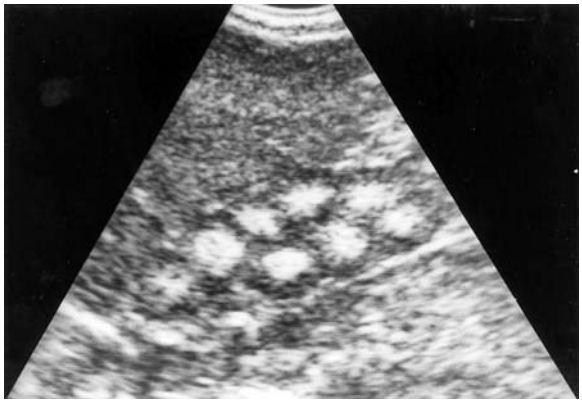


Fig. 20.13. A 7-week-old premature boy with Bartter's syndrome. Sonogram of right kidney showing medullary nephrocalcinosis

20.5.1.2 Hyperoxaluria

Hyperoxaluria is probably still an underestimated cause of stone formation, although oxalate is a more important risk factor than calcium (Fig. 20.3) (Williams and Wandzilak 1989). Therefore, even slightly elevated values are relevant (Leumann et al. 1987). Urinary oxalate is mostly of endogenous origin; only 5%–10% derive from the daily nutritional intake (Williams and Wandzilak 1989).

Primary hyperoxaluria type I (PH I) (Fig. 20.2) is a rare, autosomal recessive inherited disease caused by a defect in glyoxylate metabolism with low or absent activity of liver-specific peroxisomal alanine-glyoxylate aminotransferase (AGT) (Danpure 1989). The AGXT gene is located on chromosome 2q36–37 (Purdue et al. 1991). The disease prevalence is two patients per million population (Kopp and Leumann 1995) in Europe.

PH I is characterized by a highly elevated urinary excretion of oxalate and glyoxylate (>0.8 mmol/1.73m^2 body surface area per day, normal <0.5). The urine is saturated with respect to calcium oxalate, which causes renal calculi, (medullary) NC, or both. With disease progression and declining renal function, calcium oxalate crystals are deposited in the parenchyma of other organs, as well as in bones and the retina (Leumann and Hoppe 2001).

There is great clinical, biochemical, and genetic heterogeneity: some patients suffer early renal failure due to NC, while others only have occasional passage of stones in adult life with preserved renal function (Leumann and Hoppe 2001). Renal stones or medullary NC are usually the first signs of PH I (Akhan et al. 1995). However, diagnosis of PH I is often delayed for many years (Kopp and Leumann 1995). Thus, it is important to exclude PH I in all calcium oxalate-stone formers.

Primary hyperoxaluria type II (PH II) gene on chromosome 9p11 is less frequently observed than PH I. It is characterized by increased urinary excretion of oxalate and l-glyceric acid due to a defect of both liver-specific d-glycerate dehydrogenase and hydroxypyruvate reductase (Marangella et al. 1992; Cregeen and Rumsby 1999). Urinary glyoxylate excretion is normal. The clinical course of PH II is much milder than in PH I, although its clinical characteristics are comparable (Hicks et al. 1983). End-stage renal failure is rather the exception (5%–10% of patients) (Marangella et al. 1994).

Slightly elevated urinary oxalate excretion and plasma oxalate levels in patients may indicate another not yet well-defined form of primary hyperoxaluria (type III?) (Monico and Milliner 1999; Rose 1988). Patients have severe recurrent urolithiasis, but may respond even to low doses of pyridoxine (Edwards and Rose 1991; Hoppe et al. 2007).

Secondary-enteric-hyperoxaluria is a typical complication in patients with diseases involving fat malabsorption, e.g., cystic fibrosis, chronic inflammatory bowel diseases (Crohn's disease), and short-bowel syndrome (Hoppe et al. 1998; Karlowicz and Adelman 1998; Sidhu et al. 1998). Normally, oxalate is intestinally bound to calcium to form insoluble calcium oxalate, which is not absorbed. In patients with enteric hyperoxaluria, calcium instead binds to fatty acids, so more soluble oxalate is absorbed (Williams and Wandzilak 1989). Secondly, patients with cystic fibrosis lack intestinal oxalate-degrading bacteria, Oxalobacter formigenes, which will increase free and absorbable intestinal oxalate (Sidhu et al. 1998). Up to 50% of our patients with cystic fibrosis have hyperoxaluria and nearly 15% develop urolithiasis or NC (Hoppe et al. 2005). Enteric hyperoxaluria may also lead to progressive NC and/or recurrent urolithiasis (Neuhaus et al. 2000).

20.5.1.3 Cystinuria

Cystinuria is one of the most frequent genetic disorders with an overall prevalence of 1:7,000 and an autosomal recessive inheritance. It is caused by a defective transport of cystine and the dibasic amino

acids lysine, ornithine, and arginine through the epithelial cells of the renal tubule and intestinal tract. Two types of cystinuria are now differentiated according to the disease-specific genotype (Font-Llitjos 2005). In addition, there are differences in intestinal transport, which is either disturbed or completely blocked (Horsford et al. 1996). Whether stones are formed depends not only on cystine excretion, but also on urine volume and pH (Fig. 20.5).

20.5.1.4 Hyperuricosuria

Uric acid stones are rarely found in children. Hyperuricosuria results from high-purine diets, myeloproliferative disorders, tumor lysis syndrome, enzyme defects, etc. (Table 20.5). Many drugs, e.g., probenecid and high-dose salicylates, also increase uric acid excretion. However, low urine pH and low urine volume are far greater risk factors for stone formation than hyperuricosuria per se.

Some rare inherited deficiencies of the purine-salvage enzymes hypoxanthine-phosphoribosyltransferase (HPRT) and adenine-PRT (APRT) lead to primary purine overproduction (Table 20.5). X-linked Lesch-Nyhan syndrome occurs in complete deficiency of HPRT. It is characterized by mental retardation, self-mutilation, choreoathetosis, gout, and uric acid NC (Fig. 20.14) (Cameron et al. 1993). Partial deficiency of HPRT results in urolithiasis and renal failure (Choi et al. 1993). Gout and nephrolithiasis have also been reported in glycogen storage disease type I (Restaino et al. 1993).

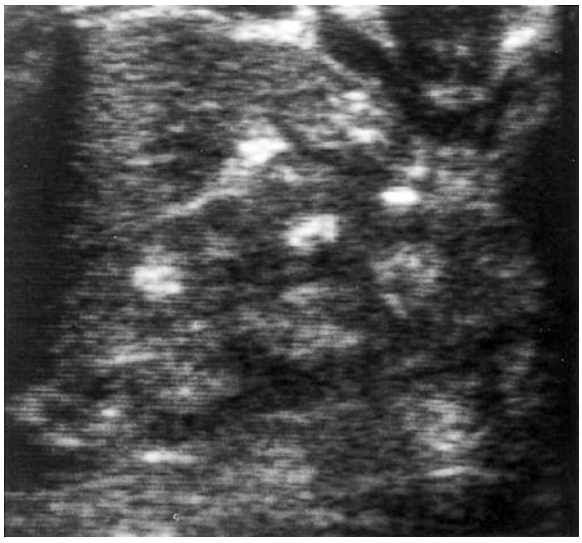


Fig. 20.14. A 10-month-old boy with Lesch-Nyhan syndrome. Sonogram of right kidney showing hyperechoic pyramids of different grades

Deficiency of adenine-phosphoribosyltransferase (APRT) results in 2.8-dihydroxyadeninuria (Cebellos-Picot et al. 1992) with autosomal recessive inheritance. Serum uric acid is normal, and the stones are radiolucent and may be confused with uric acid. The urine contains characteristic brownish round crystals. Diagnosis is confirmed from APRT activity in red blood cells or from excretion of hydroxyadenine in the urine.

In xanthinuria, the serum uric acid concentration is very low due to deficiency of xanthine oxidase, which converts xanthine to uric acid. Characteristic findings of xanthinuria are an orange-brown urinary sediment or orange-stained diapers and later xanthine stones (Arikyants et al. 2007).

20.5.2 Inhibitors

20.5.2.1 Hypocitraturia

Low citrate excretion is not always adequately recognized as a risk factor in the pathogenesis of calcium-containing stones (Miller and Stapleton 1985). Low urinary citrate excretion is characteristic for the complete form of dRTA (Preminger et al. 1985). Hypocitraturia is also observed in persistent mild or latent metabolic acidosis, in hypokalemia, and in patients with malabsorption syndromes (Hoppe et al. 2005). Idiopathic hypocitraturia may be secondary to low intestinal alkali absorption (Hoppe et al. 2007).

20.5.2.2 Further Inhibitors

Glycosaminoglycans (heparin sulphate), Tamm-Horsfall protein (THP) (Hess et al. 1991), nephrocalcin, and uropontin are other potent inhibitors of crystallization processes (Ryall 1996). However, their physiological role, if any, is disputed. The role of THP as inhibitor must be distinguished from the so-called THP kidneys, which can be seen in the first 5 days of life in neonates (Fig. 20.15) (Avni et al. 1983; Berdon et al. 1969; Starinsky et al. 1995).

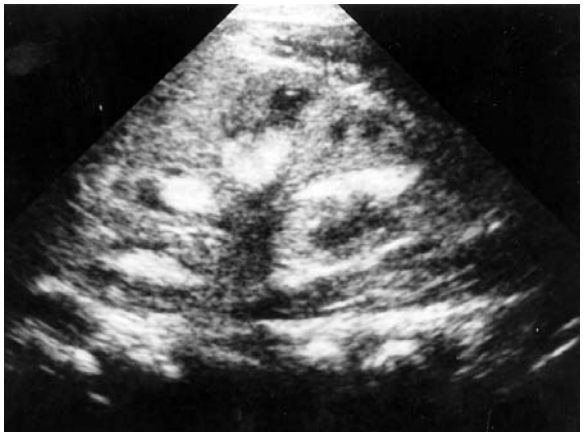


Fig. 20.15. A 5-day-old boy with Tamm-Horsfall proteinuria. Sonogram of right kidney showing hyperechoic medulla and normal cortex

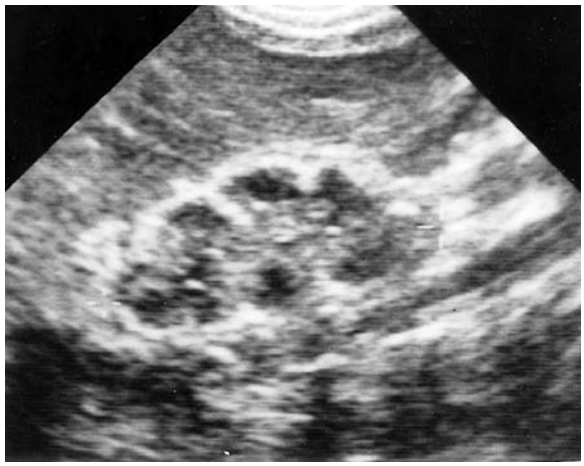


Fig. 20.16. A 2-month-old boy after renal vein thrombosis. Sonogram of right kidney showing cortical nephrocalcinosis

Conclusion

The most important task in children with nephrocalcinosis is to identify the presence or absence of hypercalcemia and hypercalciuria. After that, hyperoxaluria and hypocitraturia should be screened for.

20.6 Infectious Stones

Infectious stones are mainly composed of struvite (magnesium ammonium phosphate), but often also contain carbonate-apatite. Most struvite stones are found in the kidney, but they may also form in the bladder. Urease-producing bacteria are responsible for the formation of struvite calculi. Ammonia is hydrolyzed to ammonium ions, which results in a high urinary pH. The high pH also promotes the formation of carbonate ions and the production of trivalent phosphate ions, both components of struvite calculi. Many gram-positive and gram-negative bacteria produce urease; however, Proteus species is the predominant organism.

Struvite stones are mainly seen in boys under the age of 5 years (Fig. 20.8). In one-third of patients there is a primary anomaly of the urinary tract, most often a ureteropelvic junction obstruction (Fig. 20.9), or a primary megaureter, or more rarely a ureterocele or urethral valves, etc. (Bruziere and Roubach 1981). Patients with a neurogenic bladder, particularly those with meningomyelocele, are particularly prone to struvite stones (Raj et al.1999). Stones may also occur after renal transplantation and during secondary infection on a nidus of different composition, e.g., cystine or calcium oxalate (Hess et al. 1994). It is therefore important not to miss an underlying metabolic disorder. Urinary stasis increases the potential for crystallization to occur. Stones found in patients with ureteropelvic obstruction must therefore not necessarily be of infectious (or metabolic) origin (Oguzkurt et al. 1997). In medullary sponge kidney stones develop within the papillary tips in dilated collecting ducts (Fig. 20.12).

20.7 Extrinsic Factors

Urolithiasis may occur from crystallization of several drugs, e.g., after high-dose sulfonamide therapy (Miller et al. 1993), or after chemotherapy (Cramer et al. 1990; Hoppe et al. 2007). Bladder stones are sometimes found in association with foreign bodies or after surgical procedures, where sutures or metallic staples form the basis of crystal deposition and agglomeration in response to urine exposure.

20.8 General Preventive and Therapeutic Measures

20.8.1 Medication

Although stone removal nowadays might be easy to achieve, e.g., via ESWL, prevention of further stone formation is of utmost importance. A large fluid intake at all times, particularly during summer, is the simplest measure. Specific other procedures depend on the underlying condition. In infectious stones, all calculus material should be removed, as it may harbor the organisms. Recurrence of urinary tract infection has to be prevented, e.g., via antibiotic prophylaxis, urine acidification, or operation of a vesicoureteral reflux. For all other stones the underlying metabolic disturbance has to be treated in addition to a high daily fluid intake and to dietary advice. Calcium excretion can be reduced by hydrochlorothiazide medication; in primary hyperoxaluria therapy with pyridoxine is recommended (Leumann and Hoppe 2001). Alkaline-citrate medication is advisable in both calcium oxalate and uric acid stone disease, as well as in (idiopathic) hypocitraturia, or in patients with dRTA (Leumann et al. 1993). In cystinuria, urine alkalinization and a high urine volume are extremely helpful, in addition to effective thiol derivatives [D-penicillamine or α mercaptopropionylglycine (Thiola)], which are necessary in recurrent stone formers. Allopurinol, an inhibitor of xanthine oxidase, is given in hyperuricosuria that is not amenable to dietary restrictions, particularly in partial or complete HPRT deficiency (Lesch-Nyhan syndrome) (Cameron et al. 1993).

20.8.2 Surgery

Many pelvic or ureteral stones do not require any intervention and may pass spontaneously, helped by a large urine volume, physical activity, and spasmolytics, if needed. An intervention is required in the case of persisting or severe obstruction or infection. Small calculi, smaller than 5 mm, may be left in situ and observed. Only two kinds of stones can be dissolved chemically: cystine stones by chelating agents and uric acid by alkalization and administration of allopurinol (Chow and Streem 1996).

ESWL is now possible even in small children. Ureteral stones may also be treated by ESWL if they are not located very distally or are incrusted in the ureteral wall. Extracorporeal shock waves may damage the renal parenchyma when medullary NC is evident (Boddy et al. 1988). So-called stone streets in the ureters are very often found after successful ESWL and need specific attention (Dyer et al. 1998).

Other procedures such as percutaneous nephrolithotomy or ureteroscopy that allow the removal of ureteral stones are also kidney-protective (Durkey 2006) and constitute good alternatives to open surgery. However, the latter is still required in a considerable proportion of pediatric patients, primarily in those with urinary tract anomalies (El-Damanhoury et al. 1991).

20.9 Conclusion

- High-resolution US is the best method for detecting and monitoring nephrocalcinosis.
- For detecting urolithiasis, especially ureteral stones, low-dose CT is the method of choice. In children it is seldom necessary. The combination of high-resolution US with abdominal X-ray is usually sufficient.
- The most important task in children with nephrocalcinosis is to identify the presence or absence of hypercalcemia and hypercalciuria. After that hyperoxaluria and hypocitraturia should be screened for.
- Nephrocalcinosis may be permanent in US even after eliminating the cause.

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Renal Failure and Renal Transplantation

21

Ekkehard Ring and Richard Fotter

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E. Ring, MD
Professor, Department of Pediatrics, Division of General Pediatrics, University Hospital Graz, Auenbruggerplatz 30, 8036 Graz, Austria
R. Fotter, MD
Professor and Chairman, Department of Radiology, Head Division of Pediatric Radiology, University Hospital Graz, Auenbruggerplatz 34, 8036 Graz, Austria

21.1 Introduction

Many children who suffer from congenital, hereditary, or severe acquired renal disease, basically or caused by injury, have a substantially diminished number of functioning nephrons. Loss of nephrons cannot be replaced by new units, and recovery is impossible. Consequently, according to the patient's age, different diseases enter a common pathway of progressive renal dysfunction called chronic renal failure (CRF). Further deterioration is associated with clinical symptoms and loss of metabolic control. End-stage renal disease (ESRD) is reached when survival is possible with only renal replacement therapy. Aside from all medical and psychosocial care during CRF and ESRD, renal transplantation is the ultimate goal to optimize rehabilitation and lifestyle. This chapter is devoted to these children who need lifelong multidisciplinary care and treatment, including pediatric radiology.

21.2 Definitions

Loss of one kidney during life or being born with a single kidney may cause slight renal dysfunction but, in general, does not lead to CRF even in late adulthood (Wikstad et al. 1988). CRF can be defined as a disease state with the loss of more than 50% of nephrons, persistently increased serum creatinine above +2 SD of the age-adjusted mean, and a decreased glomerular filtration rate (GFR). It is important to note that serum creatinine must be adjusted for age as, for example, a value of 1.0 mg/dl (88 µmol/l) is normal for an adolescent, but means CRF for an infant. CRF implicates a relentless pro-

gression to ESRD without the possibility of cure. In the early stages, it is a silent disease mostly defined by biochemical values. When GFR is reduced to 25% of normal and correspondingly the number of functioning nephrons to 12% of normal, clinical symptoms of uremia appear and dominate in ESRD. To improve the detection and the treatment of children with renal disorders the term chronic kidney disease (CKD) was established (Hogg et al. 2003). Patients suffer from CKD if kidney damage–with or without a reduced GFR–is present for at least 3 months, characterized by abnormalities in the composition of the blood or urine, abnormalities on imaging tests, or lesions on renal biopsy. CKD is classified into five stages with stage 1 having a normal GFR and stage 5 meaning the need for renal replacement therapy.

21.3 Incidence

The development of registries for dialysis and transplantation has made it possible to calculate the incidence of ESRD. These data may underestimate the true incidence as probably not all children with ESRD are offered therapy. There are few epidemiological data concerning CRF. In addition, studies are not always comparable as different populations and cut-off levels for age are used. Nevertheless, the incidence of ESRD is approximately one to three children aged 0–18 years per million total population and year (Wassner and Baum 1999). The incidence seems to be similar in Europe and Northern America.

The largest survey on chronic renal insufficiency (CRI) with 4,666 patients shows that 33% of patients were 6–12 years of age and 19% less than 2 years of age (Seikaly et al. 2003). Obstructive uropathy was the most common diagnosis (23%), and 18% suffered from renal aplasia, dysplasia, or hypoplasia. Reflux nephropathy (9%), focal segmental glomerulosclerosis (8%), and polycystic kidney disease (4%) were the next most frequent diagnoses. In general, nearly two-thirds of patients had a structural anomaly. A previous study had shown that 41% had already had urological surgery. Urinary tract malformations and hypodysplasia dominated even more in patients aged less than 2 years, accounting for 67% of cases (Fivush et al. 1998). The largest study from Europe showed similar results with somewhat different groups of diagnoses (Ardissino et al. 2003). Renal hypodysplasia with or without urological malformations accounted for 58% of cases. Hypodysplasia with VUR was the most frequent single cause of childhood CRF responsible for 25.8% of cases. Almost 70% of patients with CRF reached ESRD by 20 years of age with an increasing number of patients with glomerular disorders and a decreasing number of children with hypodysplasia as primary diagnosis. Age and GFR at presentation, the primary disease, and factors like anemia or hypoalbuminemia influence the progression to ESRD (Seikaly et al. 2003). Data for patients on dialysis or after renal transplantation are similar. Obstructive uropathy is less frequent and focal glomerulosclerosis more frequent (Warady et al. 1997; Neu et al. 2002).

21.4 Pathophysiology

Whatever the underlying disease (e.g., structural anomaly, glomerulopathy, hereditary nephropathy), there is a remarkably similar histological appearance of kidneys with progressive disease, suggesting a common final pathway. Glomerulosclerosis and tubulointerstitial fibrosis are the dominant features (El Nahas and Bello 2005). Various changes seem to perpetuate a vicious cycle with permanent loss of nephrons and ESRD as the endpoint. Extensive nephron loss leads to glomerular hypertrophy (increase in cell size and number). Hyperperfusion and hyperfiltration are the consequence, and glomerular hypertension correlates best with glomerulosclerosis (Fogo and Kon 1999). There is a central role of renal hemodynamics and the renin-angiotensin system. Yet other factors such as increased glomerular metabolism, mesangial macromolecular deposition, local hypercoagulopathy, and hyperlipidemia are of importance. They influence glomerular growth promoters. These promoters (e.g., growth hormone, transforming growth factor-β, insulin-like growth factor-I, angiotensin II, endothelin) can induce glomerular hypertrophy and mesangial matrix accumulation with glomerular sclerosis as a result. There is a remarkable diversity in morphologic appearance concerning sclerosis and disease progression. Young age at onset and

severe initial renal damage are factors associated with a more progressive course (Wikstad et al. 1988). In addition, the individual genetic variability is of influence as the deletion type of angiotensin-converting enzyme gene (ACE-DD-type) seems to be associated with a severe course of IgA nephropathy and congenital uropathies (Hunley and Kon 1999; Hohenfellner et al. 1999; Yong et al. 2006). Systemic hypertension, urinary tract infections, and unrecognized or postoperative urinary obstruction perpetuate the damage and enhance progression. Recent studies could demonstrate a limited potential for regression or modulation of glomerulosclerosis with blockage of the renin-angiotensin-system (Fogo 2006). The impact of these pathophysiological considerations on therapy of CRI is that we can ameliorate the course of disease. Early diagnosis, prevention of infection, close postoperative follow-up, early administration of ACE inhibitors, and proper treatment of systemic hypertension seem to be of utmost importance.

21.5 Diagnostic Work-Up

21.5.1 Clinical and Laboratory Evaluation

Diagnosis of CRF is based on laboratory values such as serum creatinine, creatinine clearance, and calculation of the glomerular filtration rate. The Schwartz formula is used for this calculation (Schwartz et al. 1976, 1984). The patient's height, serum creatinine, and an age-dependent factor K are needed, but no urine collection (see Chap. 28). Urinalysis may show proteinuria, hematuria, or urinary tract infection. Metabolic acidosis, hyperkalemia, renal salt wasting, hypocalcemia, hyperphosphatemia, and anemia are further typical laboratory features. Alkaline phosphatase and parathormone are needed to evaluate renal bone disease (renal osteodystrophy). Patients with as yet unrecognized CRI may present with a combination of polydipsia, polyuria, secondary enuresis, vomiting, failure to thrive, short stature, systemic hypertension, cardiac failure, and eventually edema as a sign of volume overload. Therapy of patients with known CRI is devoted to preventing such deleterious metabolic derangement.

21.5.2 Renal Imaging

Diagnostic imaging is extremely helpful in unraveling the underlying renal disease. Sonography is the basic investigation focused on renal size and structure. Further imaging depends on sonographic findings. In general, the kidneys are more or less echodense, but may be small, normal sized, enlarged, or cystic.

Small echodense kidneys, possibly with a size difference, indicate hypodysplasia or renal scarring. Focal compensatory hypertrophy may have a nodular tumor-like aspect. Concomitant dilatation of the ureter and/or renal pelvis can reflect vesicoureteral reflux (VUR) or urinary tract obstruction, but may also be caused by long-standing polyuria. In general, a congenital uropathy or renal dysplasia is the most probable diagnosis. Voiding cystourethrography (VCU) and isotope studies are recommended.

Nearly normal-sized or enlarged kidneys are found in the early follow-up of acquired diseases such as glomerulonephritis and hemolytic-uremic syndrome. Loss of renal volume mostly indicates progressive CRF. The most probable diagnoses in patients presenting with as yet unrecognized CRF are Alport syndrome, juvenile nephronophthisis, oligomeganephronia, autosomal recessive polycystic kidney disease (ARPKD), and various syndromes with renal dysplasia. The nephronophthisis-medullary cystic disease complex is a distinct entity of inherited diseases with insidious onset of CRF. Renal biopsy shows a chronic sclerosing tubulointerstitial nephropathy. Sonography contributes most to the diagnosis. The kidneys are normal or slightly reduced in size, echodense, and without corticomedullary differentiation. Corticomedullary cysts are characteristic and are found predominantly in advanced CRF (Garel et al. 1984; Blowey et al. 1996; Chuang and Tsai 1998). Sometimes medullary cysts can be demonstrated by computed tomography or MRI (Elzouki et al. 1996). The latter investigations probably contribute little to the diagnosis of juvenile nephronophthisis as molecular genetic diagnosis is available (Hildebrandt et al. 1997; Hildebrandt and Otto 2005; Saunier et al. 2005).

If renal cysts are found, cystic disease must be defined as unilateral or bilateral, localized or diffuse. Extrarenal manifestations such as hepatic or pancreatic cysts should be sought as well as evidence of portal hypertension. CRF in unilateral cystic disease means renal hypo-dysplasia of the contralateral kidney even

if the parenchyma appears relatively normal. Large bilateral cysts favor autosomal dominant polycystic disease, while enlarged and echodense kidneys are found in autosomal recessive polycystic disease (see Chap. 10). Glomerulocystic disease may have a similar appearance on sonography (Fitch and Stapleton 1986). Further differentiation is based on familial history, clinical, and genetic findings (El-Merhi and Bae 2004; Guay-Woodford 2006). Renal cysts do not necessarily reflect the underlying disorder. Acquired renal cystic disease is a known complication of ESRD (Leichter et al. 1988) and may occur in CRF before the start of dialysis (Hogg 1992).

Nephrolithiasis and/or nephrocalcinosis may be additional findings on sonography and can be confirmed on plain abdominal radiograph. Renal or urinary tract stones are found in uropathies caused by recurrent urinary infections and urine stasis. Nephrocalcinosis may be the consequence of acid-base disturbance and hypercalciuria in congenital tubulopathies. The presence of nephrocalcinosis and nephrolithiasis favors primary hyperoxaluria type 1 (PH 1) as diagnosis. This autosomal recessive inherited disease is caused by a deficiency of the liver-specific peroxisomal enzyme alanine–glyoxylate aminotransferase (AGT) and leads to ESRF in many cases (Danpure and Jennings 1986). Some patients with PH 1 present with ESRD in infancy (Fig. 21.1), others are asymptomatic and discovered only by family screening. Beyond infancy, most patients show symptoms of renal stone disease with loin pain, hematuria, and urinary tract infection. Systemic deposition of oxalate crystals (oxalosis) occurs in CRF. Early liver transplantation or combined liver-kidney transplantation seems to be the single treatment appropriate for survival.

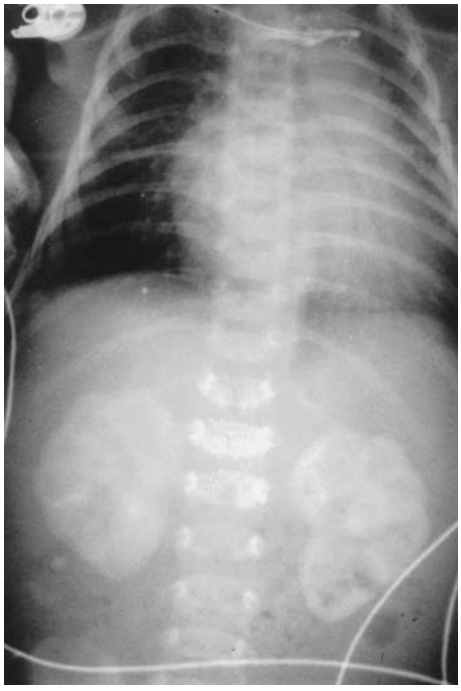

Fig. 21.1. Plain radiograph. Bilateral nephrocalcinosis in an infant with primary hyperoxaluria type 1 presenting with oliguria during the first weeks of life

21.5.3 Extrarenal Imaging

The cardiovascular system and the bones are prone to lesions in CRF and ESRD. Cardiac dysfunction is present in most patients and is a major cause of death in ESRD and after renal transplantation (Ehrich et al. 1992; Parekh and Gidding 2005). Chest X-ray may show pulmonary edema, an enlarged vascular pedicle, and cardiac dilatation in volume overload, but can be normal despite severe cardiac dysfunction. Uremic cardiomyopathy is characterized by an increased cardiac volume, a decreased number of cardiomyocytes, and an expanded interstitium. Left ventricular hypertrophy is an early prognostic sign for cardiac compromise (Schärer et al. 1999). Hypervolemia, hypertension, and anemia worsen cardiac function. Cardiac ultrasound including Doppler sonography, cardiac electron beam tomography to look for coronary calcium in young adults (Oh et al.2002), and functional evaluation can unravel these changes, and a dilated vena cava inferior indicates volume overload.

The kidneys have a major contribution in mineral and bone homeostasis. Renal osteodystrophy (ROD) is a serious consequence of CRF and ESRD. Untreated ROD is critical especially in the years of skeletal growth with growth retardation and osseous deformities as a disabling consequence. Bone pain, fractures, slipped epiphyses, muscle weakness, and extraskeletal calcifications (vascular, cardiac, pulmonary, renal, periarticular) are signs of severe ROD. Impaired renal calcitriol synthesis (1,25-dihydroxyvitamin D), phosphate retention, hypocalcemia, secondary hyperparathyroidism, alterations of parathyroid hormone action and catabolism, and alterations in the calcium-sensing receptor are the main pathogenetic factors. A broad spectrum from high-turnover to low-turnover bone lesions can be distinguished by laboratory

and radiographic findings. High-turnover disease (osteitis fibrosa) is characterized by secondary hyperparathyroidism and by increased bone resorption located in the subperiosteal and endosteal surface of cortical bone. Radiographically, the clavicles, pelvic bones, meta-diaphyseal junction of long bones, and phalanges preferably show these lesions. Focal radiolucencies and sclerotic areas are additional findings. Low-turnover disease (adynamic bone, osteomalacia) is characterized by widening of the epiphyseal growth plate and wide radiolucent bands within the cortex indicating pseudofractures and Looser zones. In the past, adynamic lesions were mostly related to aluminum toxicity caused by administration of aluminum-containing phosphate binding agents. Up to 50% of patients with ESRD have low-turnover disease, and aggressive therapy of ROD contributes in part (Salusky and Goodman 1996; Rigden 1996). Guidelines for prevention and treatment of ROD were published recently (Klaus et al. 2006).

21.6 Treatment of CRF

Treatment is devoted to ameliorating the progressive course of disease, achieving metabolic control, and preventing extrarenal organ diseases. In addition, psychosocial care and planning the future are of importance. Aggressive treatment of severe glomerulopathies with poor outcome such as focal-segmental glomerulosclerosis and early administration of ACE inhibitors are mandatory. Treatment of hypertension is best controlled by 24-h blood pressure measurement (Soergel et al. 1997). Close follow-up with ultrasound (US) can prevent a delay in treatment of postoperative complications in urological malformations. Dietary measures include adequate caloric and fluid intake; protein is given according to the recommended daily allowances. Salt and potassium requirements depend on renal losses. ROD therapy is devoted to preventing disabling lesions. It includes dietary phosphate restriction, correction of acidosis, administration of phosphate-binding agents and calcitriol. Serial determination of phosphate, calcium, acid-base-status, alkaline phosphatase, and parathormone is mandatory. Administration of recombinant human growth hormone can ameliorate growth retardation; correction of renal anemia is achieved by erythropoietin.

21.7 Planning Dialysis and Transplantation

Future perspectives must be addressed to families with a child in CRF. The child must be in good physical condition, ABO blood group and HLA system antigens must be known. All necessary vaccinations should be performed during CRF. Screening for panel reactive cytotoxic antibodies and repeated determinations of antibody status against cytomegalovirus, EBV, and hepatitis are mandatory. Urological disorders frequently need nephrectomy or nephrecto-ureterectomy before considering transplantation. Assessment of bladder function with voiding cystourethrography (VCU) and eventually with cystomanometry is mandatory to prevent bladder problems after transplantation. Children with a small noncompliant bladder frequently need bladder augmentation, which can be performed before or after renal transplantation. An augmented bladder is no contraindication for transplantation (Koo et al. 1999; Fontaine et al. 1998; Rigamonti et al. 2005). The preference of the family for peritoneal dialysis (PD) or hemodialysis (HD), for living-related donor transplantation or a deceased donor, and the option of a preemptive transplantation (before starting dialysis) must be weighed against medical indications. From a radiological point of view, renal and abdominal sonography, VCU, and eventually MR angiography to show the vascular situation in the region of transplantation are important. According to the joint decision, vascular access for HD or placement of a PD catheter can be planned. The living-related donor must undergo extensive investigations to ensure that no undue risks are incurred by removal of one kidney.

21.8 Dialysis

21.8.1 Basic Considerations

If ESRD is reached, survival is possible with only blood purification, performed as PD or HD. It is the steady state from which transplantation is planned and performed in most situations, and to which patients return in the case of graft failure. PD or

HD can only partially restore metabolic control. As in CRF, proper treatment of hypertension, acidosis, ROD, etc., is mandatory. Diagnostic imaging is mostly requested if complications such as a blocked peritoneal catheter or insufficient blood supply of Brescia-Cimino fistula are present. Interpretation of imaging in a disease state is problematic if no comparison with the normal situation is possible. Consequently, diagnostic imaging should be performed at regular intervals even if no problems are present and the diagnostic value of imaging is questionable at first sight.

21.8.2 Peritoneal Dialysis

Peritoneal dialysis (PD) is the preferred treatment in children with ESRD, and approximately 67% of patients are maintained on continuous PD (Lerner et al. 1999). It is the treatment of choice for infants (Fig. 21.2). A permanent PD catheter is placed surgically into the peritoneal cavity with the tip in the lower abdomen and a long subcutaneous tunnel. A plain abdominal radiograph can show the position that can be compared in case of catheter dysfunction. Solute clearance and removal of fluid (ultrafiltration) are achieved by changing the dialysate several times per day. PD solutions contain different concentrations of glucose as the osmotic agent. PD is relatively simple and safe and can be performed at home. Thus, a life in the normal surroundings of the family and regular school attendance for older children are possible. Further advantages over hemodialysis are the continuous character of treatment with only slow changes in body composition, a relatively free diet and fluid supply, and a stable cardiovascular situation. PD prescription mostly depends on the individual peritoneal membrane solute transport capacity. This is best determined by a peritoneal equilibration test (PET) originally described by Twardowski et al. (1987) and recently standardized for children (Warady et al. 1996). Determination of solute clearance by weekly creatinine clearance and weekly urea clearance (Kt/V) are of value to check adequacy of PD.

PD complications can be divided into acute or chronic and infectious or noninfectious. Imaging with ultrasound, CT, and eventually MRI can contribute significantly to appropriate treatment of many situations (Taylor 2002). Acute catheter dysfunction may be caused by malposition and can be seen on a plain abdominal radiograph. Development of inguinal hernias is caused by the permanently increased intra-abdominal pressure, and herniotomy is frequently needed. Acute respiratory distress should raise suspicion of hydrothorax caused by thoracic leakage of peritoneal fluid (Rose and Conley 1989). A chest X-ray can show this complication (Fig. 21.3). Infections of the exit site, the subcutaneous tunnel, and peritonitis are the most common infectious complications. Proper treatment with intraperitoneal antibiotics is mandatory. The incidence of peritonitis is estimated to be one infection per 13 treatment months. Recurrent peritonitis may lead to catheter removal. Tunnel infections typically show pericatheter fluid collection, and US is important for early detection and follow-

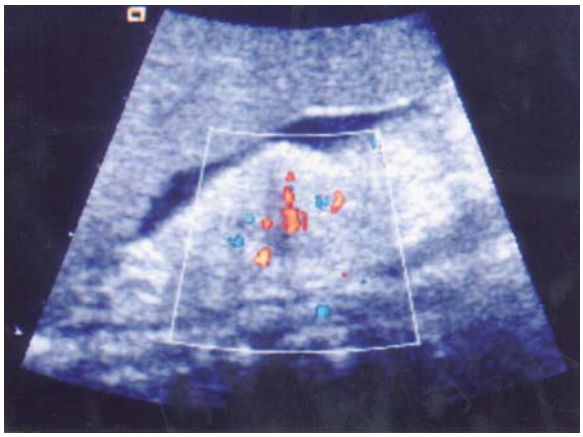

Fig. 21.2. Doppler sonography. Shrunken, nearly nonperfused end-stage kidney in an infant with peritoneal dialysis. Peritoneal fluid within Morrison's pouch

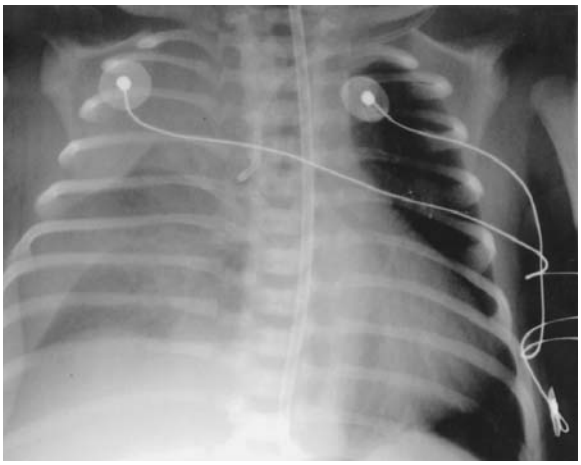

Fig. 21.3. Chest X-ray. Thoracic leak of peritoneal dialysate during peritoneal dialysis

up (Plum et al. 1994; Vychtytil et al. 1999). The peritoneal membrane is functionally stable even in children on long-term PD (Warady et al. 1999). However, development of ultrafiltration failure and of intestinal obstruction caused by sclerosing peritonitis is a possible threat, and frequent episodes of peritonitis partially are responsible for the incidence of this severe complication. Peritoneal thickening and calcifications, loculated fluid collections, and tethering of the small bowel are diagnostic and shown by sonography or computerized tomography (Stafford-Johnson et al. 1998; Krestin et al. 1995). Recently, normal values for parietal peritoneal thickness have been reported, enabling early detection of structural changes in the peritoneum by US (Faller et al. 1998).

21.8.3 Hemodialysis

Hemodialysis is a safe and effective treatment for children with ESRD and is performed in 46% of such children aged more than 12 years (Lerner et al. 1999). Technical refinements enable HD even in small children and infants (Bunchman 1995; Al-Hermi et al. 1999). In this age group, HD is mostly indicated if PD fails or is contraindicated. For technique and performance of HD, the reader is referred to a recent publication (Harmon and Jabs 1999). Vascular access is of utmost importance in pediatric HD. Central venous catheters, internal arteriovenous fistulas (Brescia-Cimino fistula), and synthetic grafts are used. Placement of central venous catheters is the preferred vascular access in many centers (Lerner et al. 1999; Neu et al. 2002). Arteriovenous fistulas are an alternative with a lower rate of complications compared to central venous catheters, and sometimes with an improved metabolic control of the patient (Brittinger et al. 1997; Chand et al. 2005; Ramage et al. 2005). On the other hand, the rapid access to renal transplantation may favor central venous catheters. US may be of value in guidance for placing the catheter and detecting thrombosis around the catheter. Duplex sonography or angiography can show stenosis of internal fistula and influence surgical therapy. Development of malignancy in acquired renal cystic disease on long-term dialysis is well recognized in adult patients and has also been reported in children (Levine 1992; Mattoo et al. 1997; Querfeld et al. 1992). Thus, a regular survey of the native kidneys with US and selective use of computerized tomography or magnetic resonance imaging must be advised for children on dialysis and even after successful transplantation.

21.9 Transplantation

21.9.1 Basic Considerations

Renal transplantation (Tx) is the treatment of choice in children with ESRD, and absolute contraindications are few. Patients with HIV disease or with malignancies and preexisting metastatic disease are generally not considered for Tx. Similarly, children with devastating neurological disorders are mostly excluded from Tx. Organ-sharing organizations exist for deceased donor Tx, and the allocation criteria mostly give priority to children. There is evidence that giving pediatric donor kidneys to pediatric recipients is the best allocation system, leading to a better prognosis of children with ESRD (Pape 2007). Tx from a living related donor is an alternative and may be performed preemptively (before starting dialysis). Preemptive registration is also accepted by most organizations for Tx. Preemptive Tx may prevent dialysis-associated morbidity and is at least as good as post-dialysis Tx (Cransberg et al. 2006). The graft is placed mostly extraperitoneally into a pelvic site. The vessels of the transplant are anastomosed with the iliac vessels or with the aorta and the inferior vena cava in small children. The ureter is connected to the bladder with an ureterocystoneostomy. Immunosuppressive therapy starts with Tx, and most centers use a combination of steroids, cyclosporine A or tacrolimus, and mycophenolate mofetil. Graft survival seems to be superior with tacrolimus (Filler et al. 2005). Yet different approaches to therapy exist, and new drugs or modifications of established treatment protocols are under investigation for initial and long-term therapy. Renal US and Doppler sonography (DS) must be recommended early after Tx as a basic investigation and for comparison during follow-up. The aspect of the renal parenchyma, presence of corticomedullary differentiation, dilatation of the renal pelvis, and length and volume of the transplant should be addressed. DS of the transplant and

the vessels including the vascular anastomoses give valuable information concerning perfusion.

21.9.2 Acute Problems

Acute tubular necrosis (ATN), graft thrombosis, and hyperacute rejection (Rx) are of major concern. ATN is observed in 5% of live related transplants and in 19% of cadaver transplants (Feld et al. 1997). These patients require dialysis after Tx. Risk factors for ATN are a prolonged duration of cold ischemia, frequent use of blood transfusions, and previous transplantations. Graft thrombosis accounts for 12% of graft failure and is more common in young patients. It should be suspected in all cases with primary engraftment and sudden onset of oliguria during the first few days after operation. Hyperacute Rx invariably leads to loss of the graft, but is exceptional nowadays. Sonography can show swelling of the Tx and loss of corticomedullary differentiation. DS and calculation of the resistive index (RI) may unravel the diminished perfusion and higher vascular resistance found in ATN and in Rx. Perfusion is nearly absent in severe graft thrombosis. Amplitude-coded color Doppler sonography (aCDS) is of value in studying perfusion of renal transplants (Hoyer et al. 1999; Riccabona 2006) (Fig. 21.4). Nevertheless, most signs on US investigations seem to be unspecific and of questionable utility for distinguishing between ATN and acute Rx (Briscoe et al. 1993). Complementary isotope investigations can also be performed. The potential of MRI to differentiate ATN and acute Rx has not been clarified (Liou et al. 1991; Nakashima et al. 1996). If graft dysfunction is prolonged, a biopsy of the transplant should be performed. Vascular complications, including renal artery stenosis, are clearly visible on DS (Mutze et al. 1997), and MR angiography can be performed as a complement.

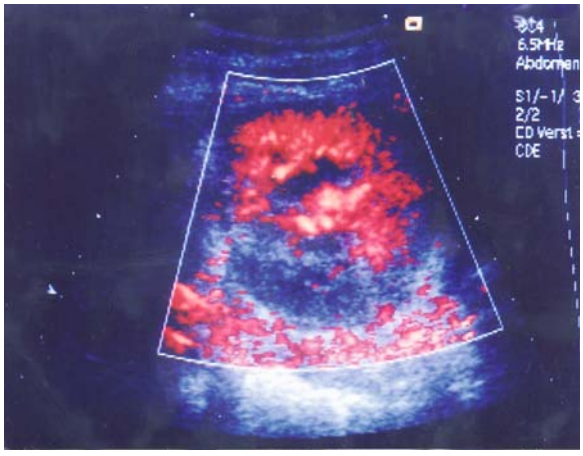

Fig. 21.4. Amplitude-coded Doppler sonography. Renal transplant with perfusion defect due to arterial occlusion (renal infarction)

Urological problems can be visualized by US in most situations. If requested, isotope studies, CT, or MRI may add valuable information. Severe bleeding around the transplant may be caused by anticoagulation for hemodialysis or a leak of the vessel anastomoses. Hydronephrosis caused by urinary tract obstruction may be the consequence of ureteral kinking, stenosis of ureteral implantation, ureteral necrosis, or large lymphoceles. It is important to note that children with acute renal failure caused by severe urinary obstruction may present with just minimal or moderate renal pelvic dilatation due to a diminished urinary flow (Fig. 21.5). In addition, these situations are painless as the transplant and the ureter have no nerves. Close follow-up is mandatory, especially in patients with bladder dysfunction or an augmented bladder.

21.9.3 Regular Follow-Up

After discharge from hospital, regular visits to the outpatient clinic are necessary. Anthropometric data and the health status are checked. Fluid intake, urine output, and blood pressure are recorded at home. Laboratory investigations include urinalysis, serum creatinine, blood levels of immunosuppressive agents (cyclosporine A or tacrolimus), and the antibody status or EBV and cytomegalovirus activity. The dosage of immunosuppressants must be adjusted frequently to obtain sufficient immunosuppression and to avoid nephrotoxicity. Seizures and altered mental status may be signs of cyclosporine-induced neurotoxicity. Cerebral MRI can show reversible hyperintense lesions on T2-weighted images in a predominantly occipital pattern, thereby establishing the diagnosis of posterior reversible encephalopathy syndrome (PRES). Aside from arterial hypertension, immunosuppressants are another main cause of PRES and toxic blood levels are not required (Lamy et al. 2004). Sonography and DS of the transplant and of the native kidneys (if left in situ) as well as cardiac ultrasound are recommended at regular intervals.

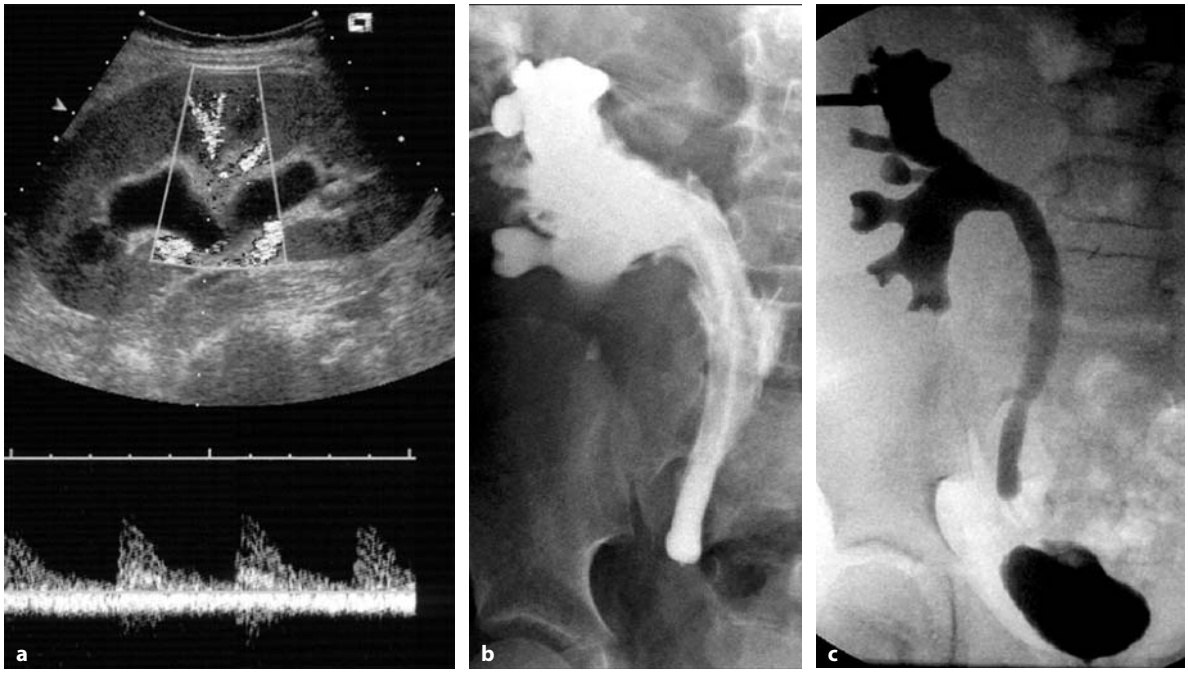

Fig. 21.5a–c. Acute rise of serum creatinine and oliguria 8 weeks after successful RTx. US with DS (**a**) shows a moderate distension of the renal pelvis without severe reduction of renal perfusion. Immediate percutaneous nephrostomy with antegrade filling (**b**) confirms distal ureteral stenosis caused by ureteral necrosis. Antegrade filling before surgical reconstruction and after stabilization of the renal function (**c**)

21.9.4 Acute Rejection

Various immunological processes are involved in transplant Rx. Without adequate therapy, destruction of the graft is the consequence. Approximately 2 months after Tx, 35% of patients with living-related Tx and 48% with cadaver Tx had acute Rx. The corresponding data for 1 year after Tx are 49% and 63%, respectively (Tejani and Harmon 1999). The latter data are similar in a more recent analysis (Smith et al. 2002). Clinical symptoms such as graft tenderness or fever are exceptional nowadays. Typical signs are a decrease in urine flow, a rise in serum creatinine, and high blood pressure. Transplant sonography and DS may show swelling of the organ, indicated by an increase in volume and loss of corticomedullary differentiation. Cortical perfusion is decreased and the RI is increased. Differential diagnosis includes urinary tract obstruction or vascular complications. Both problems are visible on sonography and DS. A transplant biopsy is necessary for definite diagnosis of Rx. Ultrasound guidance and the use of automated devices can reduce major complications. The severity of Rx is classified histologically according to the Banff criteria, which have recently been refined (Solez et al. 1993; Racusen et al. 1999). As a rule, high-dose IV methylprednisolone is the initial treatment. An even more aggressive approach is necessary in steroid-resistant Rx. For these patients who have cyclosporine as basic therapy, switching to tacrolimus is a promising therapy for steroid-resistant Rx (Corey et al. 1996). In general, more than 50% of rejections are completely reversible and only 5% lead to graft failure (Feld et al. 1997; Smith et al. 2002).

21.9.5 Infections

As a result of immunosuppression, patients are prone to viral and bacterial infections. This is an increasing problem as hospital admissions for infections nowadays exceed admissions for acute rejection. A problematic virus emerging in the last decade is polyoma BK virus (BKV). BKV-allograft nephropathy affects 2–8% of grafts, leads to early graft loss in 50% of patients, and there is no specific treatment (Acott 2006). Cytomegalovirus

infection is a serious complication with a high risk to the patient and the transplant. EBV infections are related to the development of post-transplant lymphoproliferative disease. Pneumocystis carinii pneumonia occurs in 3% of Tx patients (Fig. 21.6). These patients may present acutely with shortness of breath and hypoxemia. Immediate therapy with high-dose cotrimoxazole is frequently effective.

Approximately 50% of Tx patients have urinary tract infections. Symptomatic infections are found predominantly during the first 3 months after transplantation. Patients with preexisting urological disorders may have recurrent infections and kidney transplants seem to be prone to scarring in the case of vesicoureteric reflux (Coulthard and Keir 2006). Aside from sonography, isotope investigations and VCU to detect VUR are mandatory (Fig. 21.7).

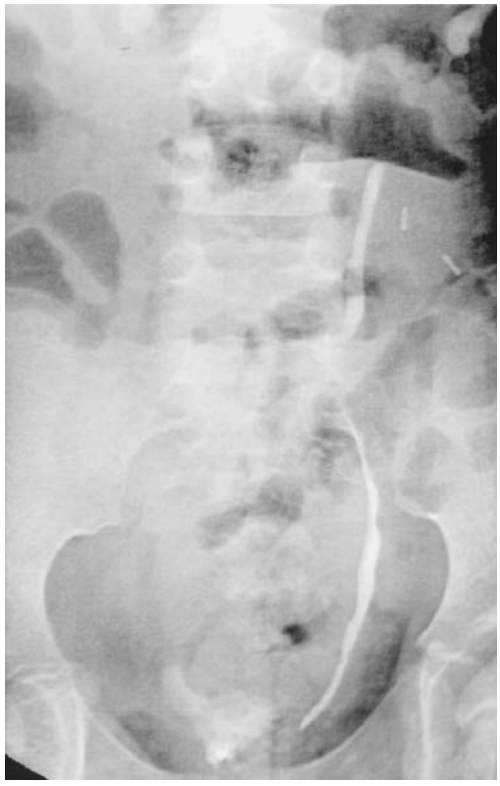

Fig. 21.7. Voiding cystourethrography. Urinary tract infections after transplantation in a patient with Denys-Drash syndrome and nephrectomy (Wilm's tumor). VUR into the blind-ending native

21.9.6 Post-Transplant Lymphoproliferative Disorder

Post-transplant lymphoproliferative disorder (PTLD) is a serious complication after solid organ transplantation, being related to chronic immunosuppression. The percentage of children with PTLD is increasing, and de novo or persistent EBV infection is present in most cases. Approximately 94% of PTLD are non-Hodgkin lymphomas. Clinical presentation mostly is not specific, and almost every organ including the graft can be affected. Tapering of immunosuppression is mandatory in children with EBV infection and a high viral load. Treatment with monoclonal antibodies or further oncologic treatment is indicated in some cases. Imaging has a key role in detecting PTLD, guiding tissue biopsy if requested, and in monitoring response to treatment. Early diagnosis may be life-saving and can improve the prognosis of the patient. Frequent routine abdominal US and a chest X-ray at least once a year seem to be of value. CT or preferably MRI is indicated in cases with questionable results on US (Claudon et al. 1998; Scarsbrook et al 2005; Burney et al. 2006).

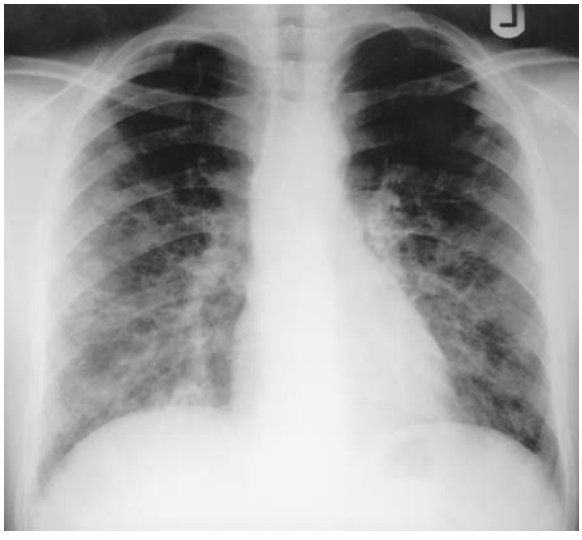

Fig. 21.6. Chest X-ray. *Pneumocystis carinii* pneumonia after transplantation

21.9.7 Prognosis

The early outcome after renal Tx improves every year. Better care for the patients during CRF and ESRD makes them better candidates for Tx. Improvement of the immunosuppressive regimen and introduction of new drugs eventually will allow a more

individual approach. Rehabilitation is optimal, and more than 90% of patients survive 5 years after Tx. More than 60% of transplanted kidneys survive at least 5 years. The rates of chronic kidney loss are unchanged during the last decade and are a cause of major concern. Chronic allograft nephropathy (CAN) is the main cause of kidney loss and is histologically characterized by tubular atrophy and interstitial fibrosis with glomerulopathy and vascular lesions in addition (Alexander et al. 2007). Many immunological and non-immunological factors influence the risk and the rapidity of progression of CAN. Major factors are acute rejections, subclinical rejections, viral infections, nephrotoxicity of calcineurine inhibitors (cyclosporine and tacrolimus), and noncompliance with immunosuppression. Protocol biopsies may be helpful to clarify main causes of CAN in the individual patient with hopefully new treatment strategies to reduce the incidence of CAN. In addition, long-term problems such as cardiovascular disease must be addressed early. The child and the family need the lifelong support of a multidisciplinary team to optimize therapy.

Conclusion

Imaging with sonography, DS, and aCDS is essential for diagnosis of CRF and to monitor therapy. Further imaging is needed to detect cardiac compromise or renal bone disease and to plan renal transplantation. During dialysis, imaging is mostly requested when complications arise. Sonography, DS, and aCDS are helpful to monitor graft function after Tx. Further imaging with VCU, isotope studies, or MRI may be necessary.

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Renovascular Hypertension

22

Melanie P. Hiorns, Clare A. McLaren, and Isky Gordon

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22.1 Introduction

Renovascular disease (RVD) is an important but uncommon cause of hypertension in children, accounting for about 10% of cases (Gill et. al 1976; Deal et al. 1992; Wyszynska et al. 1992). Renal pathology is the cause of hypertension in over 90% of children after 1 year of age; under 1 year of age, coarctation of the aorta is more common. The more severe the hypertension and the younger the child, then the more likely it is to be secondary hypertension. RVD is now well recognized in paediatrics, but the etiology and management is very different to adult practice (Sadowski and Falkner 1996).

M. P. Hiorns, MBBS, MRCP, FRCR
Consultant Paediatric Radiologist, Great Ormond Street Hospital for Children, London, WC1N 3JH, UK
C. A. McLaren, DCR(R)
Clinical Specialist Radiographer (Interventional Radiology and Cardiology), Great Ormond Street Hospital for Children, London, WC1N 3JH, UK
I. Gordon, FRCP, FRCR, FRCPaed
Professor of Paediatric Imaging, Institute of Child Health, Honorary Consultant Radiologist, Great Ormond Street Hospital for Children, London, WC1N 3JH, UK

22.2 Clinical Presentation

The presentation of RVD in childhood is variable. Occasionally a child is incidentally found to have high blood pressure (BP) on routine examination. The diagnosis is often delayed due to technical problems in measuring the BP and a low index of suspicion in children (Tullus et al. 2007). BP measurements should always be compared with published standards for age, sex and height (Goonasekera et al. 2000; Rosner et al. 1993). Other presentations may relate to secondary effects of hypertension, such as cardiac failure, an isolated lower motor neuron facial palsy, severe headaches or failure to thrive.

22.3 Causes

RVD must first be distinguished from other, more common, causes of childhood hypertension (Table 22.1). Any abnormal kidney may produce renin and therefore generate hypertension. Although renal scarring and glomerular disease are the commonest abnormalities found in children with high blood pressure, occasionally ureteropelvic junction (UPJ) obstruction, neuroblastoma, pheochromocytoma or Wilms' tumor may present with hypertension. Fibromuscular dysplasia is the commonest cause of RVD in childhood, but other associations include neurofibromatosis type 1, Williams

Table 22.1. Differential diagnosis

Primary (essential) hypertension (in older children)
Renal disease including glomerulonephritis (over 90% of children aged >1 year)
Congenital renal disease • Renal dysplasia • Ureteropelvic junction obstruction
Chronic pyelonephritis
Neonatal aortic thrombosis
Renal artery or renal vein thrombosis
Renal artery stenosis
Aortic disease • Coarctation of aorta (commonest cause in children aged <1 year) • Middle aortic syndrome
Takayasu disease
Adrenal pathology [including primary hyperaldosteronism (Conn's syndrome), Cushing's syndrome and phaeochromocytoma]
Tumors • Neuroblastoma • Wilms' tumor • Phaeochromocytoma • Adrenal cortical tumor

syndrome, idiopathic hypercalcemia of infancy, and vasculitis, especially Takayasu disease. Middle aortic syndrome is a morphological pattern in which the abdominal aorta and one or more of its major branches are stenosed. This pattern may arise from most of the major causes of RVD in childhood.

In children, especially those with an identifiable underlying cause such as neurofibromatosis type 1, arterial involvement tends to be more extensive than in adults. Bilateral disease and involvement of the intrarenal vasculature occur in 50% or more of children with RVD (Deal et al. 1992; Shroff et al. 2006).

22.4 Imaging

Non-invasive imaging alone cannot reliably exclude RVD as a cause of pediatric hypertension (Vo et al. 2006; Tullus et al. 2007), but may confirm or exclude an alternative pathology as an explanation. Ultrasound is a simple first imaging test in a child found to have high BP. It may detect small and/or scarred kidneys, renal and adrenal tumors, or hydronephrosis. Doppler studies are most useful for the diagnosis of RVD because direct visualization of renal artery stenosis is difficult. A peak systolic velocity (PSV) of greater than 1.8 to 2 m/s and/or a renal-aortic velocity ratio greater than 3.0 or 3.5 suggest RAS (Brun et al. 1997; Gao et al. 2006). Alternatively, the acceleration time may be increased (Patriquin et al. 1992; Gao et al. 2006), and in combination with a reduced PSV this is known as a *tardus et parvus* waveform. The *tardus et parvus* phenomenon may be unilateral in severe RAS, or bilateral in aortic coarctation or middle aortic syndrome (Fig. 22.1). Despite many recent advances in ultrasound, however, false-positive and false-negative studies for main renal artery stenosis may still occur (Brun et al. 1997). Ultrasound is also relatively poor in the detection of branch artery stenosis (Brun et al. 1997). A normal ultrasound study does not exclude a single renal scar, renovascular pathology, or a small pheochromocytoma (especially if it is extra-adrenal).

In the clinical context of hypertension further investigations are necessary to discern whether the ultrasound is normal or not. If ultrasound has demonstrated Doppler abnormalities clearly suggesting RVD, it is most appropriate to proceed directly to angiography (see below). If this is not the case then further investigations are focused on confirming or excluding an alternative renal cause for the hypertension and may include such studies as a diuretic renogram with ^{99m}Tc-labeled mercaptoacetyltriglycine (MAG3) in hydronephrosis (to assess function and drainage), or a dimercaptosuccinic acid (DMSA) study and a cystogram in a small kidney (to assess function and possible VUR). If the ultrasound is normal a DMSA scan may reveal focal scarring as an underlying pathology. If both the ultrasound *and* the DMSA are normal RVD should again be considered (see below).

Intravenous urography no longer plays a significant role in the investigation of hypertension. If RVD is suspected to be the cause of the elevated BP for strong clinical reasons (Table 22.2), or because of the ultrasound findings, then there is little point in performing any other non-invasive imaging. In children where the need for angiography is not clear-cut, three other imaging modalities may be considered next.

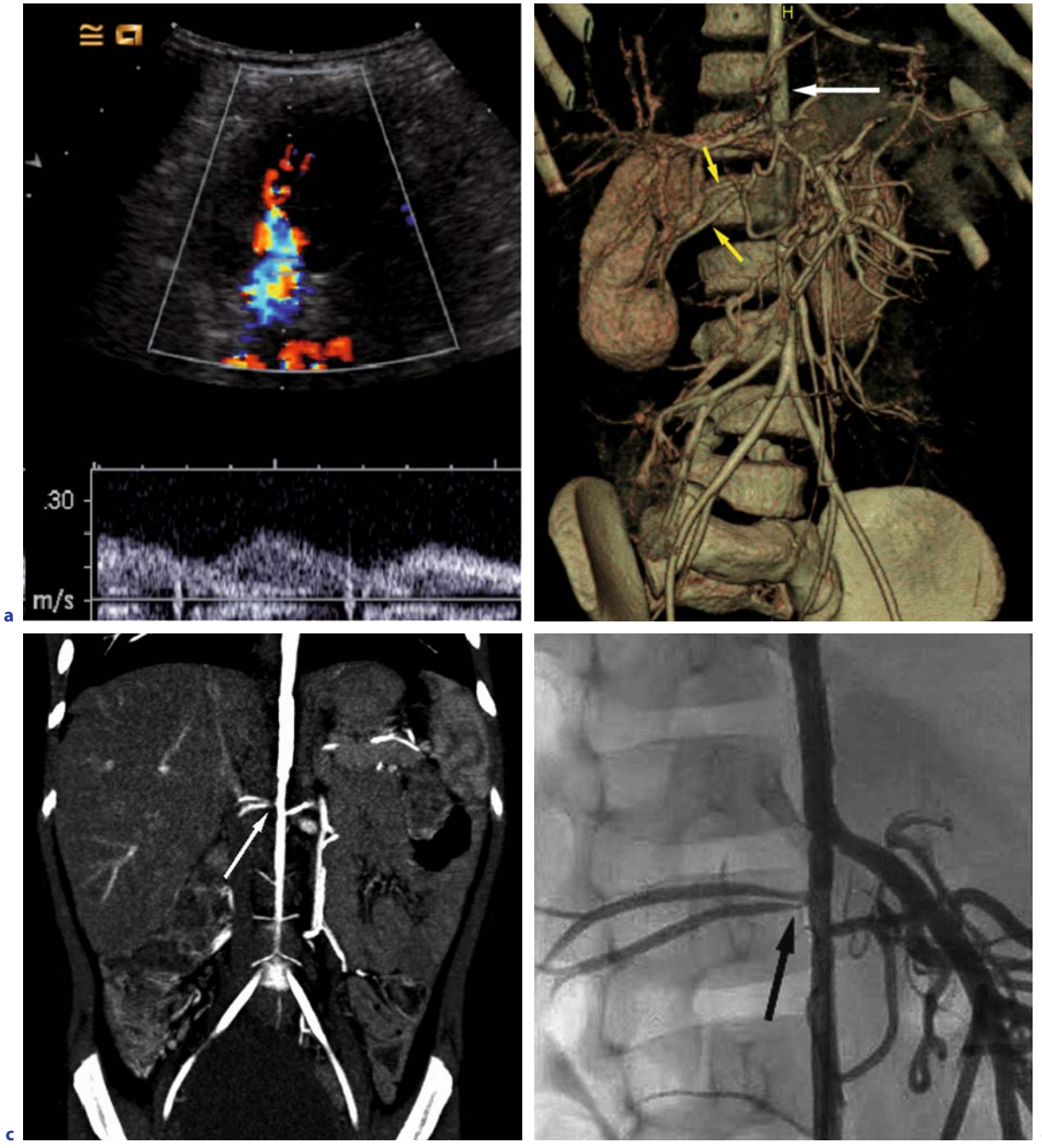


Fig. 22.1a–d. A 7-year-old male with neurofibromatosis type 1 and middle aortic syndrome. **a** Doppler ultrasound shows a "tardus et parvus" pattern with prolonged acceleration time and low velocity systolic peak in an artery at the right renal hilum. This was also present on the left side, suggesting aortic and/or bilateral renal artery stenosis. **b** Volume-rendered CT image shows an aortic stent (*large arrow*). There are two arteries to the right kidney (*small arrows*). **c** Coronal reformatted CT image shows that these two arteries have a common origin, which may be narrow (*arrow*). **d** Aortography confirms that the right renal arteries have a common origin (*arrow*) and shows that both have mild focal stenoses

Table 22.2. Potential indications for angiography in children with hypertension

Clinical indications
Extremely high blood pressure at presentation
Secondary symptoms (e.g. neurological symptoms, cardiac failure)
Syndrome associated with renovascular disease • Neurofibromatosis type 1 • Williams syndrome • Tuberous sclerosis
Evidence of large vessel vasculitis
Abdominal bruit
Anti-hypertensive treatment • Hypertension not controlled on one or two drugs • Unacceptable adverse effects of antihypertensive drugs
Renal transplant
Evidence of renovascular disease at non-invasive imaging

Renal scintigraphy using ^{99m}Tc-labeled DMSA or MAG3, before and after administration of an angiotensin-converting enzyme inhibitor such as captopril, is potentially a very elegant method of revealing RVD in children (Fig. 22.2). However captopril scintigraphy is weak in bilateral or segmental disease and it remains controversial whether it forms part of a rational algorithm for the evaluation of high BP in children. In practice, the results of this technique have not been good enough to identify with sufficient accuracy which children with severe hypertension do not need angiography.

The sensitivity and specificity for RVD are reported to be 59–73% and 68–88%, respectively (Ng et al. 1997; Minty et al. 1993). Although detection of segmental abnormalities is sometimes possible with this technique (Cheung et al. 2004), the high prevalence of bilateral and/or branch artery RVD may well limit its utility in children.

Computed tomographic angiography (Fig. 22.1) and magnetic resonance angiography (Fig. 22.2) both provide excellent images of the aorta and main renal arteries in children. Limitations of spatial resolution make it difficult to exclude stenosis of branch and accessory arteries, however, and further technical developments are required to overcome this problem. One possibility is that MR perfusion techniques may allow the indirect identification of RVD by identifying delayed perfusion of one kidney or a segment of kidney.

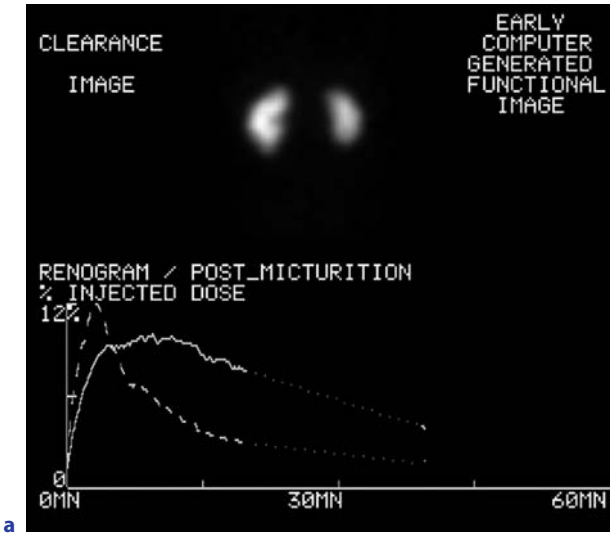
For the time being, however, the superior spatial resolution of digital subtraction angiography (DSA) means that it has the most important role in the assessment of pediatric RVD. In addition, DSA is the basis of endovascular intervention (Tullus et al. 2007).

In small children, less than about 10 years old, DSA is usually performed under general anesthesia, especially if angiography is being performed with a view to immediate intervention. Muscle relaxants are used to allow the suspension of ventilation during acquisition, to minimize subtraction artefacts. Diagnostic angiography is usually performed following ultrasound-guided puncture of the common femoral artery. Biplane aortography provides views of the origins of the renal and visceral arteries (Fig. 22.1). Selective renal angiography with oblique projections is performed to provide detailed images of the renal arteries and their branches without opacification of overlying superior mesenteric artery branches (Fig. 22.2). Views of the pelvis and celiac branches are included for surgical planning when required. Renal vein renin sampling, which can be performed at the same time as DSA, can be useful for lateralizing an ischemic focus or even localizing it within a kidney (Deal et al. 1992; Teigen et al. 1992).

22.5 Endovascular Treatment

The decision to proceed to angioplasty or stenting is best made by a multidisciplinary renovascular team (Tullus et al. 2007). The common femoral artery is the usual access point, with an appropriately sized sheath size according to the size of the child and the planned procedure. Adult coronary angioplasty systems are particularly useful for small children and segmental renal artery stenoses. These can be introduced through a 4-F sheath or a 6-F guiding catheter. Angioplasty is often successful, particularly in simple main renal artery stenoses (Fig. 22.3) (Shroff et al. 2006). In children, stenting is still controversial and is therefore usually reserved for treatment of complications or for stenoses that recur rapidly following initial clinical success (Shroff et al. 2006).

Embolization may be appropriate if DSA and renal vein renin sampling localize a segmental



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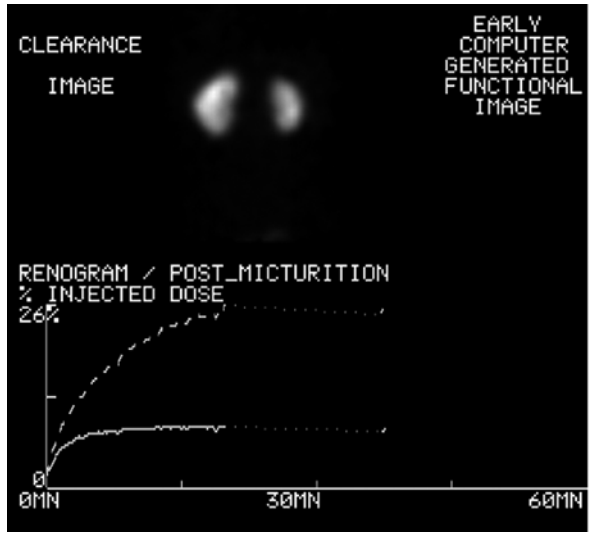

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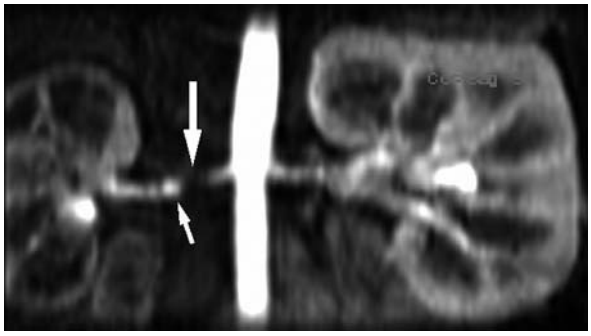

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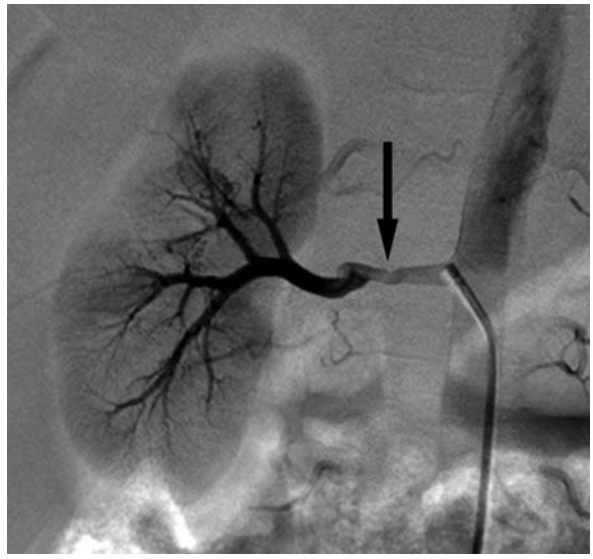

d

Fig. 22.2a–d. A 5-year-old male with right renal artery stenosis. **a** Pre-captopril scintigraphy with ^{99m}Tc-labeled mercaptoacetyltriglycine (*MAG3*). The left kidney (*dashed line*) shows normal handling of the tracer. The right kidney shows slow transit, and only 40% of total renal function. **b** Post-captopril MAG3 scintigraphy. There was a significant hypotensive response to captopril (systolic blood pressure fell from 170 to 100 mmHg). This accounts for the delayed transit on the left side. The right kidney shows more prolonged transit than before and a small fall in divided function to 37%. These findings suggest right renal artery stenosis. **c** Contrast-enhanced magnetic resonance angiography (*MRA*) shows stenosis of the right main renal artery (*large arrow*) and suggests that there may be a post-stenotic dilatation (*small arrow*). **d** Digital subtraction angiography confirms the stenosis (*arrow*) and post-stenotic dilatation. Note that the MRA underestimates the extent of intrarenal disease

ischemic focus. Ethanol is injected into a segmental artery in order to destroy the appropriate area of renal parenchyma by causing irreversible endothelial damage (Teigen et al. 1992). There are many surgical options for RVD in childhood, but these are usually reserved for children in whom endovascular therapy is not feasible or has failed (Tullus et al. 2007).

Conclusion

RVD is an important cause of childhood hypertension. When certain clinical and/or imaging findings suggest RVD, children with hypertension should be referred to a multidisciplinary paediatric renovascular team for consideration of endovascular therapy.

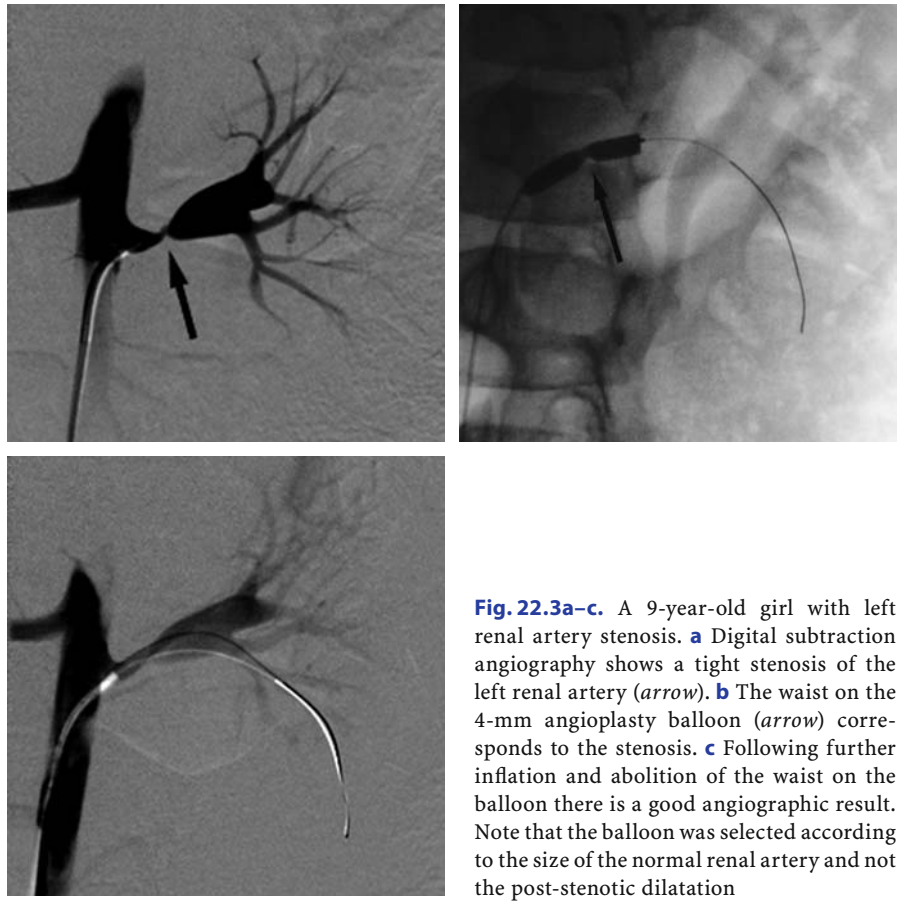

Fig. 22.3a–c. A 9-year-old girl with left renal artery stenosis. **a** Digital subtraction angiography shows a tight stenosis of the left renal artery (*arrow*). **b** The waist on the 4-mm angioplasty balloon (*arrow*) corresponds to the stenosis. **c** Following further inflation and abolition of the waist on the balloon there is a good angiographic result. Note that the balloon was selected according to the size of the normal renal artery and not the post-stenotic dilatation

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The Newborn with Oligoanuria

23

Ekkehard Ring and Richard Fotter

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E. Ring, MD
Professor, Department of Pediatrics, Division of General Pediatrics, University Hospital Graz, Auenbruggerplatz 30, 8036 Graz, Austria
R. Fotter, MD
Professor and Chairman, Department of Radiology, Head Division of Pediatric Radiology, University Hospital Graz, Auenbruggerplatz 34, 8036 Graz, Austria

23.1 Introduction

The neonatal period, defined as the first 4 weeks of life, is probably the most vulnerable period of life. The sudden change from intrauterine to postpartal life may lead to acute presentation of pre-existing renal diseases compensated by the mother prenatally. Birth may be complicated and lead to organ failure, or an acquired disease may start so early in life. The management of a baby with neonatal renal failure is a therapeutic challenge, and a well-equipped neonatal intensive care unit (NICU) is needed. This chapter describes the diagnostic and possibly therapeutic methods that can be offered by pediatric radiologists to these severely compromised neonates in an intensive care situation with sometimes limited potential for investigation.

23.2 Prenatal Situation

Significant fetal urine production starts at approximately 12 weeks of gestation and reaches values of 30–60 ml/h at the end of pregnancy. Fetal urine is a major constituent of amniotic fluid. Oligohydramnios may indicate fetal renal insufficiency such as in bilateral renal agenesis, which leads to Potter syndrome and includes pulmonary hypoplasia. Nephrogenesis has a centrifugal pattern and is completed at 36 weeks of gestation. Destroyed nephrons cannot be replaced by new filtering units. Thus, prematurely born infants are the only humans able to harvest new nephrons after birth. Fetal renal blood flow (RBF) and glomerular filtration rate (GFR) are low. Plasma renin activity is high, and production of renal prostaglandins is increased. Fetal homeostasis is maintained by the placenta and the maternal renal function.

23.3 Changes after Birth

There is a sharp rise in RBF and GFR after birth. Plasma renin activity and production of renal prostaglandins decrease, but remain elevated compared to older children. These changes with an increase in renal blood-flow velocity and a decrease in renal vascular resistance can be demonstrated by Doppler ultrasound in term and preterm neonates (Visser et al. 1992; van de Bor 1995). Maturation of renal function is mostly due to enlargement of the glomerular capillary surface area, a rise in ultrafiltration pressure, and further development of tubular function. On the first day of life, serum creatinine roughly equals maternal values even in cases with fetal renal failure. Prematurely born infants have higher levels of creatinine, and their postnatal increase in creatinine clearance is delayed compared to term neonates. This is valid especially in very low birthweight infants (Bueva and Guignard 1994; Drukker and Guignard 2002). This may reflect the lower GFR and the mean blood pressure of premature neonates being too low to eliminate the excess creatinine transferred by the mother. In addition, tubular reabsorption of creatinine through the leaky immature tubules occurs (Guignard and Drukker 1999a). Despite the various processes of adaptation and maturation after birth, the newborn is in a physiologic state of renal insufficiency with hyperactive vasoactive systems and a GFR as low as 20 ml/min for 1.73 m^2 in term infants (Guignard et al. 1991; Toth-Heyn et al. 2000). This situation is appropriate for normal life after birth, but renal functional reserve is limited in disease states. Therefore, potentially nephrotoxic agents such as contrast media should be avoided in neonates. The dosage of drugs must carefully be adjusted to the actual renal function.

23.4 Urine Production after Birth

First voiding often takes place in the delivery room. Healthy newborns pass urine during the first 24 h of life in 92%–97% of cases, and nearly all void within 48 h (Clark 1977; Wang and Huang 1994). Normal urine volume is 1–3 ml/kg and h. Thus, polyuria is defined as urine output of more than 4 ml/kg and h and oliguria as less than 0.5–1.0 ml/kg and h. Acute renal failure (ARF) is rare in apparently healthy neonates with a normal fetal ultrasound. The incidence of ARF in a NICU ranges from 1.5% to 23%. Oligoanuria is the leading symptom in about 40% of cases, and 60% suffer from non-oliguric ARF (Andreoli 2004; Hentschel et al. 1996; Karlowicz and Adelman 1995; Kupferman 1994; Stapleton et al. 1987).

23.5 Diagnostic Workup

If oligoanuria is recognized, many urgent questions arise, and the potentially underlying conditions should be recognized (Table 23.1). Before starting extensive investigations, pitfalls should be excluded. Previous voiding may have been missed; urine collection may be inappropriate with loss around the collection bag. Urine can be mixed with stool, and a previously inserted bladder catheter may be displaced or blocked. If true oligoanuria is combined with an increased serum creatinine, renal failure is proven. It is traditionally classified as prerenal, intrinsic, or postrenal failure. The term "prerenal" or "functional" implies a systemic disease with normalization of urine flow and of renal function after appropriate therapy. Intrinsic renal failure occurs in congenital or acquired renal diseases or by transition from prolonged prerenal failure. Chronic renal failure may be the long-term consequence. Postrenal failure is mostly found in obstructive uropathy.

23.6 Clinical and Laboratory Investigations

23.6.1 History

Evaluation or re-evaluation of family history and of pregnancy may reveal previous cases of fetal or neonatal death suggestive of inherited disorders or syndromes. Administration of angiotensin-converting enzyme inhibitors (ACE-inhibitors) for hyperten-

Table 23.1. Differential diagnosis of neonatal oligoanuria (adapted from Brion et al. 1997)

1. Primary non-renal diseases (prerenal failure)
a) Hypovolemia Dehydration, reduced intake, increased losses (VLBW infant, phototherapy, stool, polyuria, third space as in peritonitis or NEC)
b) Blood loss (placental, umbilical)
c) Hemodynamic compromise Cardiac failure, surgery, hypotension, shock, PDA, AIST
d) Respiratory failure (IRDS, high mean airway pressure)
e) Septicemia
f) Asphyxia, hyperviscosity, anemia
2. Primary renal diseases (intrinsic failure)
a) Congenital (dysplasia, hypoplasia, agenesis, ARPKD)
b) Acquired Acute cortical, medullary, tubular necrosis, prolonged prerenal failure Renovascular accident (arterial, venous, DIC) UTI–pyelonephritis Toxic effects, drugs (indomethacin, ACE inhibitors, aminoglycosides), contrast media, myoglobin, uric acid
3. Urinary tract obstruction (postrenal failure)
a) Congenital (UPJO, UVJO, ureterocele, prune-belly syndrome, pelvic tumor, hydrometrocolpos, neurogenic bladder)
b) Acquired (fungus balls, urolithiasis, urinary ascites)
4. Miscellaneous causes
a) Maternal drugs (such as NSAID, ACE inhibitors, immunosuppressants)
b) Twin-to-twin transfusion syndrome
c) Neonatal (syndrome of inappropriate ADH release)
5. Pitfalls
Inappropriate collection, blocked bladder catheter, inability to void (sedation, relaxation)

sion during pregnancy may cause significant neonatal morbidity including renal failure (Shotan et al. 1994). Prolonged in utero exposure to nonsteroidal anti-inflammatory agents such as indomethacin is reported to cause irreversible renal parenchymal lesions, including formation of cysts, with neonatal anuria (van der Heijden et al. 1994; Kaplan et al. 1994). In general, maternally administered drugs may cause prematurity, intrauterine growth retardation, and functional or structural renal lesions (Boubred et al. 2006; Prevot et al. 2002). Unbalanced shunting of blood in monochorionic twins (twin-to-twin transfusion syndrome, TTTS) may lead to chronic hypotension, hypovolemia, and fetal renal failure with oligohydramnios in the donor twin. The acceptor twin may suffer from hypervolemia, hydrops, and cardiac failure (Beck et al. 2005; Galea et al. 2005). Prenatal ultrasound may have shown uni- or bilateral dilatation of the fetal urinary tract, a distended bladder, an increased echogenicity suggestive of renal dysplasia, or autosomal-recessive polycystic kidney disease (ARPKD), cystic changes, or oligohydramnios as a sign of fetal renal insufficiency. Birth may have been complicated by as-

phyxia or severe fetal bleeding caused by placenta previa or rupture of the umbilical cord.

23.6.2 Clinical Status

First, the cardiocirculatory and the respiratory condition are of importance. Issues concerning the state of hydration, presence of edema, current blood pressure, and need for intensive care management with artificial ventilation or vasopressor support must be assessed. Femoral pulses are absent in aortic coarctation and pounding in patent ductus arteriosus (PDA). Further investigation of the newborn baby may show the features of malformations or syndromes. A wrinkled abdominal aspect and cryptorchism are diagnostic for prune-belly syndrome. Potter syndrome, originally described in bilateral renal agenesis, is found in all neonates with pronounced fetal renal insufficiency and is characterized by low-set ears, a small chin, and clubbed feet. Palpation of the abdomen can show a distended and nonexpressible bladder associated with posterior urethral valve or an abdominal mass suggestive of hydronephrosis, cystic kidneys, or renal venous thrombosis.

23.6.3 Laboratory Investigations

If not already performed, bladder catheterization (urethral or suprapubic) is mandatory to collect urine (if present) for analysis. Thus, continuous monitoring of persistent anuria or of increasing urine output is possible. Urinalysis may show hematuria and proteinuria, suggesting intrinsic renal failure or renovascular compromise; bacteriuria is diagnostic for urinary tract infection. Simultaneous testing of urine and plasma for electrolytes and creatinine enables determination of fractional excretion of sodium (FENa). This may be helpful to distinguish prerenal and intrinsic failure. FENa greater than 3% combined with plasma creatinine more than 1.5 mg/dl (130 µmol/l) indicates intrinsic failure. Yet FENa is not valid in very-low-birthweight (VLBW) neonates and after administration of diuretics (Chevalier et al. 1984; Guignard and Drukker 1999b). The serum creatinine levels and the urine output during appropriate therapy yield valuable information about the reversibility of acute renal failure or progression to chronic renal failure.

23.6.4 Diagnostic Imaging

23.6.4.1 Basic Situation

Renal ultrasound has dramatically changed and improved the diagnostic and therapeutic possibilities in neonatal renal disease. Fetal renal ultrasound is available in most pregnancies. Thus, we are aware in advance that many newborns have significant renal and urinary tract pathology. Yet a normal fetal and a normal neonatal ultrasound do not exclude renal disease, and the severity of prenatal and postpartal findings may be different. The basic approach to neonates with oligoanuria is: (1) stabilize the baby, (2) get basic imaging with ultrasound, including Doppler sonography (DS) and amplitude-coded color Doppler sonography (aCDS) as noninvasive bedside investigations, and (3) adjust therapy according to the findings (e.g., suprapubic catheter in suspected posterior urethral valve). If the definite diagnosis is not yet established, one has time to consider further imaging. As a rule, the impact of imaging on therapy at a given time must be weighed against the risk of compromising the baby by transport or delay of medical therapy.

23.6.4.2 Ultrasound

Normal values for renal size in newborns are available (see Chap. 28). The normal ultrasound appearance shows a bright cortical echogenicity, probably related to the high proportion of glomeruli compared to tubular structures, and almost anechoic pyramids (Scott et al. 1990; Slovis et al. 1993). Transient medullary hyperechogenicity was found in 13%–58% of neonates (Riebel et al. 1993; Starinsky et al. 1995; Howlett et al. 1997; Nakamura et al. 1999). It seems to be a transient phenomenon depending on urine flow, protein excretion, or protein cast deposition and is not a sign of renal failure. The term hyperechoic papillae has been introduced and will eventually replace other nomenclature (Nakamura et al. 1999). Five ultrasound appearances are associated with neonatal oligoanuria: (1) no kidney present, (2) uni- or bilateral hydronephrosis, (3) cystic lesions, (4) focal or generalized hyperechogenicity, and (5) focal accumulation of echodense material. These appearances, more than one of which can be present in a single patient, combined with determi-

nation of renal size (small or enlarged) and evaluation of clinical data, will point to or establish the correct diagnosis in most cases (Figs. 23.1, 23.2). For example, bilateral hydroureteronephrosis with echodense kidneys and cortical cysts in a boy with a trabeculated bladder wall is almost diagnostic for oliguric renal failure in posterior urethral valves. The differential diagnosis of oligoanuria in enlarged hyperechoic kidneys without corticomedullary differentiation is shown in Table 23.2.

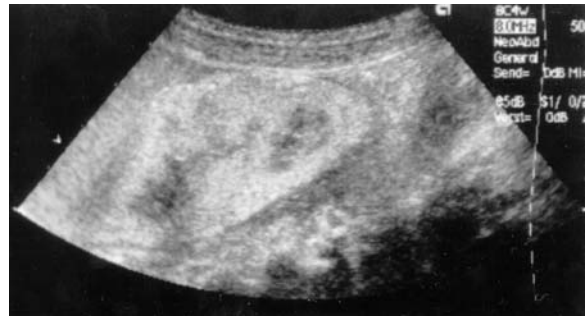

Fig. 23.1. Sonography: echodense kidneys in acute renal failure

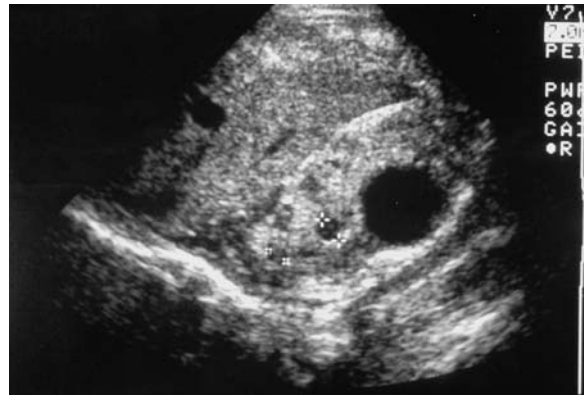

Fig. 23.2. Sonography: renal dysplasia with cortical cysts and a dilated renal pelvis in prune-belly syndrome

Table 23.2. The differential diagnosis of oligoanuria in enlarged hyperechoic kidneys without corticomedullary differentiation

Acute tubular necrosis
Renal venous thrombosis
Autosomal recessive polycystic kidney disease
Diffuse cystic dysplasia
Septicemia including renal candidiasis
Contrast nephropathy

23.6.4.3 Doppler Sonography and Amplitude-Coded Color Doppler Sonography

Both Doppler sonography and amplitude-coded color Doppler sonography investigations add functional imaging to the anatomic description of ultrasound and are mandatory in neonatal oligoanuria (Gordon and Riccabona 2003). Reduced renal systolic flow velocity in asphyxiated neonates on the first day of life has been reported to have 100% sensitivity for subsequent development of renal failure (Luciano et al. 1998). These and further findings can influence therapy significantly. Normal renal architecture with a normal perfusion may indicate a favorable outcome in prerenal failure, while focal nonperfused areas are found in renal cortical or medullary necrosis or renovascular accidents. Decreased systolic flow velocity and an increased resistive index are found in cystic dysplastic kidneys (Riccabona et al. 1993).

The ultrasound appearance of renal venous thrombosis – being unilateral in the majority of neonates – may vary with the stage of disease (Wright et al. 1996; Hibbert et al. 1997). Initially, the interlobular or interlobar thrombus may be visible as an echogenic streak. Calcification of the thrombus at diagnosis supports an antenatal onset of thrombosis being present in at least some cases. Swelling of the kidney leads to increased echogenicity with prominent echo-poor pyramids. A renal length of 60 mm or more at presentation strongly predicts permanent kidney damage as outcome (Winyard et al. 2006). Later, the kidney becomes heterogeneous with loss of corticomedullary differentiation. Focal scarring or an atrophic kidney, documented by ultrasound follow-up investigations or a DMSA-scan, may be the result. If renovascular supply is compromised, DS of the great vessels must be performed and may show thrombosis of the vena cava inferior in renal venous thrombosis or of the abdominal aorta in renal artery thrombosis (Ellis et al. 1997). ACDS may add valuable information to DS concerning the general blood supply of the kidney or the presence of focal nonperfused areas. This sensitive investigation is to a great extent dependent on the skill of the investigator and the quality of the equipment. To date, there are no data on the optimal setting and standardization for neonates.

23.6.4.4 Isotope Investigations, Computerized Tomography, and Intravenous Pyelography

Isotope investigations are widely performed in various renal diseases and give valuable results even in neonates (Wong et al. 1995; Gordon and Riccabona 2003). There seems to be no indication in acute oliguric renal failure, but results are important during follow-up for split renal function, renal scarring, and urinary obstruction. Computerized tomography and intravenous pyelography require the use of contrast medium and are contraindicated in renal failure.

23.6.4.5 Use of Contrast Medium

Use of contrast medium is contraindicated in renal failure. In general, contrast medium may decrease renal blood flow and cause contrast nephropathy with acute renal failure (Murphy et al. 2000). Contrast medium should be avoided in neonates even with normal renal function. If indicated (e.g., for cardiac catheterization), adequate hydration of the neonate is mandatory. Administration of the adenosine antagonist theophylline seems to be a promising means of preventing contrast nephropathy (Kolonko et al. 1998; Huber et al. 2006). This is also of value in neonates and preterm neonates, where theophylline was reported to improve renal function in neonates with respiratory distress syndrome (Huet et al. 1995; Cattarelli et al. 2006).

23.6.4.6 Voiding Cystourethrography

Voiding cystourethrography (VCU) is an integrative part of investigating neonates with urinary tract malformations. It may be indicated in oliguric neonates with postrenal failure due to posterior urethral valves or bilateral megaureters to differentiate obstructive and refluxive units and to determine the site of intervention (vesical or supravesical). Ultrasound-guided VCU using contrast medium for US and improvement by addition of harmonic imaging are reported as an alternative to conventional VCU (Darge et al. 1999, 2005). This setting enables bedside investigation and is of value especially in severely compromised NICU patients. Another rare indication for VCU is postrenal failure in pelvic tumors. A congenital bladder rupture may be present, and VCU can show urine extravasation (Zaninovic et al. 1992). In most situations, however, VCU can be delayed and is performed after stabilization of the baby.

23.6.4.7 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) can be performed even in neonates and provides excellent anatomic imaging in this special group of patients (Avni et al. 2002; Riccabona et al. 2002). Additional diffusion weighted MRI could be a promising future tool. Although eventually applied, we are not aware of valuable data concerning MRI in neonates with renal failure. There is no restriction to perform renal MRI without gadolinium-containing contrast media even in oligoanuric neonates. However, application of gadolinium-containing contrast media for MRI to patients with renal failure is of major concern nowadays. Development of nephrogenic systemic fibrosis (NSF) is a serious and life-threatening adverse event (see Chap. 29). NSF is directly correlated to gadolinium (mostly to gadodiamide), which was found to be deposited in affected tissues (Thomsen et al. 2006; Broome et al. 2007). Aside from emergency situations, we currently do not recommend MRI with application of intravenous contrast media in neonates and infants during the first 2 months of life, even with a normal renal function. An informed consent of the parents for intravenous application of contrast media for MRI has to be obtained like in CT with contrast media. In addition, serum creatinine representing actual renal function has to be known before the investigation. Future research will show whether the contrast-media-associated side effects can be overcome and whether MRI can offer valuable information on neonatal renal disease with oligoanuria in addition to US, DS, and aCDS. The latter investigations are performed much more easily and at lower cost.

23.7 Therapeutic Aspects

After diagnosis, therapy of oligoanuria depends on the underlying causes. Recovery of renal function may follow rehydration, blood replacement, vasopressor support to improve cardiac output, administration of furosemide, and termination of therapy with toxic drugs such as indomethacin or amphotericin.

Persistent oligoanuria indicating established intrinsic renal failure needs careful management to correct the metabolic disturbances. Renal replacement therapy is indicated in diuretic-resistant hypervolemia, electrolyte disturbances such as hyperkalemia, or prolonged oligoanuria. It can be performed as peritoneal dialysis, hemodialysis, or continuous hemo(dia)filtration, and the latter seems to be the method of choice in a NICU situation (Fischbach 1996; Sadowski et al. 1994; Zobel et al. 1998). Diagnostic imaging can show improvement of renal perfusion or deterioration indicating a poor outcome. Therapeutic interventions with ultrasound guidance such as suprapubic bladder puncture or percutaneous nephrostomy are indicated mostly in postrenal failure caused by primary obstructive malformations or in obstructive fungal infections for local application of antifungal agents (Garcia-Nieto et al. 1997; Visser et al. 1998).

Renal venous thrombosis seems to be highly associated with prothrombotic risk factors, mostly factor V Leiden mutations (Pohl et al. 1998; Kosch et al. 2004). The therapy is controversial, but anticoagulation with heparin may be recommended. Thrombolytic therapy with urokinase or plasminogen tissue activator carries the risk of severe bleeding and must be weighed against the benefit for the kidneys (Nuss et al. 1994; Brun et al. 1993). Recent publications showed that most patients do not respond to therapy (Messinger et al. 2006; Winyard et al. 2006). A more aggressive approach probably is indicated in bilateral renal thrombosis with oliguric renal failure where development of chronic renal failure is imminent. Patients with severely compromised kidneys may develop arterial hypertension, and nephrectomy is indicated in some.

Patent ductus arteriosus (PDA), found in 20%–30% of premature babies with respiratory distress syndrome, may be an ambiguous problem for the kidneys. Artificial ventilation and congestive heart failure can cause prerenal failure with renal hypoperfusion. Intrinsic renal failure may be the consequence if conservative therapy fails. Indomethacin is frequently given for closure of PDA. This drug also acutely decreases renal blood flow by inhibition of renal prostaglandin synthesis. Indomethacin-induced changes can be demonstrated by DS (Van Bel et al. 1991). Thus, therapy also may lead to oligoanuria and a compromised renal function in a significant number of patients (Akima et al. 2004). Careful treatment with dopamine or theophylline and monitoring of renal function is mandatory before indomethacin is given. It is contraindicated in established oliguric renal failure.

23.8 Prognosis

The outcome after neonatal oligoanuria depends on the underlying causes, and there is great variation among the different populations studied. Prerenal failure is reversible in more than 70% of cases. The mortality rate in intrinsic renal failure is approximately 50% (Chevalier et al. 1984; Stapleton et al. 1987), but death is mostly due to extrarenal causes such as cerebral bleeding, pulmonary failure, or low cardiac output after cardiac surgery. Improvement of intensive care medicine has influenced the outcome. Nowadays, the survival rate of neonates with renal replacement therapy is about 60% (Zobel et al. 1998). Persistently decreased creatinine clearances were found in 40% of neonates after oliguric renal failure, mostly due to asphyxia and vascular thromboses (Stapleton et al. 1987). This number may be higher if a severe malformation of the kidneys and the urinary tract is the basic disease. Most neonates with acute renal failure have such a recovery of renal function that neonatal end-stage renal disease (ESRD) requiring dialysis from birth is exceptional. The outcome of neonates with ESRD is similar to patients initiating dialysis later in infancy (Carey et al. 2007).

Prematurity, fetal growth retardation, and neonatal renal disease may cause a reduced number of nephrons, named congenital oligonephropathy, being of major concern for long-term follow-up. As initially proposed by Brenner and Chertow (1994), an association with childhood and adult arterial hypertension, and with renal or cardiovascular disease of adults was confirmed (Drukker and Guignard 2002; Rostand 2003). Thus, the origin of adult disease may be found early in infancy, indicating the need for long-term observation in prematurely born infants and in those with neonatal renal disease.

Conclusion

Sonography, Doppler sonography, and amplitude-coded color Doppler sonography are essential for differential diagnosis of neonates with oligoanuria and are useful to monitor therapy. If indicated, further investigations such as voiding cystourethrography or isotope studies can be delayed and are performed after stabilization of the neonate in most cases. Long-term follow-up is mandatory, even in cases with apparent complete recovery of neonatal renal failure.

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Renal Neoplasms

24

Hervé Brisse, Dominique Couanet, and Sylvia Neuenschwander

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H. Brisse, MD
S. Neuenschwander, MD
Department of Radiology, Institut Curie, 26 rue d'Ulm, Paris 75005, France
D. Couanet, MD
Department of Radiology, Institut Gustave Roussy, 39 Rue Camille Desmoulins, 94800 Villejuif, France

24.1 Introduction

Nephroblastoma or Wilms' tumor is the most common renal neoplasm in children and accounts for 90% of pediatric renal tumors (Grundy et al. 2002). This tumor has a good prognosis and well-established treatment strategies. Other rare renal malignant neoplasms, such as clear cell sarcoma and rhabdoid tumor of the kidney, have a poor prognosis despite aggressive treatment. Renal cell carcinoma occurs in older children, while mesoblastic nephroma is the most frequent renal tumor in the neonate. Hematological malignancies represent the most frequent neoplasm in children and may also involve the kidney, usually with other sites of disease. Infections and malformations are much more common renal diseases in children and may also present with pseudotumoral misleading patterns. In all cases, close collaboration among radiologists,

pediatricians and pathologists is essential so as to avoid diagnostic pitfalls due to atypical presentations.

24.2 Wilms' Tumor or Nephroblastoma

24.2.1 Epidemiology

Wilms' tumor (WT) accounts for 6% of childhood cancers, but for 90% of renal tumors in childhood (Grundy et al. 2002). It is the fourth most common pediatric cancer after acute leukemia, brain tumors and neuroblastoma. The incidence of WT is $8.1/10^6$ in Caucasian children below the age of 15 (Breslow et al. 1994).

The most common unilateral form occurs at a mean age of 3.5 years (mostly between 1 and 5 years, 98% before 7 years) with a male to female ratio of 0.92:1 (Grundy et al. 2002). Neonatal or prenatal WTs are extremely rare (Ritchey et al. 1995; Applegate et al. 1999). Familial cases are rare (1–2%) (Grundy et al. 2002). Bilateral synchronous WT may be observed in about 7% of cases, more frequently in girls (sex ratio: 0.6:1), at a younger age (mean: 2.5 years), and are usually associated with the presence of nephrogenic rests, congenital malformations and/or predisposing genetic syndromes such as WAGR (Wilms', aniridia, genitourinary malformation, mental retardation), Denys-Drash or Beckwith-Wiedemann syndrome (Scott et al. 2006) (Table 24.1).

24.2.2 Pathology

24.2.2.1 Wilms' Tumor

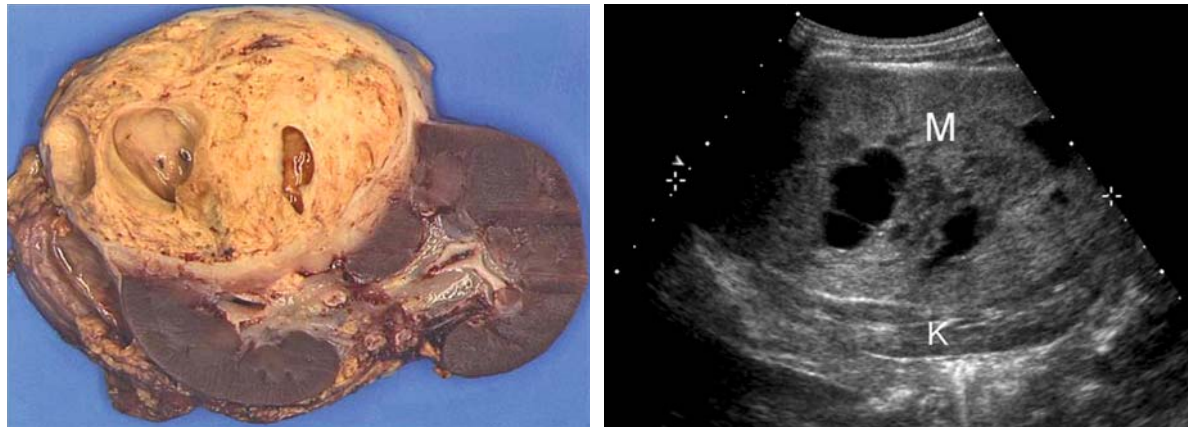
The typical form is a large lesion, surrounded by a pseudocapsule and sharply defined from the adjacent renal parenchyma. Internal structure is usually heterogeneous, with hemorrhagic and/or necrotic cystic areas (Fig. 24.1). The typical "triphasic" tumor is composed of blastemal, epithelial and stromal cells (Schmidt and Beckwith 1995), but variable patterns may be observed. Based on the correlation between the histological features and survival, three histological risk groups were defined by the International Society of Pediatric Oncology (SIOP) (SIOP 2001) (Table 24.2). "Low-risk" tumors are those completely necrotic after neoadjuvant chemotherapy and cystic partially differentiated nephroblastoma (CPDN), a variant that usually occurs in children less than 2 years of age. It is defined by lesions composed entirely of cysts with thin septa (< 5 mm) containing blastemal cells. The prognosis of CPDN is excellent (Luithle et al. 2007). "High-risk" tumors include blastemal and diffuse anaplasia types. Blastemal WT is defined by more than two thirds of the residual viable component consisting of blastema. This type is associated with worse prognosis and resistance to chemotherapy. WT with anaplasia is defined by the presence of atypical mitotic figures, marked nuclear enlargement and presence of hyperchromatic tumor cell nuclei. WT with diffuse anaplasia is a high grade malignancy subtype, uncommon in infants, observed at a mean age of 5 years (Vujanic et al. 1999), and is more frequent in black children. According to the North American National Wilms' Tumor Study (NWTS) classification, WTs with diffuse anaplasia are called "unfavorable" histology. Among the SIOP "intermediate-risk" group, some peculiar histological types are described: teratoid Wilms' tumor is a rare histological variant containing predominantly heterologous tissues (adipose, glial, muscle, cartilage, or bone) (Cecchetto et al. 2003; Park et al. 2003; Inoue et al. 2006). This variant may be bilateral and may presents with pyeloureteral obstruction, uremia and hypertension (Fernandes et al. 1988). Fetal rhabdomyomatous variant is included in the stromal type group and may be resistant to chemotherapy (Maes et al. 1999; Pollono et al. 2003).

24.2.2.2 Nephrogenic Rests and Nephroblastomatosis

Nephrogenic rests (NRs) are persistent embryonal metanephric blastema within the kidney. NRs are discovered incidentally in about 1% of normal infant's kidneys (Aronson et al. 1996). NRs are composed of small clusters of blastemal or epithelial cells, either sharply demarcated at the periphery of the renal cortex, called perilobar nephrogenic rests (PLNRs), or within the renal lobe and called intralobar nephrogenic rests (ILNRs). NRs are histologically classified as: dormant, sclerosing, hyperplastic or neoplastic. Hyperplastic nodules are considered as precursor lesions to Wilms' tumor (Beckwith 1993).

Table 24.1. Major genetic syndromes associated with Wilms' tumor (DeBaun and Tucker 1998; Bliek et al. 2004; Cooper et al. 2005; Rump et al. 2005; Scott et al. 2006a, 2006b)

	WT1 gene (11p13)			WT2 gene (11p15.5)	Other				
Syndromes	WAGR	Denys-Drash	Frasier	Beckwith-Wiedemann	Perlman	Simpson-Golabi-Behmel (type 1)	Sotos	Fanconi anemia D1	Mosaic variegated aneuploidy
Genetics	Constitutional microdeletion WT1 and PAX6	Constitutional mutation exons 8 and 9	Constitutional mutation intron 9	H19 hypermethylation, uniparental disomy	?	Xq26 GPC3 gene mutation	5q35 (NSD1) deletion mutation	13q12.3 Bi-allelic mutation BRCA2	BUB1B gene mutation
Nephrogenic rests	Intralobar	Intralobar	Intralobar	Perilobar	Perilobar				
Estimated tumor risk	50%	> 50%	8%	5–10%	?	10%	4%	?	> 20%
Other renal abnormalities	Genitourinary malformation	Glomerular disease: mesangial sclerosis		Nephromegaly, medullary cysts, caliceal diverticula, hydronephrosis, nephrolithiasis	Nephromegaly, renal dysplasia, cortical hamartomas, hydronephrosis				
Associated features	Aniridia, mental retardation	Male pseudo-hermaphroditism, gonadal dysgenesis, gonadoblastoma		Macrosomia, macroglossia, hemihypertrophy, abdominal wall defects, pancreatic islet cell hyperplasia, hepatoblastoma, rhabdomyosarcoma, adrenocortical tumor	Facial dysmorphism, diffuse muscular hypotonicity, cryptorchidism, pancreatic islet cell hyperplasia, mental retardation	Macrosomia, heart and skeletal abnormalities	Macrosomia, CNS abnormalities	Hematologic malignancies	Growth retardation, microcephalia



a b

Fig. 24.1a,b. Wilms' tumor in a 5-year-old girl. **a** Gross specimen: large, well-limited mass containing cystic areas (courtesy Prof. M. Peuchmaur, Hôpital R Debré, Paris, France). **b** Corresponding abdominal US showing a heterogeneous mass (*M*) containing fluid-filled areas and surrounded by the residual normal parenchyma of the kidney (*K*)

Table 24.2. Revised S.I.O.P. (Stockholm) working classification of pre-treated Wilms' tumors (adapted from: Boccon-Gibod et al. 2000; 2001; Weirich et al. 2001; Vujanic et al. 2002)

Low risk	Intermediate risk	High risk
Cystic partially differentiated	Epithelial type	Blastemal type
Completely necrotic	Stromal type	Diffuse anaplasia
	Mixed type	
	Regressive type (66% to 99% necrosis)	
	Focal anaplasia	

NRs are found in 41% of unilateral WT specimens, in 99% of synchronous bilateral WT and in 94% of metachronous bilateral WT. ILNRs are associated with WT1 syndromes, whereas PLNRs are more commonly observed in Beckwith-Wiedemann or WT2-related syndromes (Beckwith et al. 1990).

Nephroblastomatosis is defined by diffuse or multifocal involvement of the kidneys with NRs. Diffuse perilobar nephroblastomatosis results in bilateral enlarged kidneys with loss of corticomedullary differentiation.

24.2.3 Clinical Features

24.2.3.1 Sporadic Wilms' Tumor

WT is a very rapidly growing tumor, its doubling rate being estimated at 11 days (Craft 1999; Zoubek et al. 1999). Sporadic tumors usually reveal with non-specific clinical symptoms: abdominal mass, pain or swelling. Hematuria, fever (20%) and hypertension (25%) are other frequent findings (Grundy et al. 2002). Varicocele may be associated with renal vein or IVC thrombosis. WT-associated abnormalities are cryptorchidism (prevalence: 4.7%), hypospadias (2%) and sporadic hemihypertrophy (2.5%) (Grundy et al. 2002).

24.2.3.2 Wilms' Tumor Screening in Patients with Predisposing Syndromes

Proposal of screening for WT in children with predisposing syndromes (Table 24.1) is based on the hypothesis that the detection of tumor at an early stage may decrease morbidity and permits curative nephron-sparing surgery. This conservative strategy is now considered in WT associated with Beckwith-Wiedemann syndrome (Porteus et al. 2000; McNeil et al. 2001; McNeil et al. 2002). Screening should be offered after review by a clinical geneticist

to assess the tumor risk according to the individual genetic abnormalities. US is the primary screening examination recommended for children at more than 5% risk of Wilms' tumor. Such screening may be done every 3 or 4 months over 5 to 7 years. As false-positive exams may result in unnecessary surgery, screening-detected lesions should be managed in reference centers (Andrews and Amparo 1993; Choyke et al. 1999; McNeil et al. 2001; Scott et al. 2006).

24.2.4 Imaging of Wilms' Tumor

24.2.4.1 Common WT Radiological Pattern

Since WT is a rapidly growing tumor, the mass is usually well defined and large at diagnosis (> 5–10 cm) (Fig. 24.2). US typically shows a solid non-calcified heterogeneous lesion containing various degrees of anechoic areas representing hemorrhage, necrosis and/or epithelial cysts (Fig. 24.1). CT scan shows a heterogeneous and low attenuating lesion (Fig. 24.2). MR demonstrates a heterogeneous lesion with relative low signal intensity on T1-weighted sequences and low or intermediate signal intensity compared to the renal cortex with hyperintense necrotic or cystic areas on T2-weighted images. After intravenous injection of contrast agent, the lesion displays heterogeneous enhancement to a lesser degree than the normal renal cortex (Babyn et al. 1995; Strouse 1996; Ditchfield 1997; Geller et al. 1997; Goske et al. 1999; Lowe et al. 2000; Riccabona 2003; McHugh 2007).

24.2.4.2 Atypical Patterns

Curvilinear intratumoral calcifications may be observed in 5–10% of WT (Navoy et al. 1995). Macroscopic fatty components are rarely observed (Parvey et al. 1981), but may occur in teratoid forms (Park et al. 2003). CPDN presents as a well-limited, purely cystic mass with multiple septations (Fig. 24.3) (Agrons et al. 1995). This form has to be recognized because it is treated with primary surgery and has an excellent prognosis. "Botryoid" forms have been reported as WT with primarily intrapelvic development (Fig. 24.4) (Honda et al. 2000) and exceptional extension down the ureter into the bladder (Mitchell and Yeo 1997).

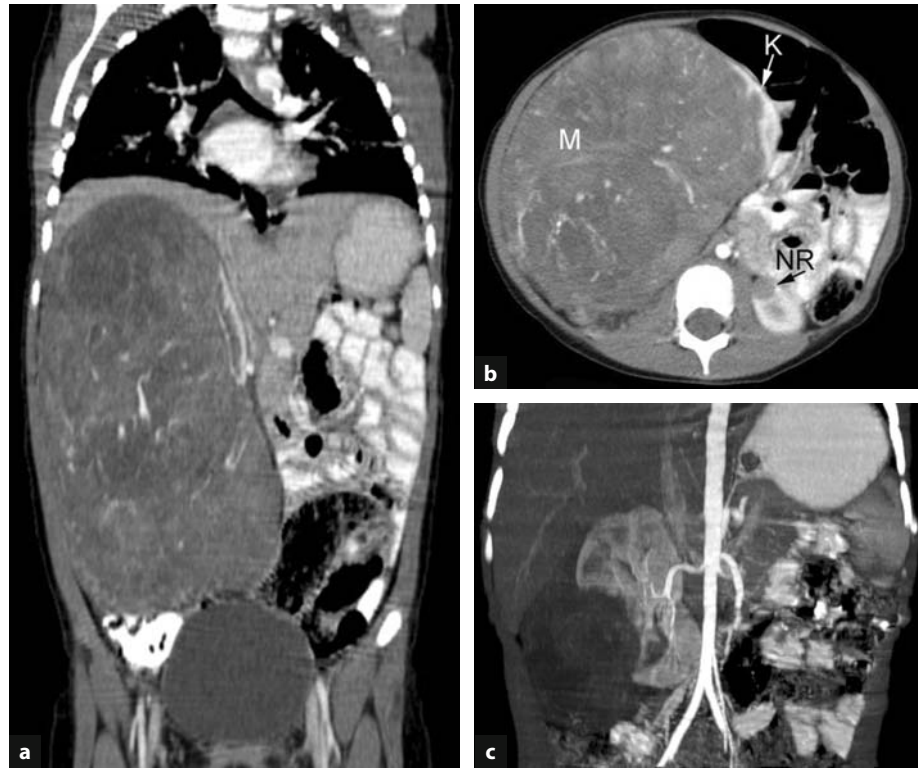


Fig. 24.2a–c. Wilms' tumor in a 4-year-old girl. Enhanced CT scan (**a** coronal, **b** axial) shows a very large heterogeneous and low attenuating right renal mass (*M*), surrounded by normal enhancing residual cortex of the kidney (*K*). One macroscopic nephrogenic rest (*NR*) is also visible at the lower pole of the left kidney (*arrow*). After chemotherapy and prior to surgery, arterial-phase enhanced-CT with MIP reconstruction (**c**) allows a precise assessment of the vascular anatomy

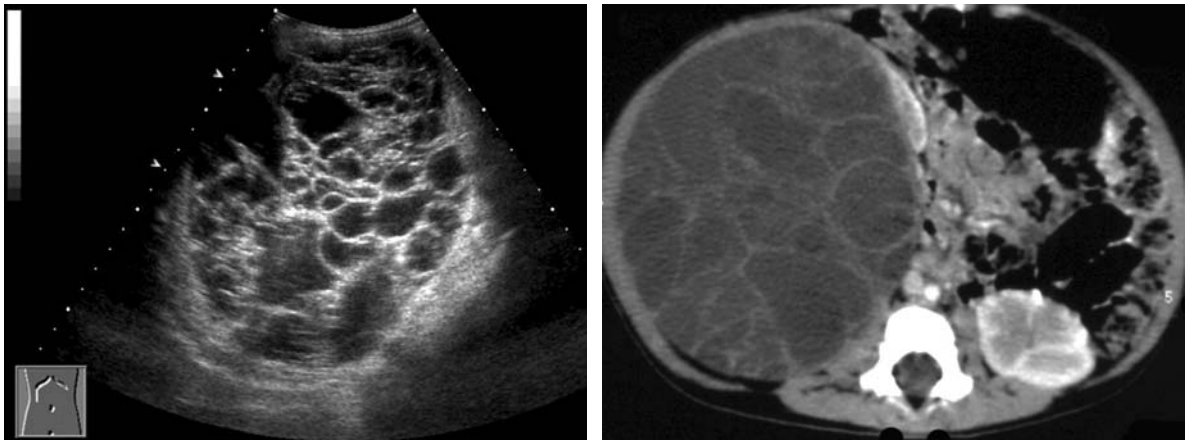


Fig. 24.3a,b. Cystic partially differentiated nephroblastoma (*CPDN*) in an 8-month-old boy. Both US (**a**) and enhanced CT scan (**b**) show a well-limited, purely cystic mass with multiple septations

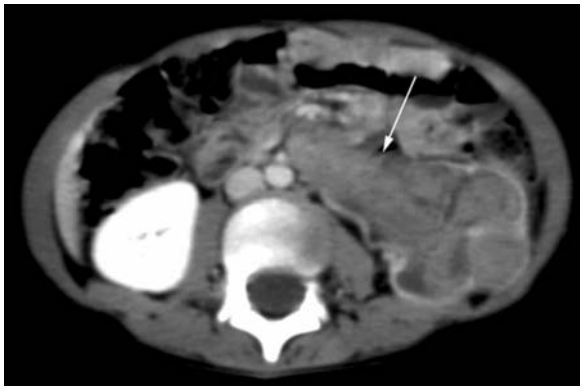


Fig. 24.4. Botryoid form of Wilms' tumor in a 4-year-old girl. Enhanced CT scan shows intrapelvic extension (*arrow*)

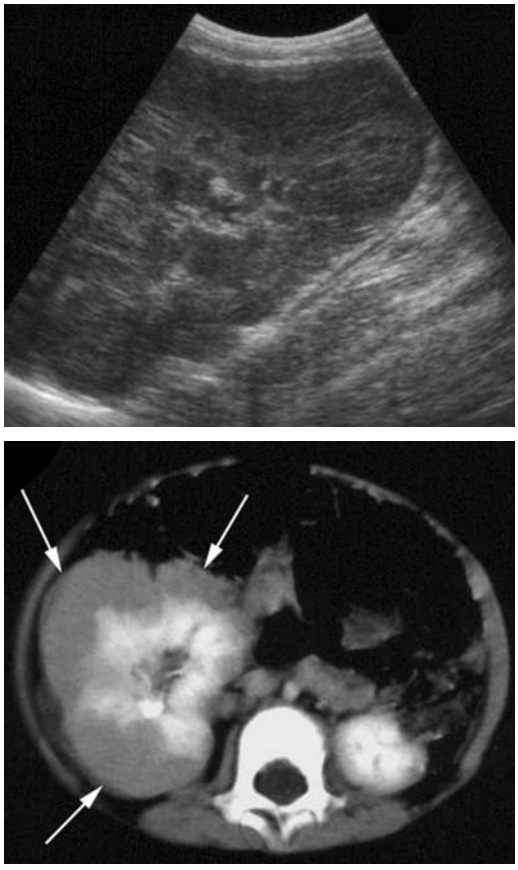


Fig. 24.5a,b. Diffuse nephroblastomatosis in a 2-year-old girl with predisposing syndrome (hemihypertrophy). US (**a**) shows a diffuse enlargement of the right kidney with loss of corticomedullary differentiation. Enhanced CT scan (**b**) shows low attenuating homogeneous peripheral plaque-like masses. Pathological analysis revealed diffuse nephroblastomatosis and three focal stage-I WT

24.2.4.3 Bilateral Disease

Bilateral and/or multifocal nodules may correspond to either bilateral WT and/or nephrogenic rests. Macroscopic NRs are occasionally observed, either in the remaining parenchyma or within the controlateral kidney. At sonography, the conspicuousness of these lesions is mild because their echogenicity is close to that of the renal cortex. Corticomedullary differentiation may be impossible in case of diffuse nephroblastomatosis (Lonergan et al. 1998). NRs appear on CT scan as homogeneous peripheral plaque-like foci or nodules with a slightly higher attenuation value than the normal renal parenchyma on unenhanced images. Nodules enhance homogeneously after intravenous injection of contrast medium, but to a lesser degree than the

normal renal cortex (Fig. 24.5). On gadolinium-enhanced MR T1-weighted images, hyperplastic NRs are hypointense to normal renal tissue. On T2-weighted images, hyperplastic NRs are isointense or slightly hyperintense to renal cortex, while sclerotic nephrogenic rests are hypointense. On all images, the signal intensity of nephrogenic rests is homogeneous (Gylys-Morin et al. 1993) (Fig. 24.6).

In kidney with predominant WT, the additional NRs are more accurately depicted with CT or MRI (sensitivity: 57% and 67%, respectively) than with US (sensitivity: 6%). The most reliable criterion to differentiate NRs from WT is their overall homogeneity (Rohrschneider et al. 1998). However, the differentiation between small WT and NRs cannot rely on imaging only (Fig. 24.7). Therefore, the term "bilateral disease" should preferably be used instead of "bilateral tumors" in imaging reports.

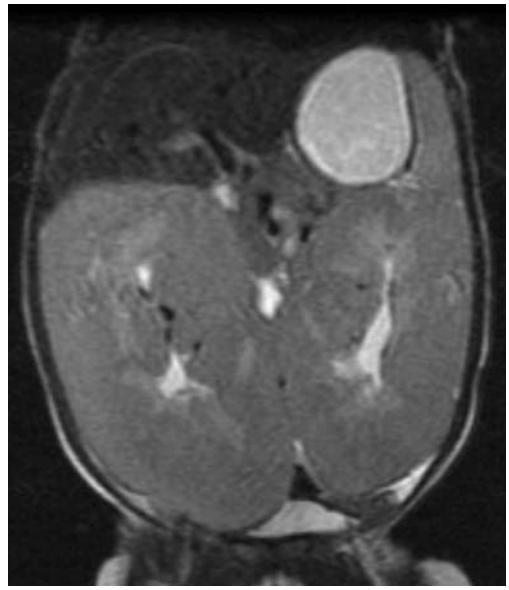


Fig. 24.6. Diffuse nephroblastomatosis. Coronal T2-W MR image showing diffuse enlargement of both kidneys and diffuse thickening of renal cortex (courtesy Dr. A. Smets, AMC, Amsterdam, The Netherlands)

24.2.4.4 Locoregional Tumor Extent

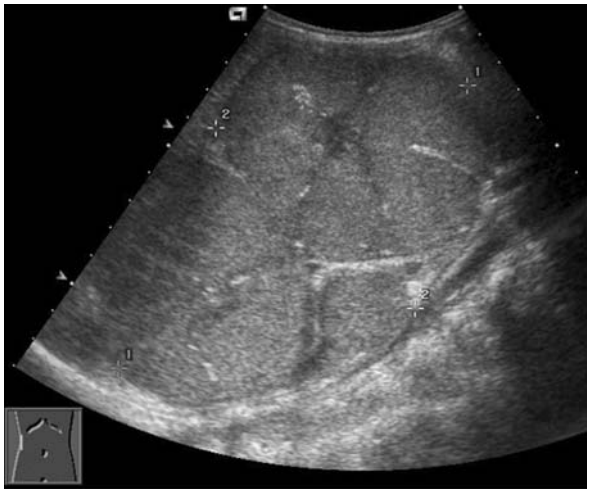
The most relevant information is the vascular extension through the renal vein (Fig. 24.8) and IVC (Fig. 24.9), occurring in 5–10% of cases. Patency of the renal vein is preferably assessed with Doppler imaging, whereas IVC thromboses are usually obvious on 2D US. The superior limit of the thrombus should be noted, and the status of the hepatic veins and the right atrium must systematically be checked in search of intravascular or intracardiac propagation.

Hilar or paraaortic lymph nodes should be mentioned in reports, but carefully interpreted, since small lymph nodes may be invaded, whereas large lymph nodes may be only related to nonspecific inflammation at pathology (Gow et al. 2000). The final local staging is obtained after surgery only, on the basis of pathological findings (Table 24.3).

Although rare, tumor rupture is a major risk factor of abdominal recurrence (Burgers et al. 1986; Shamberger et al. 1999). Tumor rupture may occur spontaneously, after minor abdominal trauma, during a biopsy procedure or during surgery. Preoperative occurrence of tumor rupture is a rare event, and the incidence of emergency surgery related to preoperative tumor rupture was recently estimated at 1.8% (Godzinski et al. 2001). Peritoneal effusion is not a reliable sign of rupture. An isolated small amount of peritoneal fluid, usually located in the Douglas recess, is frequently observed at diagnosis in patients with WT. It is thought to correspond to nonspecific inflammatory reaction of the peritoneum due to the rapid tumor growth or to IVC compression or thrombosis. Patients having retroperitoneal rupture demonstrate intratumoral, subcapsular or perirenal hemorrhage (Byerly et al. 2006) (Fig. 24.10). Spontaneously hyperdense hemoperitoneum and/or intraperitoneal (Fig. 24.11), mesenterical and/or omental masses are related to intraperitoneal dissemination (Slasky et al. 1997).

24.2.4.5 Distant Metastases

Distant metastases at diagnosis are observed in about 10% of cases. The lungs usually are the only site of metastases. The systematic use of chest CT still remains controversial because of the low specificity of lung nodules (McCarville et al. 2006), because of variability in interpretation (Wilimas et al. 1997) and because the impact on survival was not considered to be significant (de Kraker et al. 1990; Cohen 1994; Wootton-Gorges et al. 2000). As a result, in the current SIOP protocol (2001), stage-IV patients are still defined according to chest X-ray only. However, CT allows identifying subgroups of patients who are at increased risk of pulmonary relapse, notably stage I patients treated with reduced



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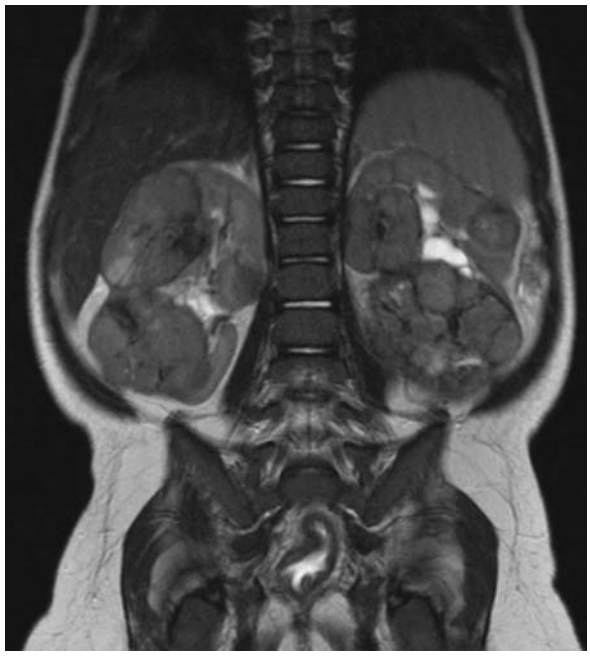

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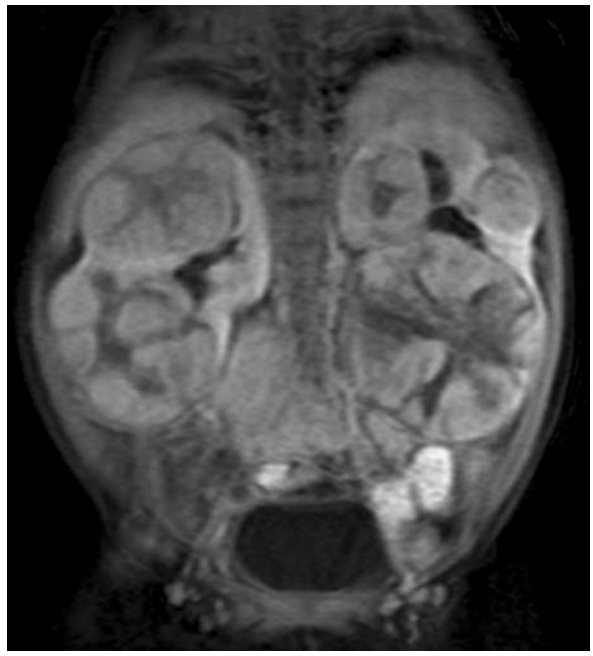


c

Fig. 24.7a–c. Macroscopic nephrogenic rests and Wilms' tumors in a 7-month-old girl. US (**a**) and MR (**b**) coronal T2-W, and (**c**) coronal contrast-enhanced T1-W show multiple bilateral heterogeneous nodules. After bilateral nephrectomy, pathological analysis showed two stage-I WT and three macroscopic nephrogenic rests on the right side and eight stage-I WT and two nephrogenic rests on the left side

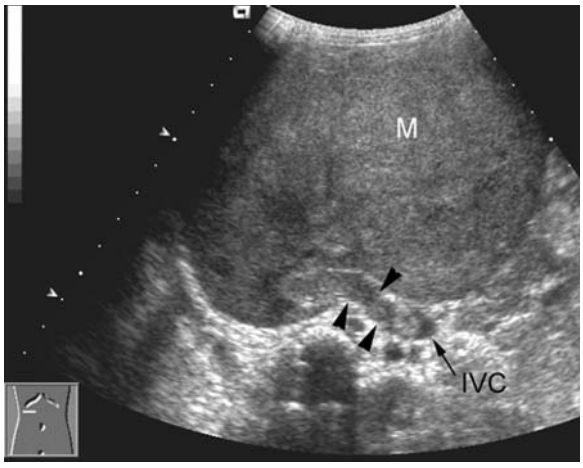


Fig. 24.8. Right renal vein tumor thrombosis associated to Wilms' tumor (*M*). US shows an enlargement of the renal vein (*arrowheads*) filled with echogenic material

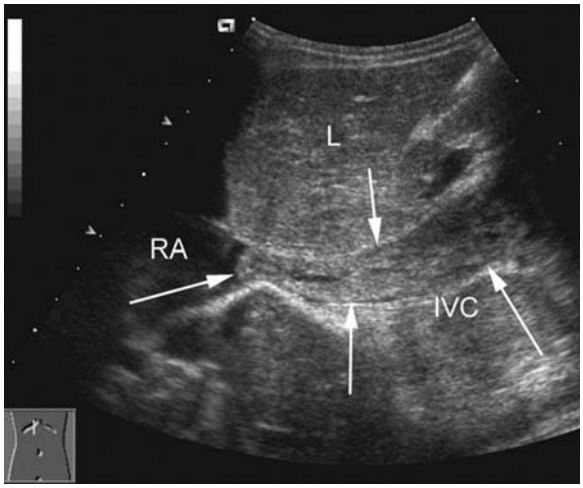
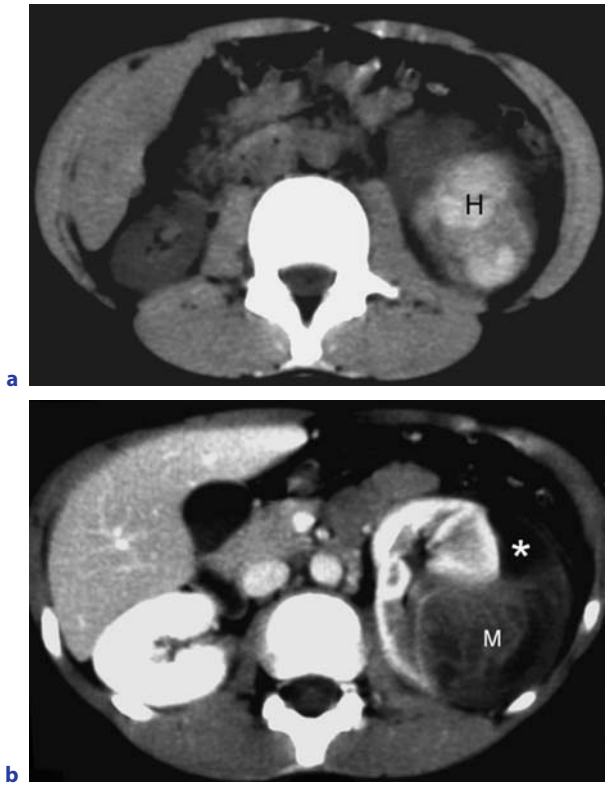


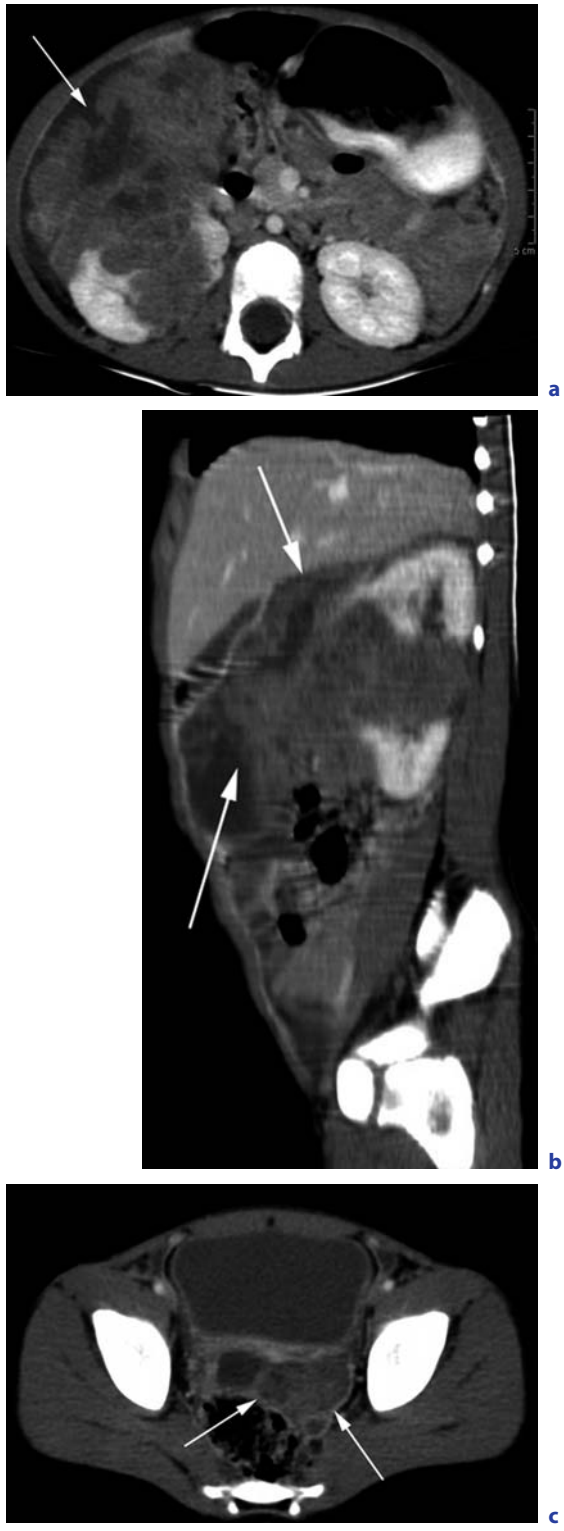
Fig. 24.9. Inferior vena cava thrombosis related to Wilms' tumor. US (*sagittal image*) shows enlargement of the *IVC* (*arrows*). The thrombosis reaches the right atrium (*RA*). *L*: liver



a

b

Fig. 24.10a,b. Retroperitoneal Wilms' tumor rupture in a 9-year-old girl presenting with acute abdominal pain. Unenhanced CT scan (**a**) shows a perirenal hematoma (*H*). Enhanced CT (**b**) shows a subcapsular effusion related to tumor rupture (*asterisk*). Wilm's tumor (*M*)



a

b

c

Fig. 24.11a–c. Intraperitoneal Wilms' tumor rupture in a 4-year-old girl presenting with painless right abdominal mass. Enhanced CT scan (**a**, **c**) with sagittal reconstruction (**b**) shows direct peritoneal extension (*arrows*, **a**, **b**) and Douglas' recess peritoneal location (*arrows*, **c**)

Table 24.3. Wilms' tumor postoperative staging according to SIOP classification (2001)

Stage I	The tumor is limited to the kidney or surrounded with a pseudocapsule if outside of the normal contours of the kidney. The renal capsule or pseudocapsule may be infiltrated with the tumor, but it does not reach the outer surface and is completely resected. The tumor may be protruding into the pelvic system and dipping into the ureter, but is not infiltrating their walls. Intrarenal vessel involvement may be present, but not vessels of the renal sinus. Necrotic tumor in the renal sinus or perirenal fat does not upstage if completely excised. Fine needle aspiration or percutaneous core needle biopsy does not upstage.
Stage II	The tumor has extended beyond the kidney or penetrates through the renal capsule and/or fibrous pseudocapsule into the perirenal fat, but is completely resected. Tumor may infiltrate the renal sinus and/or blood and lymphatic vessels outside the renal parenchyma, but is completely resected. Tumor may infiltrate adjacent organs or IVC, but is completely resected.
Stage III	Residual non-hematogenous tumor is present, confined to the abdomen. Any one of the following may occur: Incomplete excision (gross or microscopic) of the tumor Any abdominal lymph nodes involved Tumor rupture before or intraoperatively Tumor penetration through the peritoneal surface or implants on the peritoneal surface Tumor thrombi present at resection margin of vessel or ureter, transsected or removed piecemeal by surgeon Surgical (wedge) biopsy prior to preoperative chemotherapy or surgery Presence of necrotic tumor in a lymph node or at the resection margins
Stage IV	Haematogenous metastases or lymph node metastases outside the abdominopelvic region
Stage V	Bilateral renal involvement at diagnosis (each side should be sub-staged)

postoperative chemotherapy (Owens et al. 2002). Liver metastases, depicted by US and/or CT, rarely occur in about 2% of patients (Szavay et al. 2006). Bone metastases are exceptional, observed in only 0.8% (Gururangan et al. 1994). Bone scan is not required at diagnosis in typical WT.

24.2.4.6 Preoperative Imaging

US is sufficient in most unilateral WT patients to assess tumor size reduction during neoadjuvant chemotherapy. Absence of tumor response may be related to histological type (high-risk form or stromal type). Progression of localized WT is rarely seen in patients during preoperative chemotherapy. However, these cases are known to have poorer survival (Ora et al. 2007).

In patients with nephroblastomatosis, the impact of MRI during chemotherapy was recently addressed (Grundy et al. 2005). T2-weighted images may actually help to distinguish sclerosing NRs from residual hyperplastic rests requiring further therapy.

Preoperative CT or MR is of special interest when partial nephrectomy is considered (Brisse 2005). Multiphase spiral CT (Herts et al. 1999) or uro-MR may be used (Avni et al. 2002; Riccabona et al. 2002). Image reconstruction techniques with volume rendering and virtual simulation of tumor resections may also help surgeons in planning surgery (Gunther et al. 2004; Fuchs et al. 2005). Assessment of tumor location and residual normal kidney is critical. Polar location is the most favorable, whereas central tumors usually require total nephrectomy. The location and the number of renal arteries represent crucial information (Fig. 24.2c). Various criteria allowing partial nephrectomy have been published (Verga and Parigi 1986; Wilimas et al. 1990; Urban et al. 1995; Moorman-Voestermans et al. 1998; Guglielmi et al. 2000; Cozzi et al. 2001; McNeil et al. 2002). Involvement of adjacent organs and structures should be excluded (liver, diaphragm, spleen, pancreas and adrenal glands); neither hepatic nor peritoneal location should be observed; the collecting system should not be invaded; the renal hilum should be free of disease; no venous invasion in the renal

vein or IVC should be observed; visualization of clear margins (or pseudocapsule) between tumor, kidney and surrounding structures is recommended.

24.2.5 Principles of Treatment

24.2.5.1 Unilateral Wilms' Tumor

According to SIOP protocols, treatment is based on preoperative chemotherapy to reduce the risk of peroperative tumor rupture and reduce the local stage (Lemerle et al. 1976; Tournade et al. 1993; Godzinski et al. 1999; 2001; Tournade et al. 2001). Chemotherapy regimens consist of dactinomycin, vincristine ± doxorubicin. Conversely, the NWTS approach is based on primary nephrectomy. Total nephro-ureterectomy remains the surgical reference treatment.

Partial nephrectomy is sometimes considered in unilateral WT when the child has contralateral non-functioning kidney or associated renal disease or associated predisposing syndrome (SIOP 2001). Nevertheless, partial nephrectomy is contraindicated in unilateral multifocal tumors, central location, involvement of more than 1/3 of kidney, preoperative tumor rupture or biopsy, infiltration of extra-renal structures, intra-abdominal metastases or lymph nodes, thrombosis of RV or IVC, involvement of calyces or hematuria (SIOP 2001).

After pathological analysis, postoperative treatment is stratified according to stage and histological risk group and consists of adjuvant chemotherapy and abdominal radiation therapy ("flank RT") for stage-III patients. Children with pre- or preoperative tumor rupture with peritoneal spillage receive a whole abdominal radiotherapy (SIOP 2001). Stage-IV children with residual pulmonary nodules have lung wedge resections to assess histological response and adjuvant chemotherapy in case of incomplete response and lung radiotherapy in case of incomplete response after chemotherapy and/or high-risk histology.

24.2.5.2 Bilateral Wilms' Tumor

The SIOP and NWTS experiences now converge on the same strategy: prolonged primary chemotherapy in order to decrease tumor volume, followed by partial surgery in order to preserve the maximum amount of renal tissue (Coppes et al. 1989; Montgomery et al. 1991; Shaul et al. 1992; SIOP 2001). The goal is bilateral partial nephrectomy or wedge resection, performed in two separate operations after an interval of 1–2 weeks. The less involved kidney is first operated on, either in situ or extra-corporally with subsequent auto-transplantation ("bench surgery"). Following this strategy, 64% of the kidneys in the NWTS-4 had more than half of the original tissue preserved (Horwitz et al. 1996) and the incidence of renal failure decreased from 16.4% for NWTS-1&2 to 3.8% for NWTS-4 (Ritchey et al. 1996), while the survival rate remained excellent, with a 4-year overall survival (OS) of 81.7% (SIOP 2001). In patients with nephroblastomatosis, since differentiation by imaging between nephrogenic rests and small WT may be difficult, the treatment strategy close to stage V tumors is now adopted (SIOP 2001).

24.2.6 Prognostic and Follow-Up

24.2.6.1 Prognostic Factors

The most important prognostic factors are the stage and the histological risk group. Tumor shrinkage under preoperative chemotherapy is also considered as a prognostic factor. Preoperative volume more than 500 ml is associated with poorer survival (SIOP 2001). The prognostic signification of various genetic abnormalities are currently under study (loss of heterozygosity for chromosomes 16q, 1p and 22q, p53 mutation or overexpression, telomerase activity, gain of 1q, expression of TRKB) (SIOP 2001). Tumor-specific LOH for both chromosomes 1p and 16q identifies a subset of favorable histology WT patients who have a significantly increased risk of relapse and death (Grundy et al. 2005).

24.2.6.2 Survival

The overall prognosis of localized WT is currently excellent, with a 5-year overall survival of about 93 to 100% for stage I, 85 to 88% for stage II and III of low and intermediate risk groups, and 71% for diffuse anaplasia WT in the SIOP 9 protocol (SIOP 2001; Tournade et al. 2001) and a 4-year overall survival of 98% for "favorable" histology stage I, 96% stage II,

95% stage III and 90% stage IV in the NWTS-4 trial (Green et al. 1998). According to SIOP 93.1 trial results, postoperative chemotherapy for patients with stage I can be limited to only 4 weeks, even in the high risk group (de Kraker et al. 2004).

24.2.6.3 Relapses

The most common site of WT recurrence is the lung (58%), sometimes with pleural extent, whereas abdominal recurrences represent only 29% of all relapses (Grundy et al. 1989). The risk factors for local recurrence are local stage III and high-risk histology (Shamberger et al. 1999). Abdominal recurrences may arise in the lumbar fossa, in the liver, in the regional lymph nodes and in the peritoneal cavity when peritoneal spillage had occurred before or during surgery. The survival of children after local recurrence is poor (average survival rate at 2 years after relapse: 43%) (Shamberger et al. 1999).

Metachronous contralateral Wilms' tumor is rare. The percentage of patients who develop contralateral disease is 1.5% at 5 years after diagnosis (Coppes et al. 1999). The knowledge of nephrogenic rests depicted by either initial imaging (Daw et al. 2002) or pathological analysis of the non-tumoral part of the kidney (Coppes et al. 1999; Bergeron et al. 2001) and age at initial diagnosis less than 12 months are recognized risk factors

24.2.6.4 Imaging Follow-Up

Regarding the overall good prognosis of WT, follow-up imaging should be made with minimally invasive techniques. However, since relapsed patient may be cured with salvage therapies, depiction of recurrences is important and should be performed carefully with the knowledge of both recurrence patterns and risk factors. Ninety percent of relapses occur during the first 4 years after diagnosis (Table 24.4) (Grundy et al. 2005).

Chest X-ray is currently the only modality used for follow-up, chest CT being only indicated in patients with suspected lung recurrence. US surveillance for 3 years after therapy is considered to reveal most abdominal recurrences (Daw et al. 2002).

The remaining kidney should be regularly assessed during surveillance to depict possible contralateral tumor. Growth of the remaining kidney is also part of the nephrological surveillance, together with blood pressure and serum creatinine. Focal glomerulosclerosis secondary to hyperfiltration following nephrectomy has been reported, presenting as an abnormal ultrasonographic "tiger-striped" pattern (Munden et al. 1999).

Conclusion

Ninety percent of renal neoplasms in children are Wilms' tumor, having an overall good prognosis. The median age at diagnosis is 3.5 years (1–5 years). Bilateral WT and/or nephroblastomatosis are associated with genetic predisposing conditions requiring US individual screening. WT is a rapidly growing tumor that may invade the renal vein, IVC and lymph nodes. Intraperitoneal rupture is rare, but associated with a high risk of abdominal recurrence. Distant metastases are mainly located in the lung. Preoperative imaging is crucial before nephron sparing surgery in bilateral diseases

Table 24.4. Proposal for long-term radiological follow-up of children with Wilms' tumor

Investigation	Frequency after stopping therapy
Chest X-ray	1st and 2nd years: every 3 months (every 2 months for metastatic patients) 3rd year: every 6 months 4th to 5th years: every 12 months
Abdominal sonography	End of treatment 1st and 2nd years: every 6 months 3rd to 5th years: every year
	If nephrogenic rests, local-stage III and/or high-risk histology: 1st and 2nd years: every 3 months 3rd to 5th years: every 6 months 6th to 10th years: every year

24.3 Non-Wilms' Malignant Tumors

24.3.1 Clear Cell Sarcoma of the Kidney

Clear cell sarcoma of the kidney accounts for approximately 5% of renal neoplasms in childhood. Mean age at diagnosis is 36 months (range of 2 months to 14 years), and the male to female ratio is 2:1. Typical gross features included large size (mean diameter 11.3 cm), a mucoid texture, foci of necrosis and prominent cyst formation. Nine major histological patterns have been identified (classic, myxoid, sclerosing, cellular, epithelioid, palisading, spindle, storiform and anaplastic); virtually all tumors contained multiple patterns that blended with one another (Argani et al. 2000). Metastases may be present at diagnosis or occur several years after treatment, involving the skeleton, brain, lungs or liver (Marsden et al. 1978; Morgan and Kidd 1978). Bone metastases are highly suggestive for this diagnosis in childhood (Fig. 24.12). No specific pattern permits discrimination between clear cell sarcoma and WT. Masses are predominantly solid and contained well-defined portions of low attenuation or hypoechogenicity that represented tumor necrosis. Tumors may contain uncomplicated fluid-filled cysts with diameters ranging from a few millimeters to 5 cm. Some cases may have features that simulate those of benign conditions, such as renal abscess, whereas multilocular cystic nephroma or segmental cystic dysplasia usually have thin septations without tissue components (Glass et al. 1991) (Table 24.5).

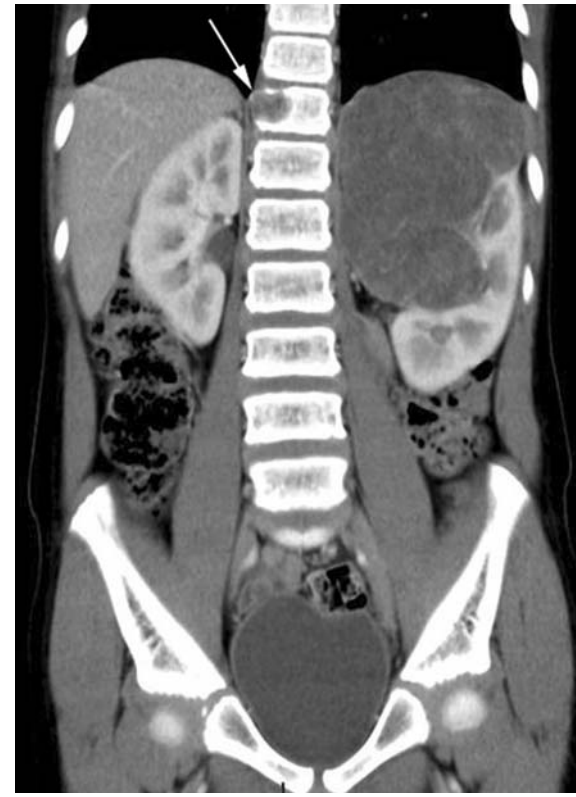


Fig. 24.12. Clear cell sarcoma of the kidney in a 9-year-old boy presenting with hematuria. Contrast-enhanced CT (*coronal reconstruction*) shows a left upper pole renal mass and a spinal bone metastasis (*arrow*) (courtesy Dr. J.-L. Ferrand, Clinique Saint-Jean, Montpellier, France)

24.3.2 Rhabdoid Tumor of the Kidney

Rhabdoid tumors are extremely aggressive cancers of early childhood. They can occur in various locations, mainly the kidney, brain (atypical teratoid/rhabdoid tumors) and soft tissues. Cytogenetic and molecular analyses have shown that the deletion of 22q11.2 is a recurrent genetic, associated with alteration of the hSNF5/INI1 gene (Versteege et al. 1998; Biegel et al. 2002). Rhabdoid tumor of the kidney accounts for about 1% (Vujanic et al. 1996) of all renal neoplasms in childhood. Median age at diagnosis is 11 months (range from 0 to 106 months), and the male:female ratio is 1.5:1 (Weeks et al. 1989). Gross features included a characteristic involvement of perihilar renal parenchyma. A wide histological spectrum is encountered, including nine major morphological patterns (classical, epithelioid, sclerosing, lymphomatoid, histiocytoid, etc.). These appearances invite confusion with other renal neoplasms. Several findings suggest that rhabdoid tumor might arise from primitive cells involved in formation of the renal medulla (Weeks et al. 1989). Although nonspecific, clinical presentation with fever, hematuria, young age and high-tumor stage at presentation suggests the diagnosis (Amar et al. 2001). About 20% may have associated hypercalcemia (Vujanic et al. 1996). Imaging findings described are: a central location, subcapsular hematoma, a lobulated surface of the tumor, calcification and tumor necrosis or hemorrhage (Fig. 24.13) (Chung et al. 1995; Han et al. 2001). However, 12% of renal neoplasms that occur more commonly than rhabdoid tumor in children had CT findings indistinguishable from those of rhabdoid tumor (Agrons et al. 1997).

Table 24.5. Non-Wilms' renal tumors in childhood

	Tumors	Genetics	Age of onset	Distinctive features
Malignant	Clear cell sarcoma of kidney		36 m (2 months–14 years)	Bone metastases, hypercalcemia, cystic components
	Juvenile renal cell carcinoma	t(X;1)(p11.2;q21) PRCC-TFE3 t(X;17)(p11.2;q25) ASPL-TFE3 Von Hippel-Lindau	10–20 years	Small size, calcifications, lymph nodes
	Rhabdoid tumor ok kidney	Deletion 22q11.2 hSNF5/INI1 gene	11 months (0–106 months) 80% <2 years	Central location, lobulated, peripheral calcifications, hypercalcemia, CNS-associated tumor (ATRT), extrapulmonary metastases
	Renal medullary carcinoma		Adolescent (5–34 years)	Black sickle cell trait, hemoglobin SC disease, aggressive features
	Atypical/cellular mesoblastic nephroma/fibrosarcoma	t(12–15)(p13;q25) ETV6/NTRK3	< 6 months	
	PNET	t(11;22)(q24;q12) EWS-FLI-1		
	Non-Hodgkin lymphoma (Burkitt's, lymphoblastic, large cell)	t(8;14) Burkitt	7–10 years	Bilateral nodules, kidney enlargement
	Leukemia (ALL)	Many	2–6 years	Bilateral nodules, kidney enlargement
Benign	Congenital mesoblastic nephroma (Bolande's tumor)		< 6 months (0–1 years)	Ante/neonatal diagnosis, kidney enlargement, infiltrative pattern, hypercalcemia
	Multilocular cystic nephroma			Multicystic pattern, non-distinguishable from CPDN
	Metanephric adenoma		> 5 years	Polycythemia, spontaneous high density, iso-intensity T1- and T2-WI
	Ossifying renal tumors of infancy		< 3 months (0–14 months)	Small mass, calcifications
	Angiomyolipoma	Tuberous sclerosis	10 years (6–41 years)	Bilateral, fatty component, associated renal cysts
Pseudo-tumors	Renal abscess, xanthogranulomatous pyelonephritis, segmental multicystic dysplasia, renal lymphangioma, obstructive urinoma, renal sarcoïdosis			

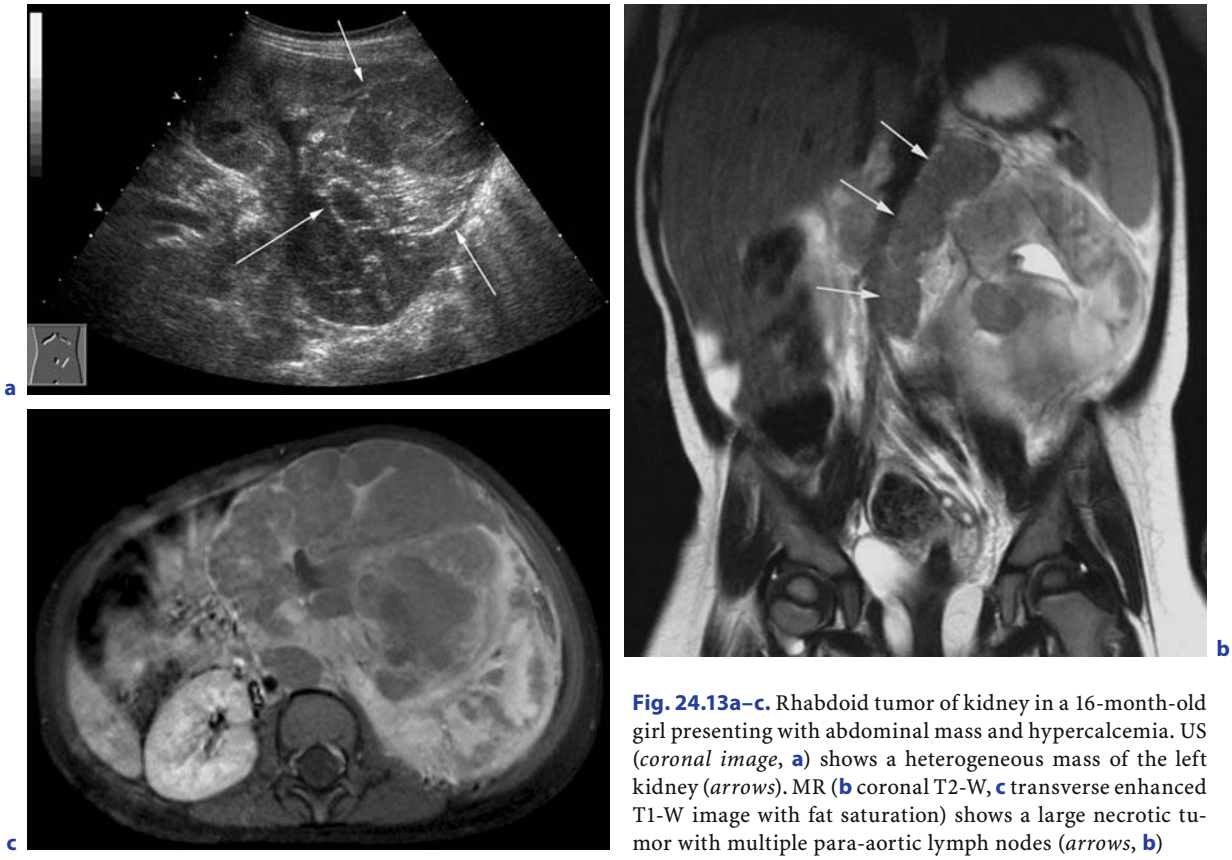


Fig. 24.13a–c. Rhabdoid tumor of kidney in a 16-month-old girl presenting with abdominal mass and hypercalcemia. US (*coronal image*, **a**) shows a heterogeneous mass of the left kidney (*arrows*). MR (**b** coronal T2-W, **c** transverse enhanced T1-W image with fat saturation) shows a large necrotic tumor with multiple para-aortic lymph nodes (*arrows*, **b**)

Metastases are observed in about 80% of children (lung, abdomen, lymph nodes, liver, bone and brain) (Vujanic et al. 1996). The prognosis is poor, and 80% of patients died despite aggressive treatments (Weeks et al. 1989).

24.3.3 Juvenile Renal Cell Carcinoma

Juvenile renal cell carcinoma is a rare disease in children and adolescents. The median age at diagnosis is about 10 years. Histological features may be papillary or clear-cell carcinoma. Tumor stage and complete surgical resection are the only meaningful prognostic factors (Aronson et al. 1996). Patients with localized disease can be cured by nephrectomy alone (Indolfi et al. 2003). Lung and liver are the most common distant lesions and are associated to bad prognosis. Overall survival at 20 years is 55% (Indolfi et al. 2003).

Recent studies suggest that renal cell carcinoma in children and young adults may represent a distinct group of tumors (Renshaw 2000). Molecular features observed are t(X;1) (p11.2;q21) resulting in PRCC-TFE3 gene fusion or t(X;17)(p11.2;q25) resulting in ASPL-TFE3 fusion (Argani et al. 2002), with the latter known to be also characteristic of alveolar soft part sarcoma (Argani et al. 2001). Juvenile renal cell carcinoma with translocations involving Xp11.2 form a specific entity characterized by subtle pathologic features and younger age of occurrence, especially for those with the t(X;17) (Heimann et al. 2001; Perot et al. 2003). Thus, a subset of tumors previously considered to be renal cell carcinoma in young people are in fact genetically related to alveolar soft part sarcoma, although their distinctive morphological and genetic features justify their classification as a distinctive neoplastic entity (Argani et al. 2001).

Clinical findings are hematuria, pain and abdominal mass. Renal cell carcinoma tends to be smaller than WT at diagnosis (Fig. 24.14). Intratumoral calcification and enlarged lumbar-aortic lymph nodes are frequently observed. The tumor appears hypervascular and heterogeneous; areas of necrosis are

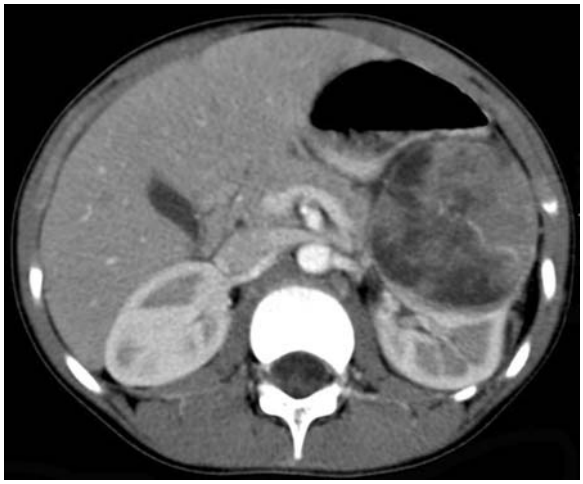


Fig. 24.14. Juvenile renal cell carcinoma in a 9-year-old girl presenting with abdominal pain. Enhanced CT scan shows a non-specific heterogeneous tumor of the left kidney. Relative small tumor size and patient age are suggestive criteria for renal cell carcinoma and must lead to a diagnostic biopsy

uncommon. However, imaging techniques cannot confidently distinguish renal cell carcinoma from WT (Hartman et al. 1982).

Von Hippel-Lindau disease predisposes to the development of various tumors (hemangioblastomas of the neuraxis and retina, tumors of the membranous labyrinth, renal clear cell carcinomas or cysts, pheochromocytomas, pancreatic cysts or tumors, and epididymal cystadenomas). Renal cancer constitutes one of the main causes of death (Richard et al. 1998). Conversely, meta-analysis of cases of coincident tuberous sclerosis complex shows that the risk of malignancy is comparable with the normal population (Tello et al. 1998).

24.3.4 Renal Medullary Carcinoma

Renal medullary carcinoma is a rare and aggressive tumor occurring in black adolescent or young adults (range 5 to 34 years) with sickle cell trait or hemoglobin SC disease (Swartz et al. 2002). Immunohistological findings (strong vascular endothelial growth factor and hypoxia inducible factor expression and positivity for TP53) suggest that chronic medullary hypoxia secondary to hemoglobinopathy may be involved in the pathogenesis (Swartz et al. 2002). The most common presenting signs and symptoms include hematuria, abdominal or flank pain, and weight loss. Sickle cell trait as the sole cause of hematuria in young black patients is therefore a diagnosis of exclusion (Warren et al. 1999). Renal medullary carcinoma probably arises in the calyceal epithelium in or near the renal papillae (Davis et al. 1995), develops centrally within the kidney, grows in an infiltrative pattern and invades the renal sinus. Contrast enhancement and echostructure are heterogeneous (Davidson et al. 1995). Survival is poor (mean: 4 months) (Swartz et al. 2002).

24.3.5 Malignant Hematologic Diseases

Primary unilateral renal lymphoma is exceptional, presenting as a solid renal tumor without distinctive characteristic (Hugosson et al. 1997). Renal involvement is observed in less than 20% of abdominal non-Hodgkin lymphomas (Ng et al. 1994). Lymphomatous renal involvement occurs more frequently in Burkitt's lymphoma, lymphoblastic lymphoma or large cell lymphoma, while renal location of Hodgkin's disease remains exceptional (Chepuri et al. 2003). Lymphoma of the kidneys is usually bilateral, associated with other sites of disease and affects older children than bilateral WT, usually between 7 and 10 years. Lymphoma locations usually appear homogeneously hypoechoic on abdominal US (Fig. 24.15) and as low-density images on CT scan (Fig. 24.16). Several patterns may be encountered: multiple low attenuation nodules of varying size, diffuse renal infiltration with nephromegaly or retroperitoneal infiltration with encasement of the kidneys (Strauss et al. 1986; Weinberger et al. 1990). These features may also be encountered in acute lymphoblastic leukemia.

24.3.6 Peripheral Primitive Neuroectodermal Tumor

Peripheral primitive neuroectodermal tumor (pPNET) of the kidney is a very rare entity with high malignant potential and no specific radiological pattern described. The diagnosis is based on histopathology with subsequent demonstration of typical chromosomal translocations of the PNET/Ewing tumor family (Doerfler et al. 2001; Vicha et al. 2002; Lam et al. 2003).

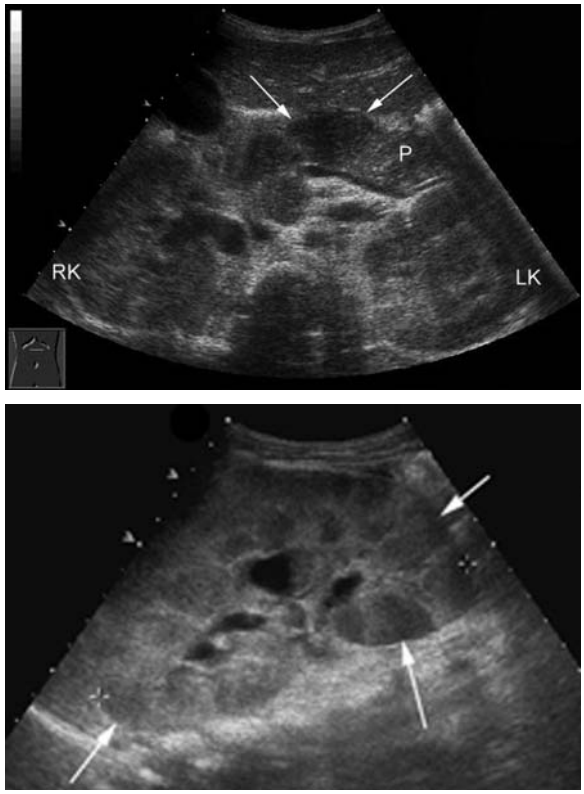


Fig. 24.15a,b. B-cell high grade abdominal non-Hodgkin lymphoma in a 5-year-old boy presenting with abdominal pain. US show enlarged kidneys (**a**, **b**) with cortical hypoechoic nodules (*arrows*, **b**), pancreatic (*P*, *arrows*, **a**) and testis (not shown) locations

24.3.7 Metastases

Renal metastases are exceptional in children. Few cases have been described in metastatic neuroblastoma (Filiatrault et al. 1987; Panuel et al. 1992)

Conclusion

Bone metastases associated to renal neoplasm are suggestive of clear cell sarcoma. Rhabdoid tumor affects young children, and hypercalcemia and metastases at diagnosis are frequent in this highly aggressive tumor. Juvenile renal cell carcinoma occurs in the second decade and is frequently calcified and smaller than WT. Renal medullary carcinoma occurs in black adolescents with sickle cell trait; involvement of the renal sinus results in caliectasis. Renal lymphoma is usually bilateral and associated with other sites of involvement.

24.4 Benign Tumors

24.4.1 Congenital Mesoblastic Nephroma or Bolande's Tumor

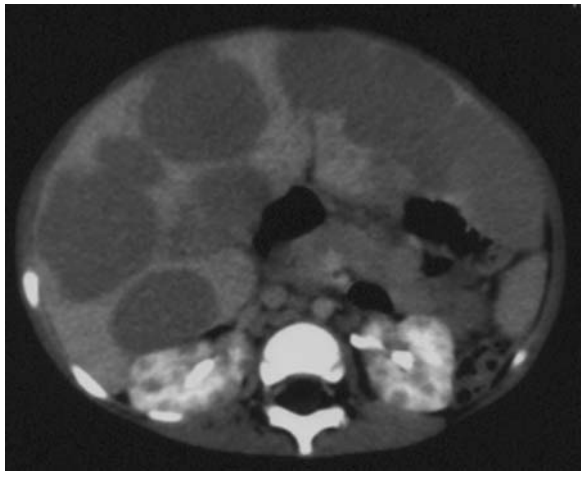


Fig. 24.16. Burkitt's lymphoma in a 2-year-old boy presenting with increasing abdominal volume. Enhanced CT scan shows multiple low attenuating cortical nodules together with large liver locations

Congenital mesoblastic nephroma is the most frequent solid renal tumor in the neonate (Chan et al. 1987). About 75% of cases are diagnosed during the first 4 months of life (Furtwaengler et al. 2006). For this reason, and because of the high toxicity of chemotherapy in infants, initial surgery is mandatory in renal tumor before 6 months of age (SIOP 2001). At gross analysis, congenital mesoblastic nephroma is an infiltrative mass with ill-defined margins and no capsule. This tumor predominantly contains bundles of spindle cells resembling fibroblasts and myofibroblasts that present many histological features reminiscent of infantile fibromatosis (Bolande et al. 1967). The tumor border is irregular and long radial finger-like extensions of tumor tissue into the adjacent renal tissue are a characteristic finding (SIOP 2001).

Congenital mesoblastic nephroma usually presents as an abdominal neonatal mass. Some cases are

discovered at prenatal US examination (Irsutti et al. 2000; Kelner et al. 2003; Murthi et al. 2003), sometimes associated with polyhydramnios and neonatal hypercalcemia (Ferraro et al. 1986; Daskas et al. 2002). US shows a large solid renal mass exhibiting low echogenicity or mixed echostructure. A distinctive "ring sign" (concentric hyperechoic and hypoechoic rings) (Fig. 24.17) is a suggestive pattern (Chan et al. 1987), the anechoic ring surrounding the tumor containing abnormal vessels depicted with Doppler (Kelner et al. 2003). CT scan demonstrates a homogeneous renal mass, or a large tumor with areas of low attenuation representing fluid collection, hemorrhage (Christmann et al. 1990) or necrosis. At arterial phase, residual renal cortex trapped into the tumor resulting from the infiltrative growing is a suggestive pattern (Kelner et al. 2003). On excretory phase, contrast medium within the tumor may be observed representing functioning nephrons trapped within the tumor (Hartman et al. 1981). Nephrectomy is the radical treatment prescribed for these benign tumors. The prognosis is excellent.

A more aggressive form, called "cellular" or "atypical" congenital mesoblastic nephroma (Fig. 24.18), is characterized by a dense fibroblastic proliferation with increased cellularity and numerous mitoses. Those patients may develop local recurrence or metastases (Schlesinger et al. 1995). A close link between cellular congenital mesoblastic nephroma and congenital fibrosarcoma is now identified: both have identical cytogenetic abnormality t (12–15) (p13;q25) and molecular markers (ETV6/NTRK3 fusion transcripts). Therefore, they are likely to represent the same neoplasm, but occurring at different locations (Knezevich et al. 1998; Henno et al. 2003).

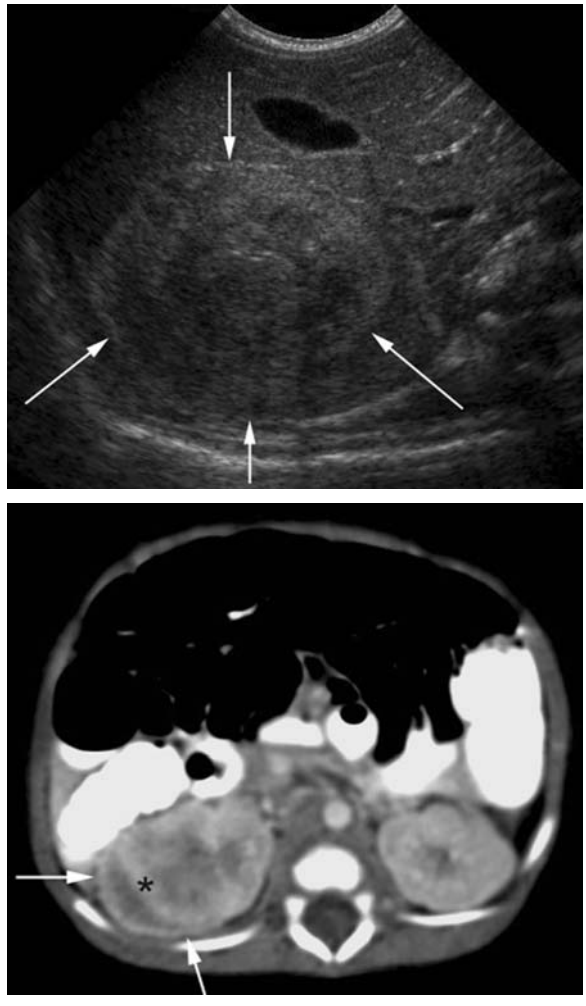


Fig. 24.17a,b. Congenital mesoblastic nephroma in a neonate. US (transverse image, **a**) shows a large solid renal mass (*arrows*) exhibiting concentric hyperechoic and hypoechoic rings. Enhanced CT scan (**b**) shows residual renal cortex (*asterisk*) trapped within the tumor (*arrows*) resulting from the infiltrative growing

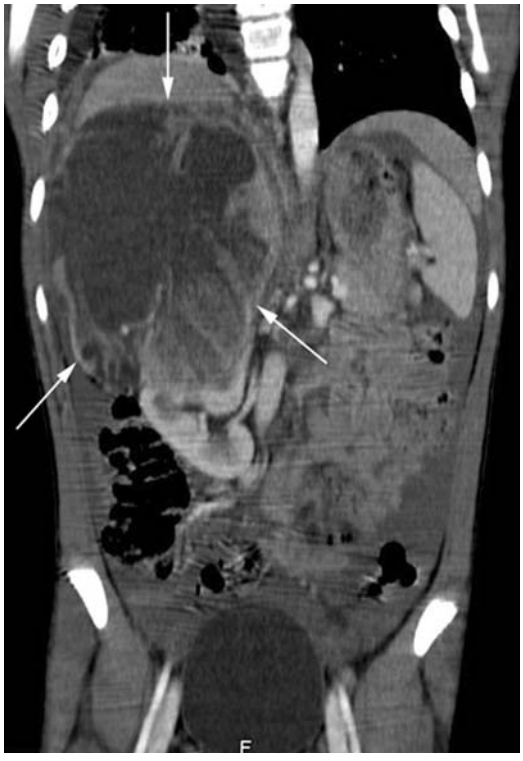


Fig. 24.18. Renal fibrosarcoma ("cellular" mesoblastic nephroma) in a 14-year-old boy. Enhanced CT scan (*coronal reconstruction*) shows a large necrotic tumor of the upper pole of the right kidney (*arrows*) with ascites related to tumor rupture

24.4.2 Multilocular Cystic Nephroma

Multilocular cystic nephroma is a segmental, purely cystic mass characterized by multiple septations composed entirely of differentiated tissues, without blastemal elements. Rarely observed in children, the lesion is more frequently described in adult women.

Multilocular cystic nephroma and cystic partially differentiated nephroblastoma cannot be distinguished on imaging, and biopsy is not recommended because it is usually not informative. The only difference between these two entities is the presence of embryonal cells within the septa in CPDN. Therefore, it is recommended that purely cystic renal tumors should be first surgically removed (SIOP 2001), the final diagnosis being obtained after pathological analysis.

The differential diagnosis of multicystic renal masses also includes WT with cyst formation due to hemorrhage and necrosis, cystic clear cell sarcoma, cystic mesoblastic nephroma, cystic renal cell carcinoma, multicystic dysplastic kidney and segmental multicystic dysplasia (Agrons et al. 1995).

24.4.3 Benign Stromal Tumors

24.4.3.1 Metanephric Adenoma

Metanephric adenoma is a rare benign tumor that predominates in females (Davis et al. 1995; Navarro et al. 1999). The mean age at diagnosis is 41 years, but it may be observed in children (range of 5 to 83 years). The mean size at diagnosis is 5.5 cm (range 0.3 to 15 cm) (Davis et al. 1995). Presenting signs and symptoms included pain, hematuria and palpable mass. The tumor is sometimes incidentally discovered. Polycythemia is a suggestive sign, but observed in only 12% of cases.

This tumor is more commonly calcified than other renal neoplasms. Microscopically, MA consists of very small epithelial cells that form very small acini in an acellular stroma. Less often, it forms tubular, glomeruloid or polypoid and papillary formations. These lesions seem histogenetically related to epithelial WT, and, in fact, the two may occur together. They are histologically very similar to the metanephric hamartomatous element of nephroblastomatosis.

At US, the mass is well circumscribed, hypo- or hyperechoic. Unenhanced CT scan shows a spontaneously hyperdense mass, in some cases with punctuate calcifications. On MRI, the lesion appears iso-intense on both T1- and T2-weighted sequences (Fig. 24.19).

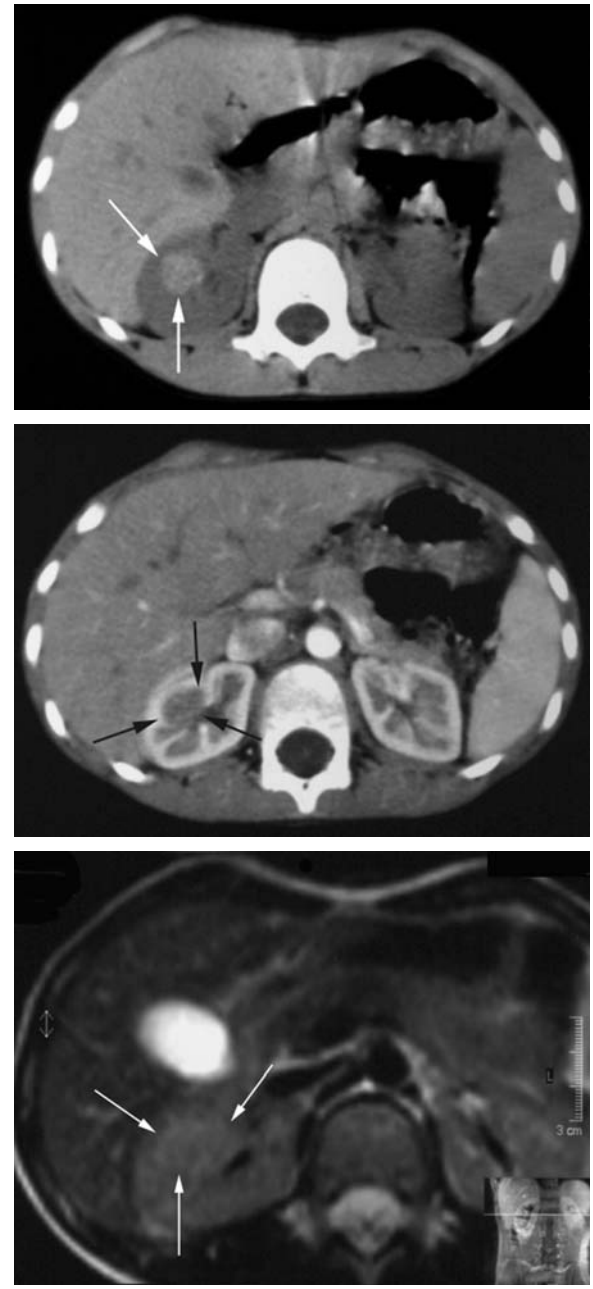


Fig. 24.19a–c. Metanephric adenoma in a 7-year-old boy. CT scan (unenhanced, **a**; enhanced, **b**) shows a spontaneously hyperdense small mass. On MR T2-W images (**c**) the lesion is almost isointense to the normal parenchyma (courtesy Dr. C. Treguier, Hôpital de Pontchaillou, Rennes, France)

24.4.3.2 Metanephric Stromal Tumor

Metanephric stromal tumor was more recently described (Fig. 24.20) (Argani and Beckwith 2000). Mean patient age at diagnosis is 2 years. Gross examination typically revealed a fibrous lesion centered in the renal medulla containing smooth-walled cysts. Metanephric stromal tumor is histologically identical to the stromal component of metanephric adenofibroma. Patients may be treated with surgical excision alone.

24.4.3.3 Metanephric Adenofibroma

Metanephric adenofibroma (previously termed nephrogenic adenofibroma) contained a variable amount of a bland spindle cell stroma (Arroyo et al. 2001). Metanephric adenofibroma is a biphasic tumor that spans the morphologic spectrum between benign pure stromal and pure epithelial lesions, and can merge with the morphology of WT, supporting the concept that these are all related lesions. A relationship to papillary renal cell carcinoma is also suspected.

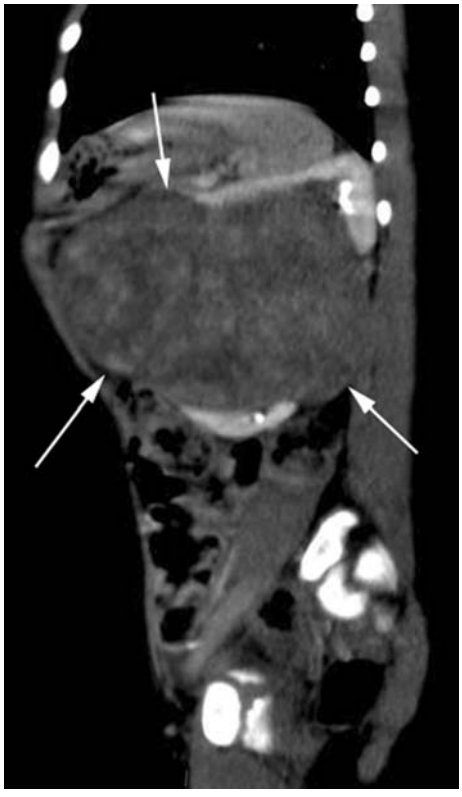


Fig. 24.20. Metanephric stromal tumor in a 3.5-year-old girl. Contrast-enhanced CT (*sagittal reconstruction*). Renal mass incidentally discovered during US performed for enuresis. Pathological diagnosis obtained after neoadjuvant chemotherapy (30% volume response only) and nephrectomy for presumed Wilms' tumor

24.4.3.4 Ossifying Renal Tumor of Infancy

Ossifying renal tumors of infancy are exceptional tumors of infancy. The mass arises in the renal medulla, involving the collecting system. It contains varying proportions of osteoid, osteoblastic cells and spindle cells. The proportion of osteoid and degree of osseous maturation are increased with increasing age of the patient. Imaging usually displays a small-size mass located within the kidney, sometimes associated with dilatation of the collecting system (Fig. 24.21). Calcifications are frequent (Sotelo-Avila et al. 1995; Ito et al. 1998; Vazquez et al. 1998).

24.4.3.5 Angiomyolipoma

Angiomyolipoma in childhood is associated with tuberous sclerosis complex (Bourneville's disease). Both angiomyolipomas and cysts occur commonly in pediatric patients and tend to increase in size and number with increasing age. Angiomyolipomas are more common than cysts and tend to be numerous (Avni et al. 1984; Casper et al. 2002). Renal angiomyolipomas larger than 3.5 cm. in diameter have a substantial risk for severe hemorrhage and therefore require preventive surgery (van Baal et al. 1994). As in adults, the fatty component appears hyperechoic on US and associated with low attenuation on CT scan (Fig. 24.22). Other fat-containing renal masses in children are teratoid WT and xanthogranulomatous pyelonephritis.

24.4.3.6 Juxtaglomerular Cell Tumor or Reninoma

Juxtaglomerular cell tumor is essentially discovered in the second decade of life, when hypertension and hyperaldosteronism lead to the diagnosis. MRI combined with MR angiography may be proposed in this context to detect the tumor and to evaluate the status of the renal artery (Agrawal et al. 1995).

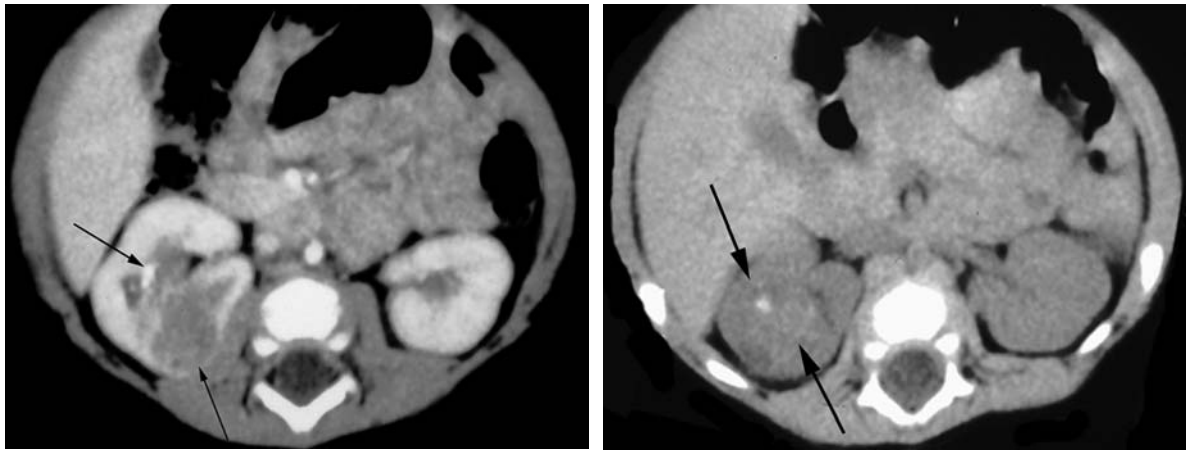


Fig. 24.21a,b. Ossifying renal tumor of infancy in a neonate with seizures, hypercalciuria, and microscopic hematuria. CT scan (**a**, unhenanced; **b**, enhanced) shows a calcified (*arrow*) intrarenal mass (courtesy Dr. C. Baunin, Hôpital des Enfants, Toulouse, France)

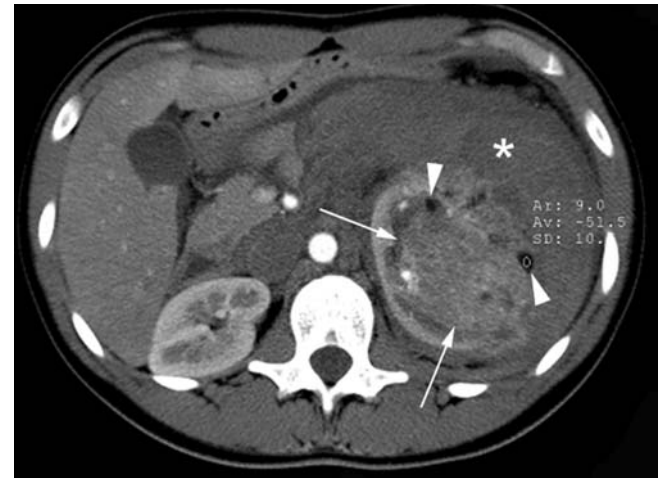


Fig. 24.22. Angiomyolipoma in a 15-year-old girl with tuberous sclerosis and acute abdominal pain related to tumor rupture. CT scan shows a vascularized intrarenal mass (*arrows*) containing fatty areas (*arrowheads*) and peri-renal hematoma (*asterisk*) (courtesy Prof. H. Ducou-Lepointe, Hôpital A Trousseau, Paris, France)

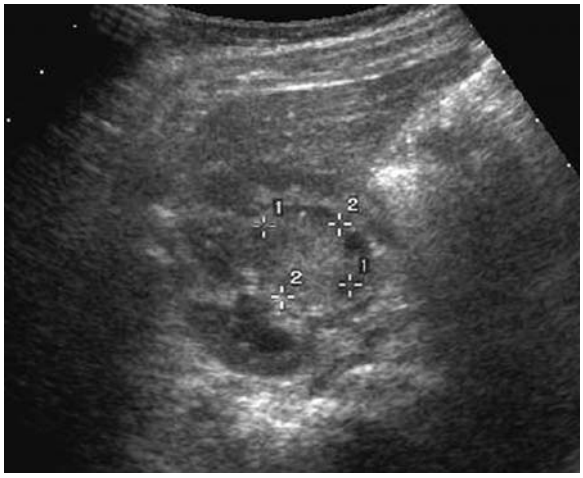
Conclusion

Mesoblastic nephroma is the most common renal tumor in the neonate. Other benign tumors of the kidney are very rare in childhood. Multilocular cystic nephroma is indistinguishable from cystic partially differentiated nephroblastoma on all imaging modalities. Metanephric adenoma is strongly associated with polycythemia. Ossifying tumor of infancy is typically calcified, deeply located within the kidney. Multiple angiomyolipomas are seen in tuberous sclerosis. Juxtaglomerular tumor is revealed by hypertension and hyperaldosteronism.

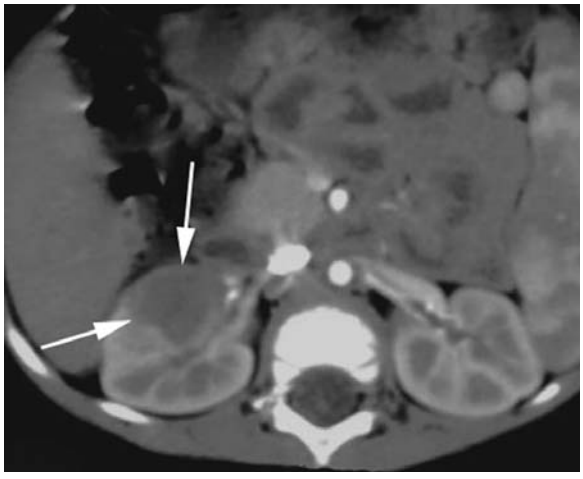
24.5 Pseudotumoral Conditions

24.5.1 Infectious Diseases

Pseudotumoral acute pyelonephritis (Fig. 24.23), renal abscess and a necrotic renal tumor may have similar features. Inflammatory clinical and biological signs may also be observed in WT. Abdominal wall infiltration, when visible, is more suggestive of infectious disease. Fine-needle aspiration may help in such circumstances. Xanthogranulomatous pyelonephritis is a specific form of chronic



a



b

Fig. 24.23a,b. Focal pseudotumoral pyelonephritis in a 15-month-old girl presenting with fever. Homogeneous small hyperechoic area on US (**a**) and hypoattenuating area on enhanced CT scan (**b**) without mass effect. No biopsy performed. Urinary tract infection diagnosis was based on bacteriuria (E. coli) and disappearance of the lesion on US under antibiotic therapy

inflammatory kidney disease that may involve both sexes at any age. Xanthogranulomatous pyelonephritis usually occurs in association with urinary tract obstruction, infection and/or renal stones. The most common offending organisms are E. coli and Proteus mirabilis (Marteinsson et al. 1996). Focal pseudotumoral xanthogranulomatous pyelonephritis may be difficult to diagnose. A small mass effect, multiple microcysts within the mass, the presence of a pelvic lithiasis, associated triangular areas in the renal parenchyma and obliteration of fatty tissue in the perirenal space are suggestive signs (Cousins et al. 1994; Bingol-Kologlu et al. 2002).

24.5.2 Malformations

Differential diagnosis with renal malformation has to be suspected in cases of cystic lesions. A history of urinary tract infection and an associated ureterocele suggest a segmental multicystic dysplasia (Agrons et al. 1995; Jeon et al. 1999).

Neonatal urinoma related to urinary tract obstruction (posterior urethral valve) may be misleading. Vascular malformation such as lymphangioma is a rare cause of multiloculated renal mass (Pickering et al. 1984; Jacobs et al. 1989).

24.5.3 Miscellaneous

Granulomatous nephritis with renal masses is a very uncommon complication of sarcoidosis. One pediatric case was reported with echogenic masses on US and low-density lesions with mottled contrast enhancement on CT (Herman et al. 1997).

24.6 Diagnostic Strategy of Renal Neoplasms in Children

Step 1: Always begin with non-invasive techniques

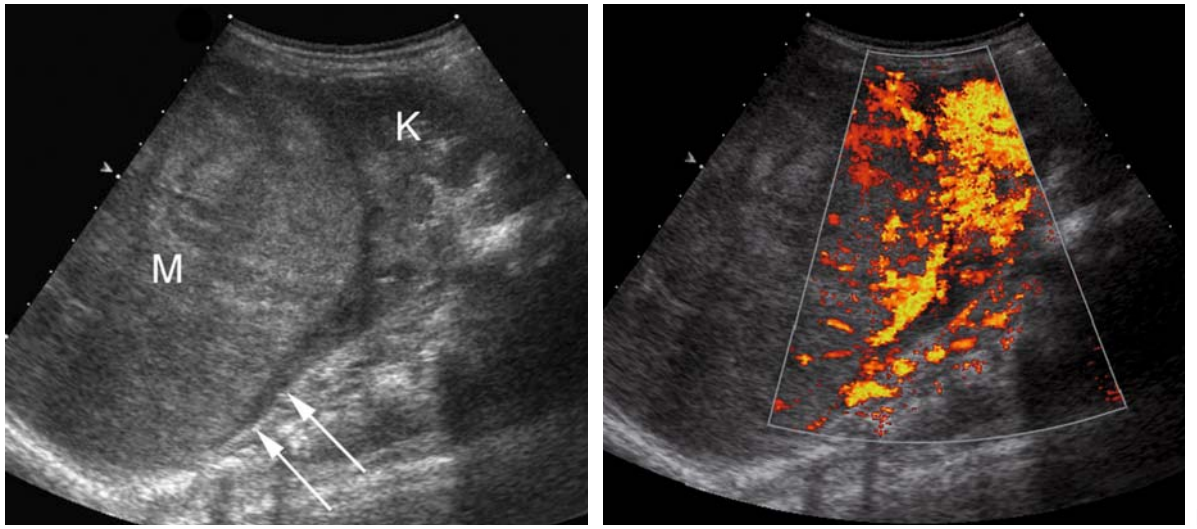
US is the first line imaging technique. It is available in all centers and does not require any sedation or injection. US rapidly confirms the location of the mass, assesses its volume and depicts emergency situations such as vascular invasion or obvious peritoneal rupture.

Step 2: First confirm the renal origin of the mass

The mass is usually very large, and radiologists should look for the residual normal renal parenchyma in order to confirm the renal origin of the mass. Power or color Doppler may be helpful in doubtful cases in enhancing the normal parenchyma around the mass, which is always more vascularized than the mass (Fig. 24.24).

Step 3: Depict relevant tumor extents

Vascular extension usually occurs in renal vein and in IVC.



a b

Fig. 24.24a,b. Wilms' tumor in a 2-year-old girl. US (**a**) at diagnosis shows residual normal renal parenchyma (*arrows*) surrounding the mass (*M*) and therefore confirms the renal origin of the mass. Color Doppler (**b**) may be helpful in doubtful cases in enhancing the normal parenchyma

Peritoneal dissemination is associated with hemoperitoneum and/or intraperitoneal masses.

Step 4: Precisely assess the contralateral kidney

Use high-frequency probes (7–12 MHz) and look for contralateral nodules, associated renal dysplasia (mesangial sclerosis) or malformation.

Step 5: Perform secondarily a CT scan or a uro-MR

- To confirm the renal origin of the tumor in difficult cases (use sagittal or coronal MR sequences or multiplanar reconstructions of CT images, Fig. 24.25)
- To precisely measure the three tumor diameters (sometime impossible with US)
- To confirm a suspicious tumor rupture
- To depict contralateral disease with higher sensitivity than US
- To confirm the normal function of contralateral kidney (after contrast agent administration)

Step 6: Be aware of pitfalls

- An adrenal neuroblastoma may invade the upper pole of the kidney (Fig. 24.26).
- A ruptured WT may present as a renal fracture.
- Renal infection, notably xanthogranulomatous pyelonephritis, may mimic WT.

Step 7: Check the relevant criteria for the diagnosis of Wilms' tumor

- Age ranges between 1 and 5 years
- No clinical sign of infectious disease
- Common radiological pattern
- No extrapulmonary metastasis

Step 8: Check if any indication for needle core biopsy

The question of tumor biopsy at diagnosis is relevant for patients treated with primary chemotherapy (SIOP strategy) and not for patients treated by primary surgery (NWTS strategy). Since WT has a very high prevalence in children, the diagnosis is usually based on clinical and radiological criteria only in most countries. According to the current SIOP-2001 protocol (SIOP 2001), core-needle biopsy at diagnosis is not recommended for all renal masses, but must be considered in cases of atypical presentation, i.e.:

- unusual clinical or biological presentation: age >5 years (higher risk of non-Wilms' histology like juvenile renal cell carcinoma),
- suspected urinary infection or septicemia (differential diagnosis with pseudotumoral or xanthogranulomatous pyelonephritis),
- hypercalcemia (observed in rhabdoid tumor or bone metastases in clear cell sarcoma)
- uncommon radiological pattern: extensive calcification (renal cell carcinoma, neuroblastoma), large lymph nodes (renal carcinoma, clear cell sarcoma, rhabdoid tumor),
- renal parenchyma not visible or almost totally extra renal process (neuroblastoma invading the kidney)
- extrapulmonary metastases

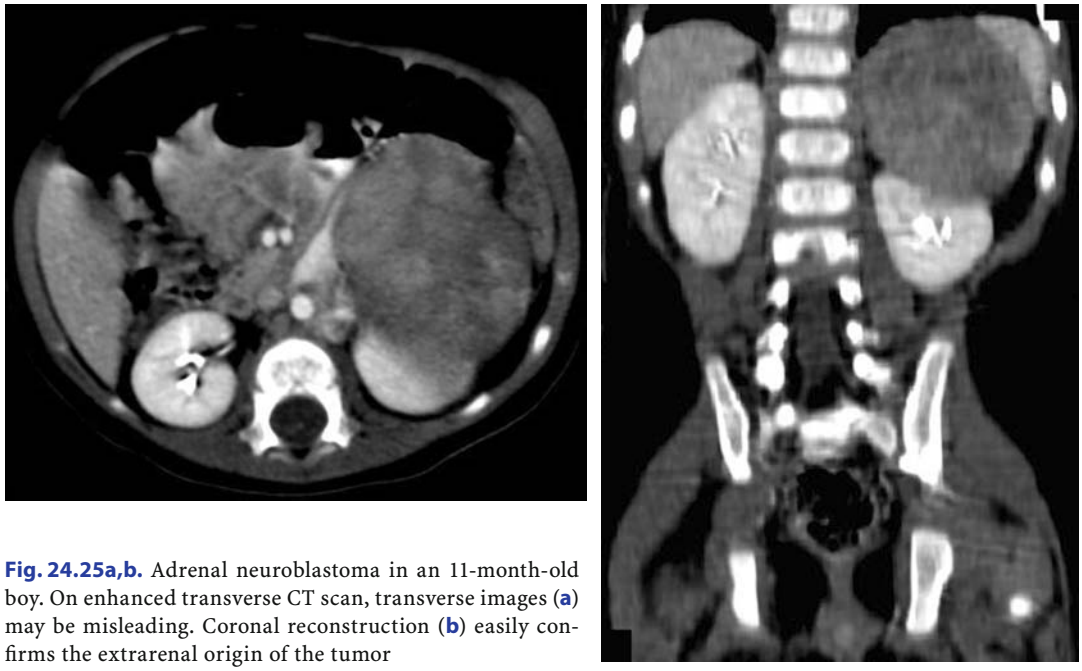


Fig. 24.25a,b. Adrenal neuroblastoma in an 11-month-old boy. On enhanced transverse CT scan, transverse images (**a**) may be misleading. Coronal reconstruction (**b**) easily confirms the extrarenal origin of the tumor

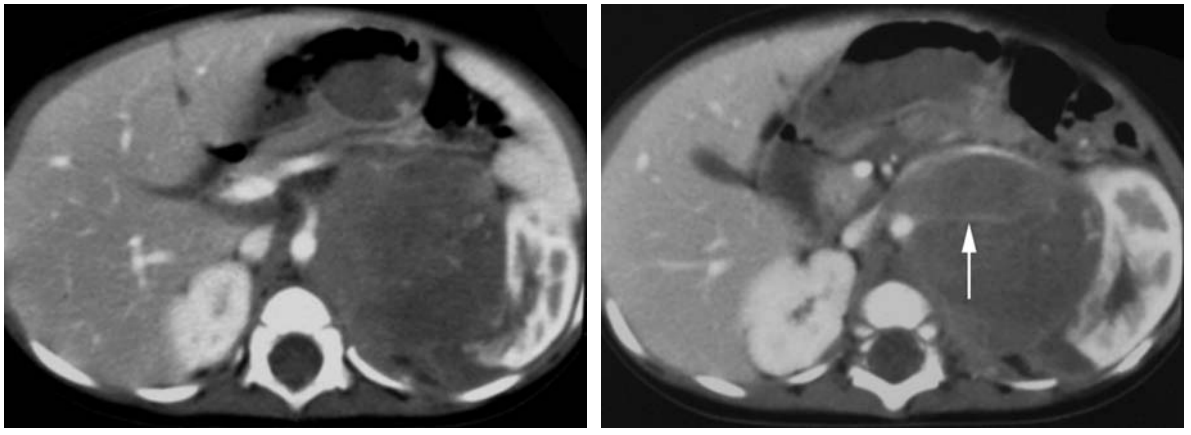


Fig. 24.26a,b. Adrenal neuroblastoma in a 10-month-old boy invading the upper pole of left kidney. **a** On unenhanced transverse CT scan the mass is almost totally extra-renal; on enhanced scan (**b**) the renal artery (*arrow*) is encased by the tumor. These features are suggestive of neuroblastoma and rarely observed in WT

If performed, the biopsy must be done by a trained radiology/pathology team, under general anesthesia, with normal blood coagulation tests, using sonographic guidance, always from a posterior approach to avoid peritoneal dissemination. The maximum external diameter needle currently recommended is 1.2 mm (18 G). Part of the tissue sample must be appropriately frozen to allow genetic and biological studies. Actually, several tumors may now be identified on the basis of genetic abnormalities, notably juvenile renal cell carcinoma, rhabdoid tumor, "cellular" or "atypical" congenital mesoblastic nephroma or renal fibrosarcoma.

The most common complication associated with core-needle biopsy is a fall in hemoglobin (20%) (Vujanic et al. 2003). Massive tumor bleeding, tumor rupture leading to death or needle track recurrences have been infrequently reported (Dykes et al. 1991; Saarinen et al. 1991; Lee et al. 1995; Skoldenberg et al. 1999; Vujanic et al. 2003) and remain exceptional in trained hands.

Needle biopsy is contraindicated in some situations: suspected rupture, bilateral disease (differential diagnosis between nephrogenic rests and WT is usually not possible on small samples), and of course in patients requiring primary surgery, i.e., age less than 6 months (congenital mesoblastic nephroma is highly probable and chemotherapy tolerance is low), or in suspected cystic partially differentiated nephroblastoma (differential diagnosis with the benign cystic nephroma is usually impossible on a biopsy specimen, and both tumors do not respond to chemotherapy).

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Urinary Tract Trauma

25

Jean-Nicolas Dacher and Cécile Cellier

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25.1 Introduction: The Context

Evaluating a child who has sustained abdominal injury is daily practice in a department of pediatric radiology. In this chapter, emphasis will be put on pediatric particularities of renal injuries. Obviously, renal trauma cannot be separated from associated traumatic lesions. This is especially true in organizing the imaging strategy.

Blunt abdominal trauma is much more frequent than penetrating ones. Various mechanisms may be involved, but discrepancy between the deceleration and severity of renal trauma can be encountered. For example, a relatively minor trauma can induce a severe renal fracture in cases of underlying kidney/urinary tract malformation (Fig. 25.1) or tumor (Fig. 25.2). The most severe lesions are usually observed following motor vehicle accidents, pedestrian crashes or sport injuries (biking, skiing, and horseback riding). On the other hand, minor trauma represents the most frequent situation: a fall while playing for toddlers, bathroom accidents for neonates and young children. Inflicted injury should always be kept in mind as a potential cause (Fig. 25.3).

Nowadays, in the vast majority of trauma patients, the management is non-operative and non-interventional. This principle was first applied in children; it is now becoming a rule in adult traumatology as well. A trend toward non-operative management naturally impacts on imaging strategies.

Conclusion

In cases of discrepancy between a relatively minor trauma and intense symptoms (pain, hematuria, and shock), underlying renal disease or malformation is likely.

J-N. Dacher, MD, PhD
Professor, Department of Radiology, University Hospital of Rouen 1, Rue de Germont, 76031 Rouen, France
C. Cellier, MD
Department of Pediatric Radiology, University Hospital of Rouen 1, Rue de Germont, 76031 Rouen, France

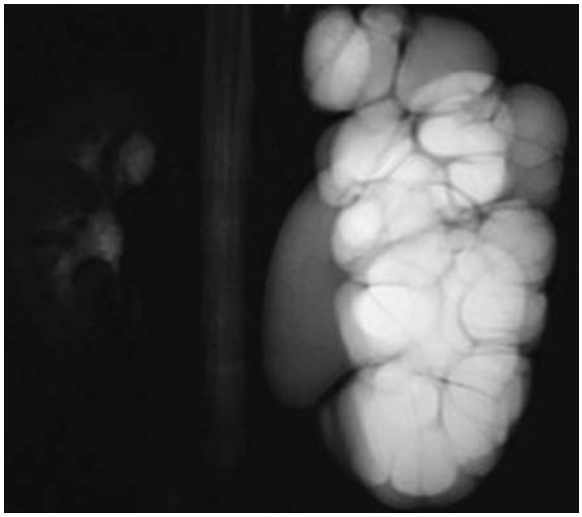


Fig. 25.1. A 12-year-old boy referred for evaluation of hematuria following minor trauma. Ultrasound had revealed left hydronephrosis. T2-weighted coronal image shows severe dilatation of multiple calyces contrasting with a slightly dilated pelvis. Megacalycosis was diagnosed

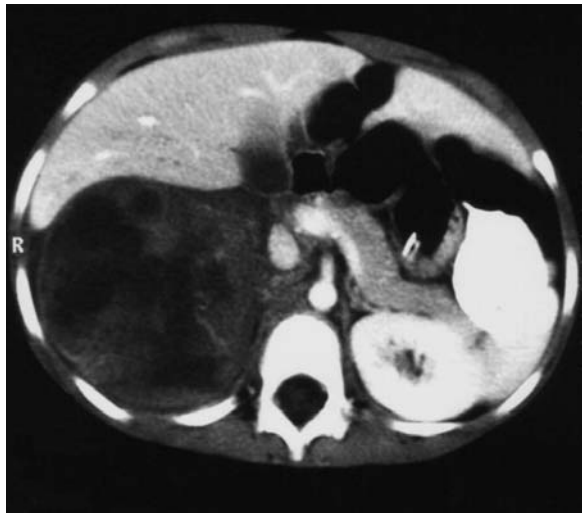


Fig. 25.2. Acute lumbar pain and hematuria induced by minor trauma in this adolescent girl. Discrepancy between the history and ultrasound findings (huge right renal mass) led to enhanced CT, which confirmed the diagnosis of right renal tumor

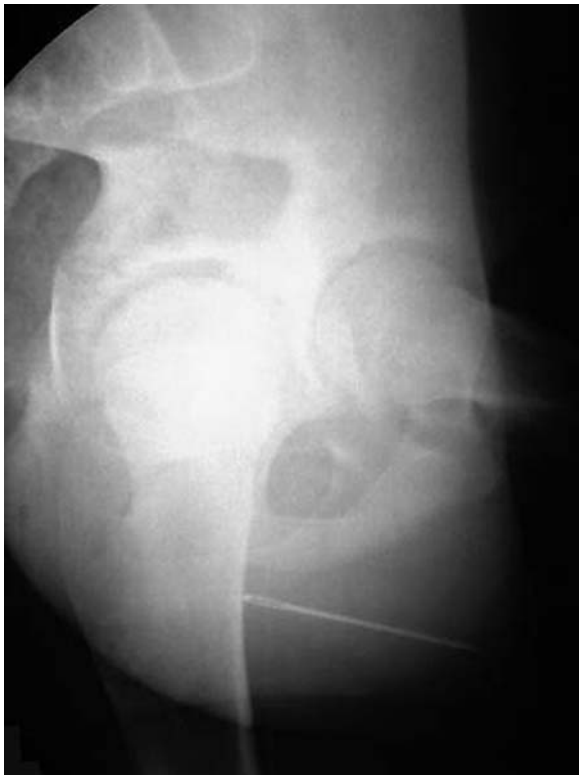


Fig. 25.3. Recurrent macroscopic hematuria in a 5-year-old boy. Clinical examination disclosed unexplained perineal inflammation. A lateral plain film showed a subcutaneous needle supposed to hurt the urethra. Inflicted injury has been suspected, but not proven

25.2 Clinical Evaluation and Imaging Strategies

25.2.1 Children with Severe Trauma and Multiple Injuries

Clinical findings are frequently limited, and even may be misleading. The mechanism of trauma and level of deceleration are essential elements of the diagnosis and imaging strategy. The presence of abdominal (the "seat belt sign") or lumbar ecchymoses correlates positively with severe intra-abdominal injuries. The gastrointestinal tract (duodenum) and the pancreas are more frequently involved in this situation (Sokolove et al. 2005). Skin lesions have to be considered in the imaging management since they may represent a contraindication to ultrasound examination. The localization of pain can point toward a specific organ lesion; for example, left upper quadrant pain points to the spleen and left kidney. Hemodynamic parameters (heart rate, blood pressure) are crucial in organizing the child's management and imaging workup.

In cases of unstable, non-transportable children, surgery could be performed on an emergency basis. The role of imaging is extremely limited; a "focused assessment with sonography for trauma" (FAST) is

able to identify the presence of peritoneal free fluid before proceeding to surgery (Walcher et al. 2006). FAST can be efficiently performed by licensed emergency department physicians or professional sonographers.

In cases of multiple traumas and a stable child, CT is unequivocally the modality of choice. If cranial trauma is present, a non-enhanced head CT is first performed in order to detect intra-cranial bleeding. Then a TAP (thorax abdomen pelvis) CT is carried out with contrast enhancement.

The priority of the radiologist is to detect the conditions that should lead to very urgent treatment including resuscitation techniques, surgery, percutaneous drainage or embolization. Among these conditions are: hemopericardium, rupture of the thoracic aorta, compressive pneumothorax, post-traumatic diaphragmatic hernia, intra-peritoneal rupture of the urinary bladder, pneumoperitoneum and active intra-abdominal bleeding.

25.2.2 Children with Minor Trauma

In cases of blunt abdominal trauma, the kidneys seem to be more frequently injured in children than in adults (Brown et al. 1998). Some reasons could be the relative weight and mobility of kidneys in the pediatric abdomen as well as their only fair degree of protection (non-ossified thoracic cage, thin abdominal wall and paucity of perirenal fat). Either gross or microscopic hematuria is frequent. However, it has been established that the severity of the renal lesion does not correlate with the degree of hematuria (Mayor et al. 1995). For example, the renal vascular pedicle lesion, one of the most severe renal injuries, rarely is revealed by gross hematuria (Fig. 25.4). Moreover, gross hematuria is not always a sign of renal involvement; on the contrary, it is known to be an excellent marker of bladder injury (Stuhlfaut et al. 2007). For these reasons, it should be acknowl-

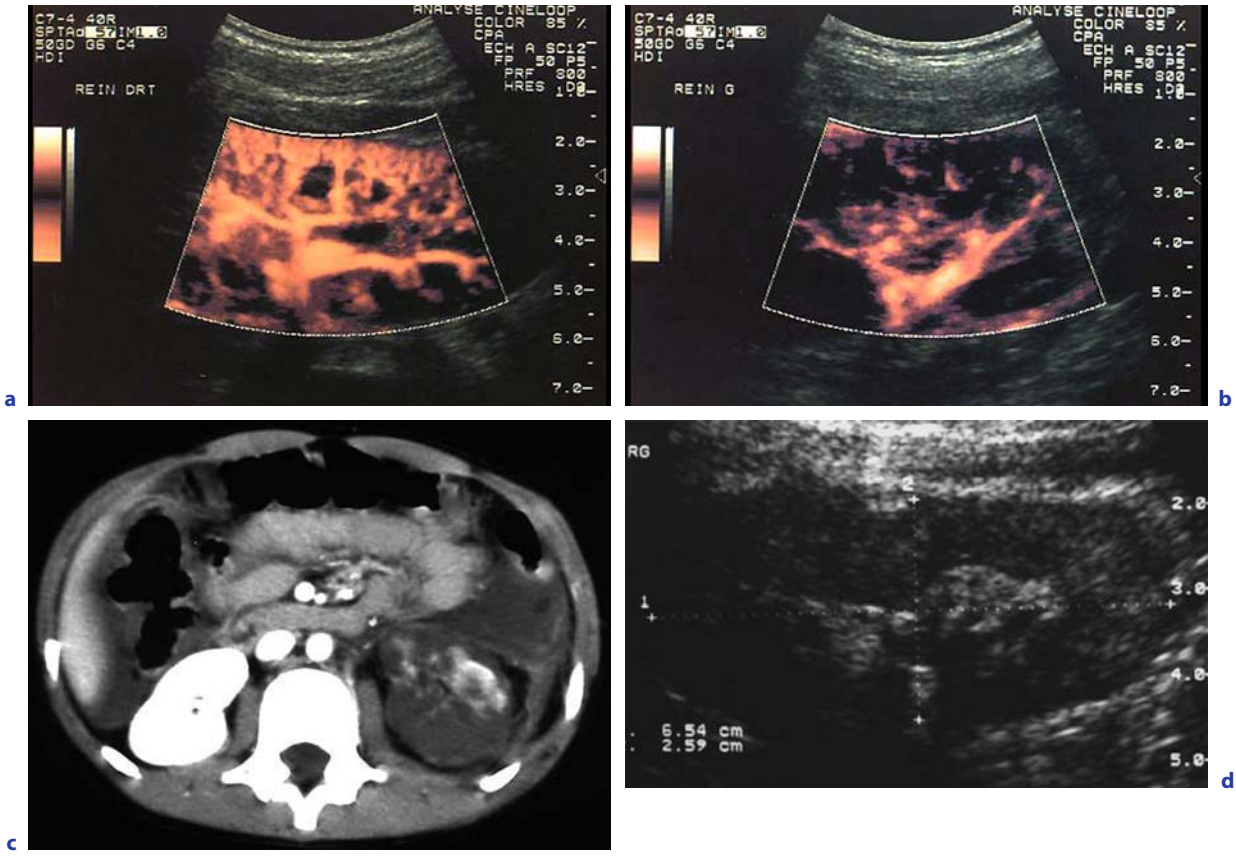


Fig. 25.4a–d. Motor vehicle accident involving this 7-year-old girl. On arrival, she complained of lumbar pain. Microscopic hematuria was revealed by a dipstick test. Power Doppler of the right kidney was normal (**a**). It showed severely decreased vasculature on the left side (**b**). Vascular pedicle injury was confirmed by enhanced CT (**c**). Note that conventional grey scale ultrasound of the left kidney was normal (**d**)

edged that in those less severely injured children, the imaging strategy is not as straightforward as in multiple trauma patients. Enhanced CT remains the unquestionable reference technique, though it was shown to be non-cost effective when performed without prior selection of the patients. The rate of negative studies can be close to 80% in spite of the administered radiation dose (Filiatrault et al. 1995). On the other hand, the limitations of ultrasound, the concurrent imaging modality, should be kept in mind. These limitations (diagnosis of free peritoneal gas, detection of spleen or liver injury during the first hours following trauma and characterization of a solid organ injury) may decrease the sensitivity of the examination even in experienced hands (Richards et al. 2002).

Conclusion

The severity of hematuria cannot be the only criterion for deciding the strategy of imaging examinations in cases of minor trauma.

25.2.3 Impact of Technical Environment on Imaging Strategy

Non-medical considerations have to be stated in the imaging management of children with blunt abdominal trauma. The available imaging modalities and organization of the hospital obviously impact on the management of trauma children. For many years, the English language literature has been reporting a poor sensitivity of ultrasound in the diagnosis of abdominal injuries (Benya et al. 2000). However, some conclusions were drawn from series of ultrasound examinations that had not been performed by expert pediatric radiologists. Results obtained by sonographers or emergency department physicians using portable equipment cannot be compared with those from experts using last generation equipment, color and power Doppler (Fig. 25.4), high frequency transducers and in some instances intravenous contrast medium (Fig. 25.5). Due to differences in the practice of ultrasound, studies originating from different countries or institutions cannot be directly compared.

In many children's hospitals throughout the world, CT is not as easily available as in the United States, Japan or Germany (Chirdan et al. 2007). For example, in our University Hospital, short vehicle transportation to the adult hospital is required for any pediatric CT. This situation explains why many pediatric radiologists have had to develop expertise in emergency ultrasound. Any transportation outside the intensive care unit carries its own risk. One should remember that cardiovascular shock occurs much more abruptly in children than in adults. In children, the blood pressure is known to remain within the normal range much longer than in adults in spite of a severe blood volume loss (Le Dosseur et al. 2005). The hematocrit can be a tricky marker as well. The ideal solution would certainly be to implement modern CT equipment in any department taking care of pediatric emergencies. However, the negative consequence would be to perform CT in every case of a traumatized child, thus increasing the radiation dose delivered to the pediatric population.

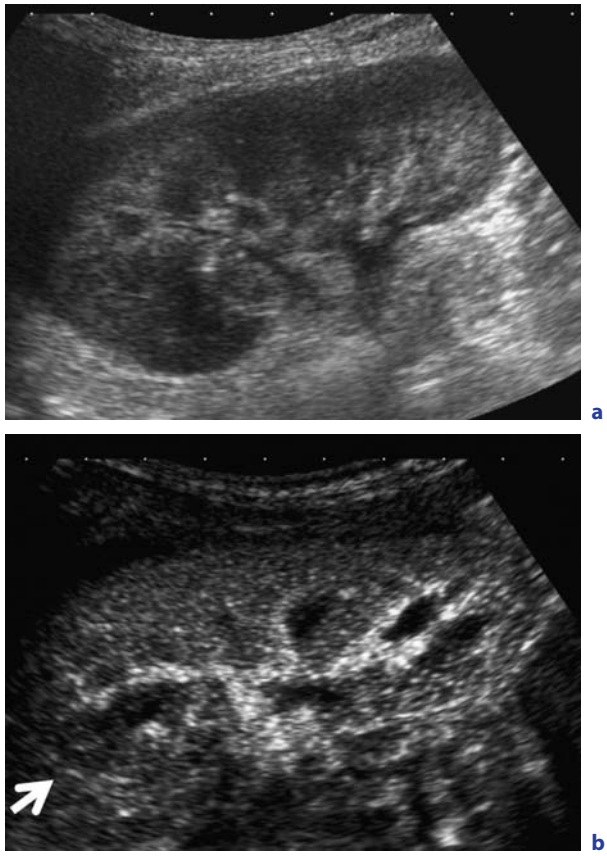


Fig. 25.5a,b. US examination of a 7-year-old girl with laceration of the upper pole of the left kidney. Slight hyperechogenicity was observed on conventional grey scale ultrasound at the upper pole (**a**). IV injection of contrast medium improved the visualization of the hypo-perfused lesion (*arrow*) (decreased echogenicity as compared to that of normal cortex) (**b**) (courtesy of Michel Claudon, MD)

Conclusion

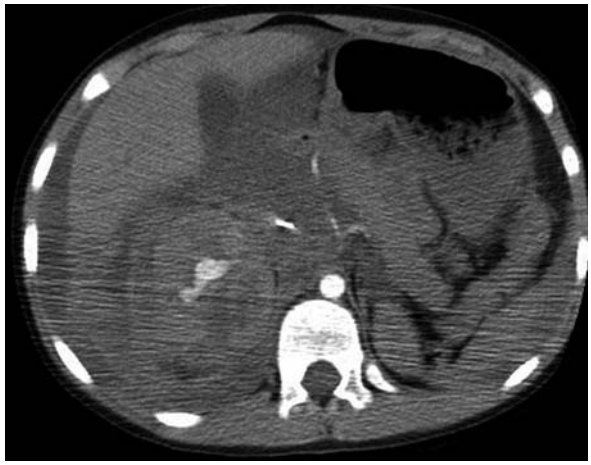
In the context of trauma, ultrasound series should be interpreted with regard to the expertise of the operators, to the employed equipment and to the local context (availability of CT).

25.2.4 Strategy

Some decision algorithms have been suggested; for example, a group from Atlanta (Perez-Brayfield et al. 2002) proposed to reserve CT for traumatized children with 50 or greater red blood cells on urinalysis, hypotension on presentation at the emergency room or based on the severity of the mechanism of injury. In our institution, we use color and power Doppler ultrasound as the first line examination in children with minor trauma and microscopic hematuria. CT is performed immediately thereafter in cases of any ultrasound abnormality (Pietrera et al. 2001) or any discrepancy between clinical findings and ultrasound examination (Lougué-Sorgho et al. 2006). Ultrasound is also adapted for the follow-up of children with renal traumatic lesions initially evaluated by CT. At least, CT is recommended as the first step examination when ultrasound is not feasible (severe pain, obesity or skin lesions).

MRI can be performed successfully instead of MDCT, for example, in children with a known allergy to iodinated contrast media (Marcos et al. 1998). However, MR is usually less available and more time consuming than CT. Otherwise, reliable monitoring of vital parameters inside the magnet requires sophisticated devices. Either ultrasound or CT can be suitable to guide percutaneous drainage (urinoma). In the era of CT, intravenous urography is no longer indicated.

No indication remains for angiography in the diagnostic evaluation of blunt abdominal trauma. On the one hand, the risk of the examination is relatively high. On the other hand, vascular injuries are extremely well depicted by the association of color Doppler ultrasound and MDCT. Angiography can be proposed in relatively rare instances when percutaneous treatment (embolization, angioplasty) appears to be the best option (Fig. 25.6). In the con-



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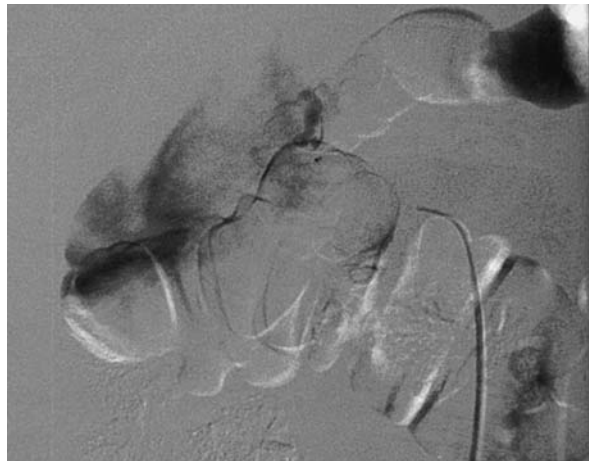


b

c

Fig. 25.6a–c. Six-meter fall in a 10-year-old boy. Liver and right kidney injury. Enhanced CT (**a**) performed on admission showed intra- and retroperitoneal effusions. Active bleeding of the right renal artery was demonstrated by CT, then confirmed by angiography (**b**). Selective embolization of the injured artery was carried out with immediate satisfactory result. Loss of renal function on the right side was detected 1 year later by DMSA scintigraphy (**c**)

text of emergency, angiography/interventional radiology is an excellent tool to treat active bleeding. Later in the course, recurrent gross hematuria is an important indication; it is frequently due to traumatic arteriovenous fistula (which can occur after blunt trauma or after percutaneous renal biopsy). In cases of occlusion, dissection or pseudoaneurysm of a renal artery, percutaneous treatment can be justified in order to reopen or to occlude the involved arterial segment.

25.3 Renal Injuries

25.3.1 The AAST Classification

The most commonly used classification was proposed by the American Association for the Surgery of Trauma (AAST). Minor injuries include grade I (renal contusion, isolated sub-capsular hematoma) and II lesions (cortical laceration less than 1 cm deep not reaching the excretory urinary tract). Patients with minor injuries were shown to recover without sequelae. They represent 75% of all blunt abdominal trauma cases (Wessel et al. 2000). Major injuries include grade III (cortical laceration more than 1 cm deep not reaching the excretory urinary tract) (Fig. 25.7), IV (cortical laceration more than 1 cm deep reaching the excretory urinary tract or segmental infarct) and V lesions (renal fracture or vascular pedicle lesion) (Figs. 25.4, 25.8). A recently published study showed that the AAST Organ Injury Scale for kidney injuries could predict nephrectomy, dialysis and death in patients with blunt injuries as well as nephrectomy in cases of penetrating injuries (Kuan et al. 2006). It is noteworthy that treatment and prognosis of the two types of grade V injuries are completely different. Vascular pedicle lesion is considered as an extreme urgency; a revascularization procedure should be started within the 6 h following injury. In most cases, the functional prognosis of the kidney or involved segment is extremely poor (Fig. 25.6). On the contrary, renal fractures (Fig. 25.8) are usually managed non-operatively, with a much better functional prognosis. Prognosis depends more or less on the volume of devascularized kidney.

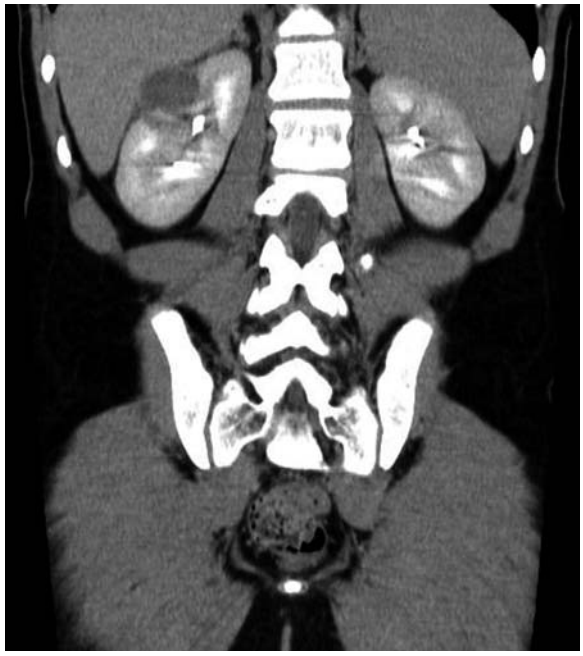


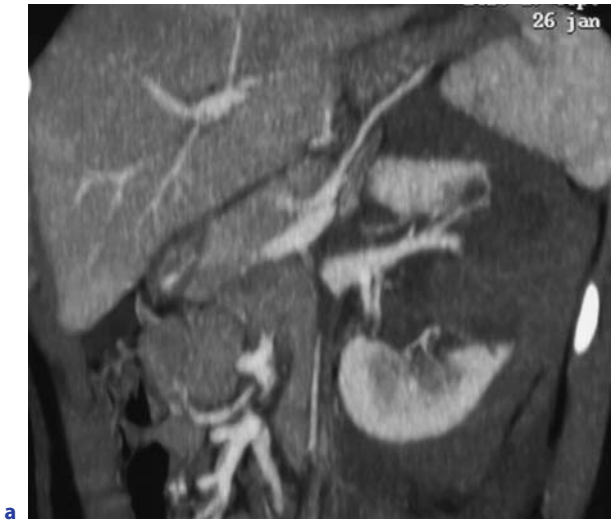
Fig. 25.7. Enhanced MDCT. Coronal reformatted view. Grade III AAST injury

This classification does not take into account the possible ureteric injuries that are known to be more frequent in children than in adults (Reda and Lebowitz, 1986). Uretero-pelvic junction disruption is the most common location in cases of blunt abdominal trauma; it predominates in children with ureteropelvic junction obstruction. Diagnosis is difficult due to the usual absence of hematuria.

Other lesions do not belong to this classification either. As stated above, intra-renal arteriovenous (or arterio-calyceal) fistulas or pseudo-aneurysms represent an excellent indication for super-selective angiography. Adrenal hematoma is frequently associated; the diagnosis by CT is straightforward, the endocrine prognosis is usually excellent, and calcification is frequent on follow-up.

25.3.2 Ultrasound

Ultrasound is efficient to show perirenal collected fluid, hematoma or a mixture of urine and blood. A focal impression on the kidney is identified in subcapsular hematoma, while a collection with a ruptured capsula tends to surround and displace the whole kidney. Renal contusion can be identified as



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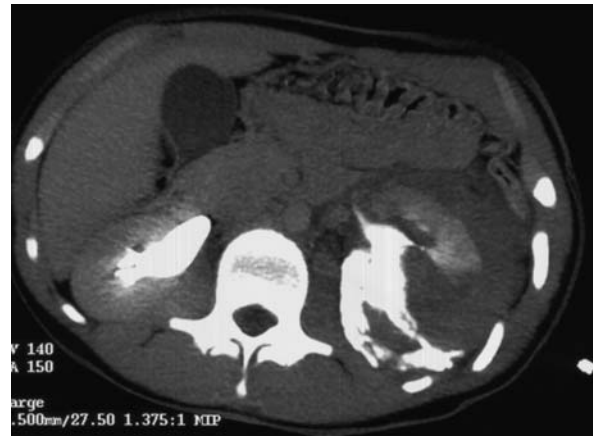

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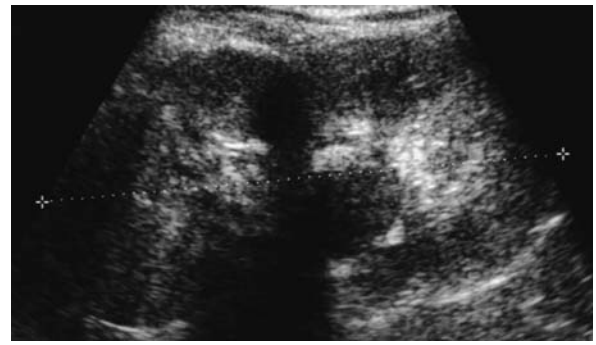


c

Fig. 25.8a–c. Left renal fracture in an 11-year-old girl. No associated intra-abdominal or bone lesion was found by CT (**a**). Delayed scan (**b**) showed opacification of the urinoma by the contrast medium. In spite of this severe leak, the urinary excretory system remained patent. Six months later, follow-up ultrasound showed the fracture between two normal-sized segments (**c**). Excellent function of the left kidney was shown by nuclear medicine studies (not shown)

a hyperechoic lesion with loss of cortico-medullary differentiation (Fig. 25.9). A grey scale ultrasound examination can be completely normal in case of a vascular pedicle lesion (Fig. 25.4d); any examination should include color and/or power Doppler, which can detect complete or partial loss of vascularization (Fig. 25.4). If such examination is not possible for any reason, CT should be performed.

Renal fracture is usually more difficult to characterize by grey scale ultrasound or Doppler (Pietrera et al. 2001); injection of intravenous contrast medium can help approach that diagnosis (Fig. 25.5). Of course, the ultrasound examination of the abdominal cavity should be complete. For example, in cases of a right kidney lesion, it is common to find an associated liver lesion.

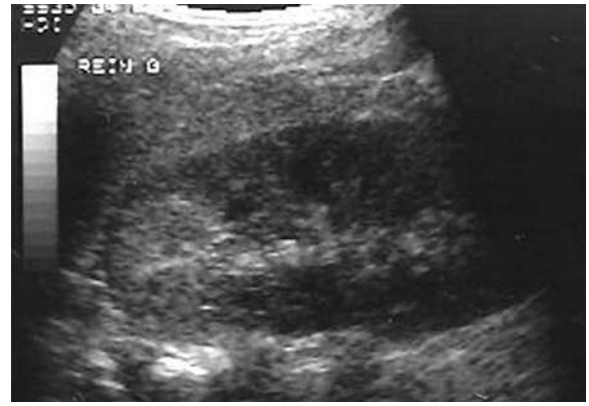


Fig. 25.9. Grey-scale ultrasound 48 h after blunt abdominal trauma in a 10-year-old boy. Loss of cortico-medullary differentiation at the upper pole of the left kidney. Color Doppler showed decreased vasculature in the same area

25.3.3 MDCT

If any abnormality is found by ultrasound, or in case of any discrepancy between clinical and biological findings and a normal ultrasound, enhanced CT should be performed. The injection technique depends on preliminary results. In most cases, we scan the child at the tubular phase (approximately 60 s after 2 cc/kg of contrast medium) and again at 10 min if the first scan showed fracture and/or perirenal hematoma (Fig. 25.8). A preliminary non-enhanced acquisition is rarely useful. An arterial phase scan

can be performed when an arterial lesion is suspected (Figs. 25.10, 25.11). Such a diagnosis is based on the following signs: decreased attenuation of the renal parenchyma at arterial phase, non- or delayed opacification of the excretory tract, cortical rim sign and medullary enhancement (Fig. 25.11a) (Malmed et al. 1992). Nowadays, MDCT allows approaching the vascular lesion; it may show thrombosis, rupture or dissection. Multiplanar two- or three-dimensional reformatting is another advantage of this new technology.

25.3.4 Imaging Complications and Sequelae

In the hours and days following the acute phase, intra- or extra-renal secondary bleeding is the main risk. It justifies hospitalizing traumatized children at the intensive care unit for a close clinical, biological and imaging follow-up. Ultrasound is the modality of choice for bedside follow-up when transportation to the radiology unit is considered difficult or even

Fig. 25.10a,b. Motor vehicle accident in an adolescent boy. Enhanced 16-detector MDCT. No opacification of the right kidney is visible at arterial phase (**a**). The right renal artery is occluded close to its origin (**a**,**b**)

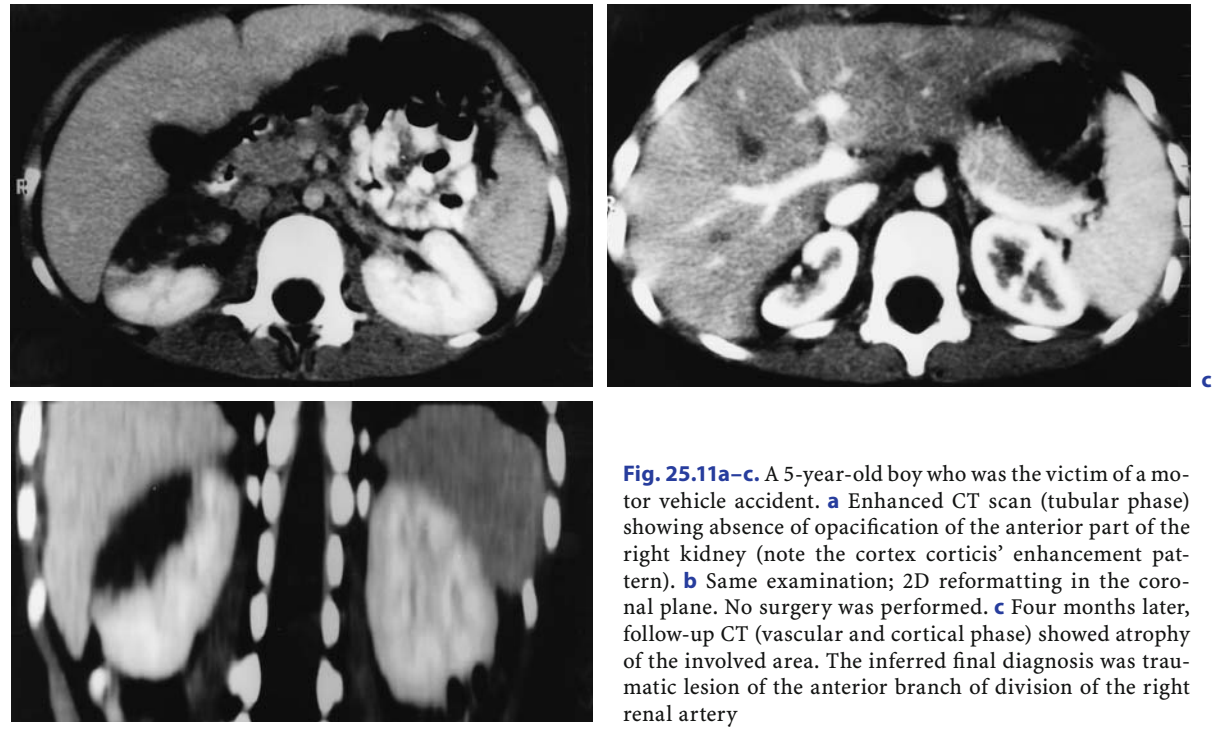


Fig. 25.11a–c. A 5-year-old boy who was the victim of a motor vehicle accident. **a** Enhanced CT scan (tubular phase) showing absence of opacification of the anterior part of the right kidney (note the cortex corticis' enhancement pattern). **b** Same examination; 2D reformatting in the coronal plane. No surgery was performed. **c** Four months later, follow-up CT (vascular and cortical phase) showed atrophy of the involved area. The inferred final diagnosis was traumatic lesion of the anterior branch of division of the right renal artery

dangerous. The quality of equipment and experience of the examiner strongly impact the quality of information provided by bedside examinations. Otherwise, perirenal urinoma or hematoma can become infected and justify percutaneous drainage under ultrasound or CT guidance.

Later on, partial or complete lack of renal function is the most frequent complication in high-grade renal injuries (Fig. 25.6c). Arterial hypertension could develop in 7–10 % children with severe lesions (Delarue et al. 2002).

Nuclear medicine studies can be performed in the late stage of renal trauma to evaluate the residual renal function. Either DMSA-^{99m}Tc or MAG3-^{99m}Tc studies can be performed. MAG3-^{99m}Tc is preferred in patients in whom excretion should be assessed as well. Functional MR urography is a promising examination in that field (Fig. 25.12).

Conclusion

Clinical follow-up of high-grade injuries can be completed by targeted isotopic or MR examinations.

25.4 Bladder Injury

Bladder injury is relatively infrequent in children. It is usually the consequence of blunt abdominal trauma in a child with a full bladder. Motor vehicle accident is a common cause. Seat belt ecchymosis, hematuria and pelvic fractures can be associated. Urinary leakage into the peritoneum is more fre-

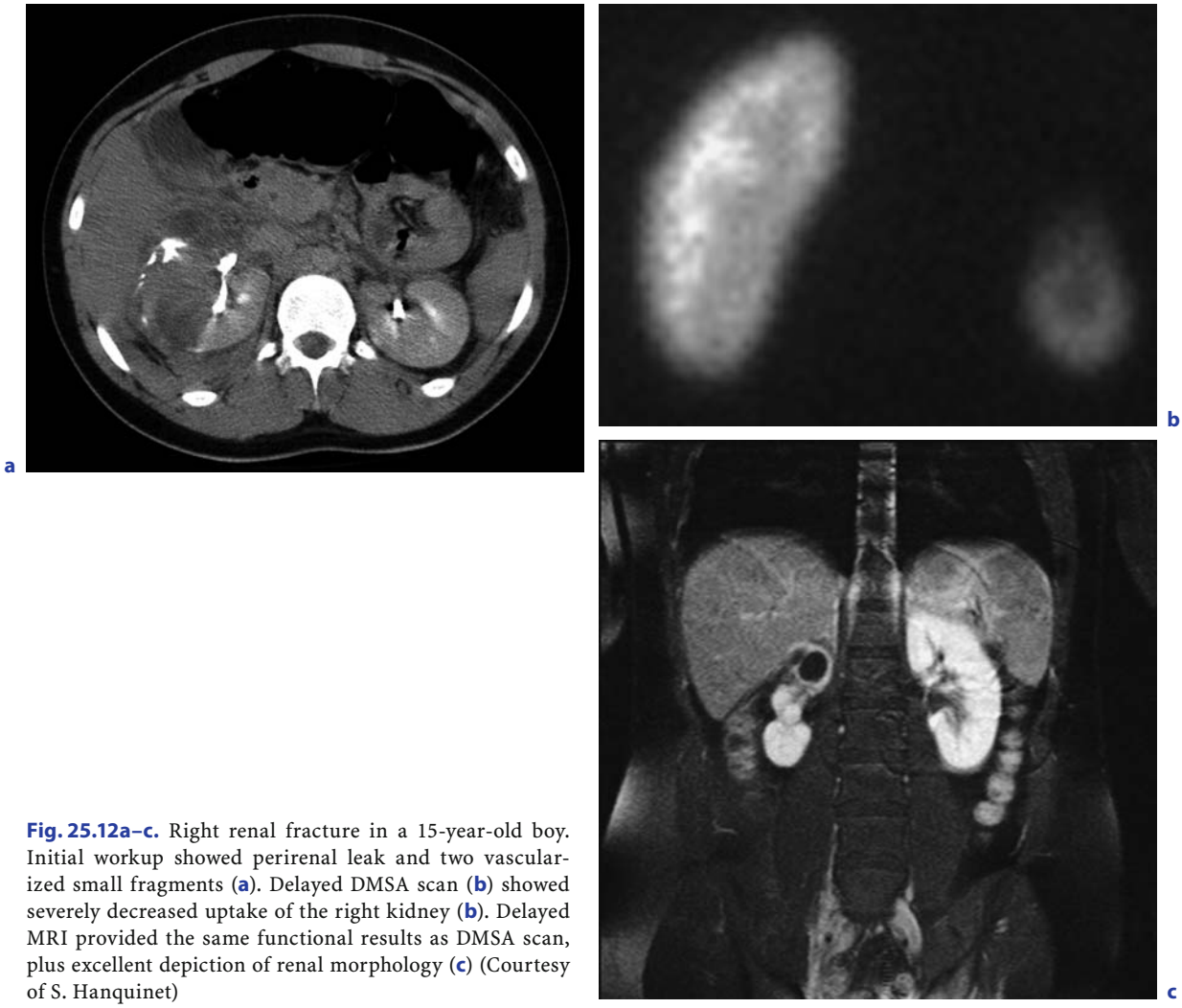


Fig. 25.12a–c. Right renal fracture in a 15-year-old boy. Initial workup showed perirenal leak and two vascularized small fragments (**a**). Delayed DMSA scan (**b**) showed severely decreased uptake of the right kidney (**b**). Delayed MRI provided the same functional results as DMSA scan, plus excellent depiction of renal morphology (**c**) (Courtesy of S. Hanquinet)

quent in children than in adults for anatomical reasons (Sivit et al. 1995). Intra-peritoneal bladder rupture should be differentiated from perivesical hematoma or leakage into the perivesical space, which can be managed conservatively. Radiological differential diagnosis is important because surgery has to be performed urgently in case of peritoneal leakage. Ultrasound is not the modality of choice. It can show hematoma and free fluid in the pelvic cavity that does not seem to be delineated by a normal bladder. VCU or CT cystography is more valuable to establish the diagnosis of rupture. When performing VCU, it can be recommended to start with opacification of the urethra, to make sure there is no associated lesion and to complete the examination with bladder opacification (Bisset et al. 1991). Associated bone fractures should not be overlooked.

25.5 Urethral Injuries

Urethral lesions occur much more frequently in male children for evident anatomical reasons. The adult-type lesion involving the membranous urethra complicates perineal injury and remains the most frequent one in adolescents. In adult men, the posterior urethra is relatively protected by the mature and firm prostate tissue. On the contrary, in children, urethral injuries may occur anywhere along the posterior urethra because the small soft prostate provides little stabilizing effect (Avanoglu et al. 1996). Hence, either partial tear or complete rupture of the posterior urethra can be observed. Management of partial tears is based on either prolonged catheter drainage of the urethra or suprapubic cystostomy (Glassberg et al. 1979).

In cases of complete disruption of the posterior urethra, the first step treatment is suprapubic drainage. The Mitrofanoff principle (interposition of the appendix between the urinary bladder and the abdominal wall), has been occasionally applied in severely crushed patients to divert the urine (Freitas Filho et al. 2003). No consensus has been made regarding the surgical strategy (Onen et al. 2005). Either primary realignment over a urethral tube, immediate surgery or delayed repair can be performed.

Urethral injuries may be iatrogenic (Fig. 25.13) or inflicted. Bladder neck disruption seems to occur more frequently in children than in adults (Fig. 25.14). It may be the consequence of blunt abdominal trauma and may be associated with pelvic fracture involving displacement of the pubic symphysis. It should be differentiated from urethral disruption because it may need primary repair rather than a cystostomy tube and secondary surgery. Anterior disruption at the bladder neck (vesicoprostatic junction) may occur in boys, while rupture through the vesicovaginal septum may occur in girls (Merchant et al. 1984).

The radiologist should avoid any urethral catheterization when urethral disruption is suspected. Secondary repair is the rule for urethral injuries, so that a minimal imaging evaluation should be performed in emergency situations (Baskin and McAninch 1993). Retrograde opacification of the urethra by water-soluble iodinated contrast medium is the reference examination (Fig. 25.15). A Foley catheter with a balloon inflated in the fossa navicularis is used. CT cystography can be considered in cases of bladder neck disruption and/or pelvic bones fractures.

The key questions to address by imaging are as follows: is there any urethral leak (the absence of a leak cannot exclude hematoma or contusion) and is there any retrograde opacification of the bladder (allowing the differential diagnosis between complete and partial disruption of the urethra)? The follow-up of patients is of primary importance. The aim is to detect urethral stenosis or diverticulum. Again, prudent retrograde opacification is the optimal examination.

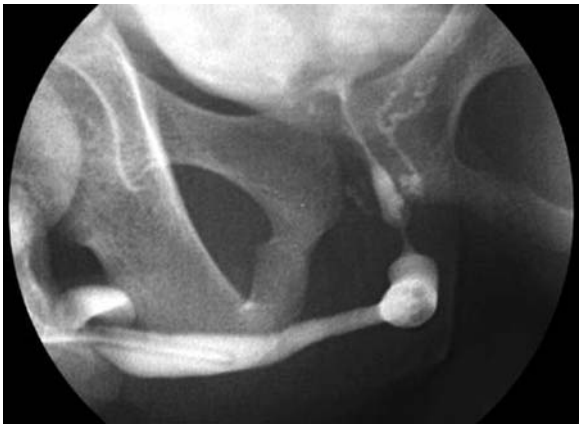
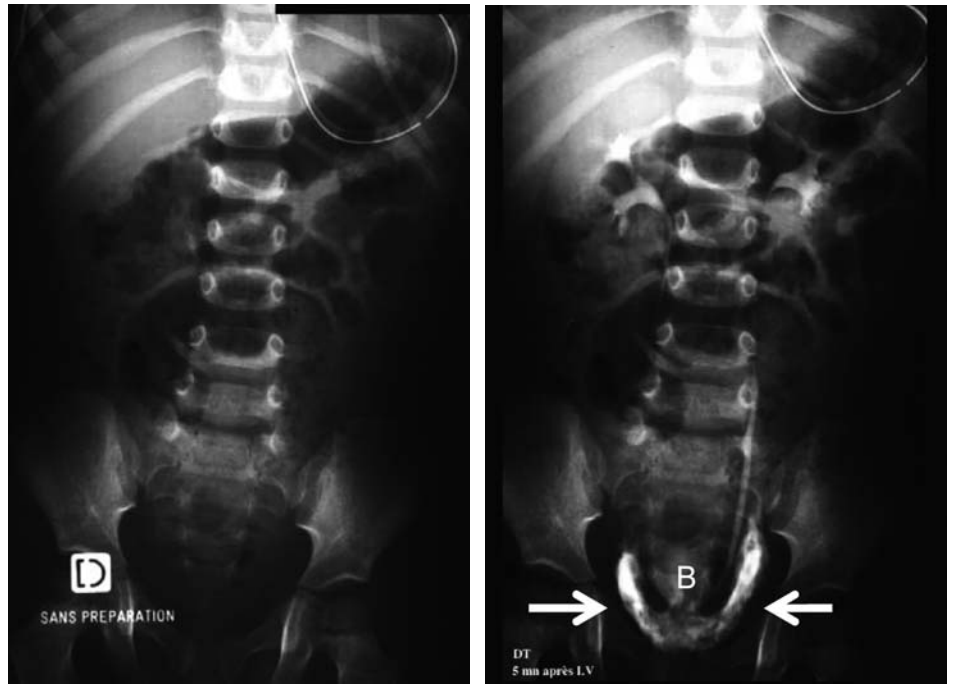


Fig. 25.13. Retrograde urethrography. Urethral stenosis following a long-standing urethral catheterization for cardiac surgery. Note reflux into the prostatic ducts



a b

Fig. 25.14a,b. Bladder neck disruption in a young boy who underwent blunt abdominal trauma. Intravenous urography. Plain film (**a**) showed traumatic widening of the pubic symphysis. (**b**) As soon as 5 min, the faintly opacified urinary bladder (*B*) appears elevated by an infravesical leak (*arrows*)

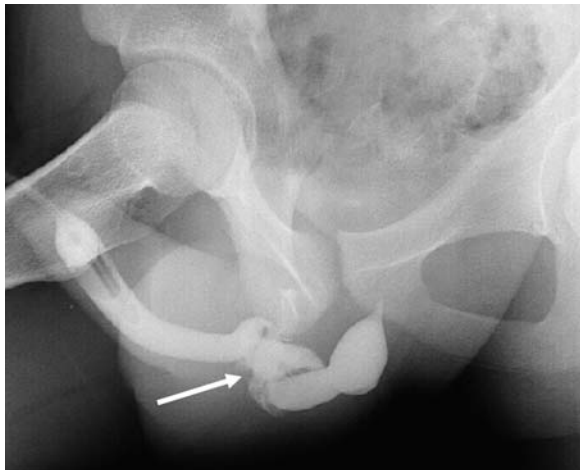


Fig. 25.15. Complete disruption of the membranous urethra in an adolescent boy shown by retrograde urethrography (*arrow*). Note the inflated balloon of the Foley catheter in the fossa navicularis

Conclusion

In cases of bladder or urethral trauma, imaging studies should be scheduled and oriented accordingly with surgical management.

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Pediatric Genitourinary Intervention

26

Richard B. Towbin, Christopher Kuhn, and Anne Marie Cahill

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26.1 Introduction

Percutaneous techniques offer several advantages over open surgery in the treatment of many pediatric genitourinary diseases. The pediatric interventionalist routinely treats patients with conscious sedation on an outpatient basis that would require general anesthesia and lengthy hospital admissions if treated surgically. The minimally invasive nature of percutaneous therapy also results in cost reduction. The outcomes of percutaneous techniques have now been established as equal to or better than the corresponding surgical technique in many instances. In spite of this, pediatric genitourinary intervention has grown relatively slowly over the past decade. Limited growth in this area is likely due to a variety of factors, especially the preference of urologists to perform combined percutaneous and surgical procedures in the operating room. Most referrals to pediatric interventional radiologists are cases that are difficult to treat operatively or with endoscopic techniques. Consequently, a minority of children is referred for routine procedures.

Percutaneous treatment of diseases affecting the urinary tract most often begins with accessing a collecting system and placing a nephrostomy tube. Thus, nephrostomy insertion is the basic technique upon which percutaneous surgical procedures are built. This chapter discusses nephrostomy tube insertion, ureteral stent insertion, ureteral stricture dilatation, nephrostomy tract dilatation, percutaneous removal of calculi, endopyelotomy techniques used in the treatment of UPJ strictures and percutaneous renal angioplasty for treatment of renovascular hypertension.

R. B. Towbin, MD
Radiologist–in–Chief, Phoenix Children's Hospital, 1919 East Thomas Road, Phoenix, Arizona 85016, USA
C. Kuhn, MD
Department of Radiology, Mercy Hospital, 144 State Street, Portland ME 04101, USA
A. M. Cahill, MD
Head, Division of Interventional Radiology, The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104, USA

26.2 Percutaneous Nephrostomy

Nephrostomy insertion is the building block for most urinary tract interventions. The percutaneous nephrostomy technique was first described for the treatment of hydronephrosis (Goodwin et al. 1955). About 20 years later, the first percutaneous stone removal was performed (Fernstrom and Johanasson 1976). Endourologic technology was

further extended when electrosurgical instruments were safely used. These developments, combined with new interventional and endoscopic equipment, have led to the development of complex endourologic techniques. These advances have led to better patient care and a closer working relationship among the nephrologist, urologist, pediatric surgeon, transplant surgeon, and pediatric interventionalist. In many instances, these collaborations have led to a reduced need for open surgical procedures.

Percutaneous nephrostomy has been successful in over 97% of pediatric patients ranging in age from 1 day to 18 years (Irving et al. 1987; Winfield et al. 1984; LiPuma et al. 1984). These results compare favorably with surgical management (Gonzalez-Serva et al. 1977).

The most common indications for percutaneous nephrostomy is for relief of symptomatic urinary tract obstruction (Fig. 26.1) and pyonephrosis (Man et al. 1983; Pode et al. 1982). In a series of 50 percutaneous nephrostomies in the pediatric population reported by Stanley and colleagues (1983), the most frequent causes of obstruction were ureteropelvic junction (UPJ) narrowing and obstruction after ureteral reimplantation.

The benefits of percutaneous nephrostomy are related to the ease of placement under sedation and to the rapid relief of obstruction and improved renal function. Infected and obstructed systems can be drained, and fever management becomes possible (Gonzalez-Serva et al. 1977). Other indications for percutaneous nephrostomy include assessment of renal function, demonstration of pathologic anatomy, and differentiation between obstructed and nonobstructed dilated systems using a pressure flow study (Whitaker perfusion test) (Fig. 26.2) (Whitaker 1981).

Percutaneous nephrostomy can be utilized as a temporizing measure prior to definitive therapy of underlying obstruction. Percutaneous decompression of the obstruction allows time for improvement in renal function, treatment of urinary sepsis, and a more accurate assessment of the renal unit. Children with postoperative ureteral edema, leakage, or obstruction from extrinsic compression of calculi insertion or a percutaneous nephrostomy may be cured.

In rare instances, obstruction caused by a fungus ball may be treated with a combination of percutaneous nephrostomy and infusion of amphotericin (Fig. 26.3) (Matsumoto et al. 1990). In asymptomatic children with hydronephrosis, antegrade pyelography and pressure measurement (Whitaker test) may be performed prior to surgical or endourologic correction to document the level and nature of the obstruction. Finally, percutaneous nephrostomy

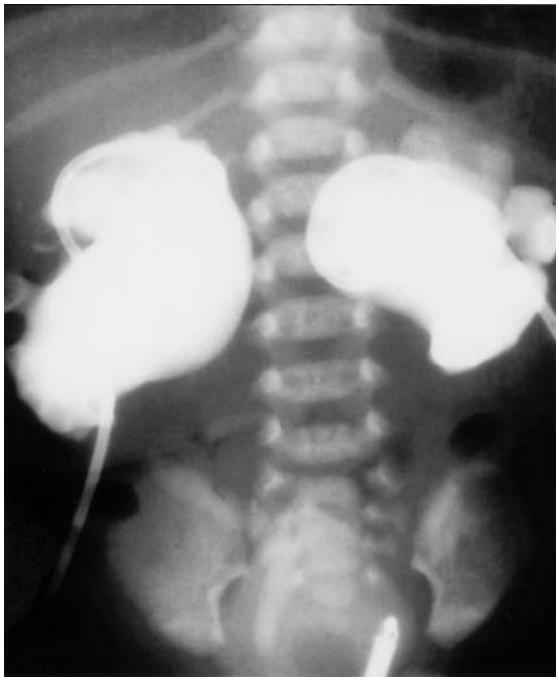


Fig. 26.1. Neonate with bilateral UPJ obstructions. Five-French nephrostomy tubes in place

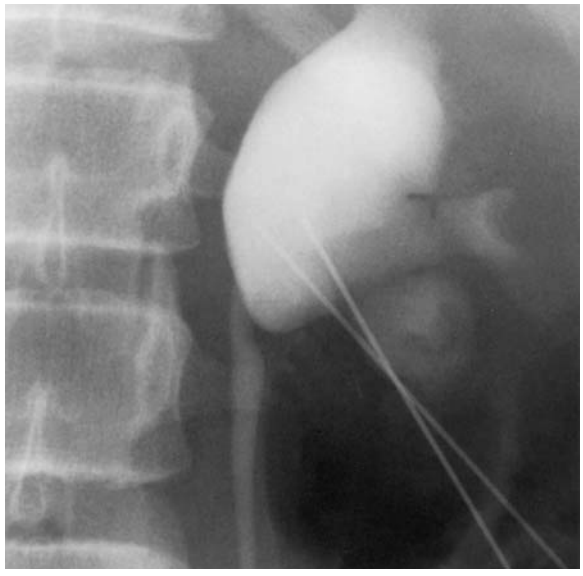


Fig. 26.2. Teenage girl with a dilated renal pelvis and equivocal Lasix renogram after a dismembered pyeloplasty. Whitaker test performed using a 2 needle technique demonstrating an enlarged renal pelvis due to an UPJ obstruction

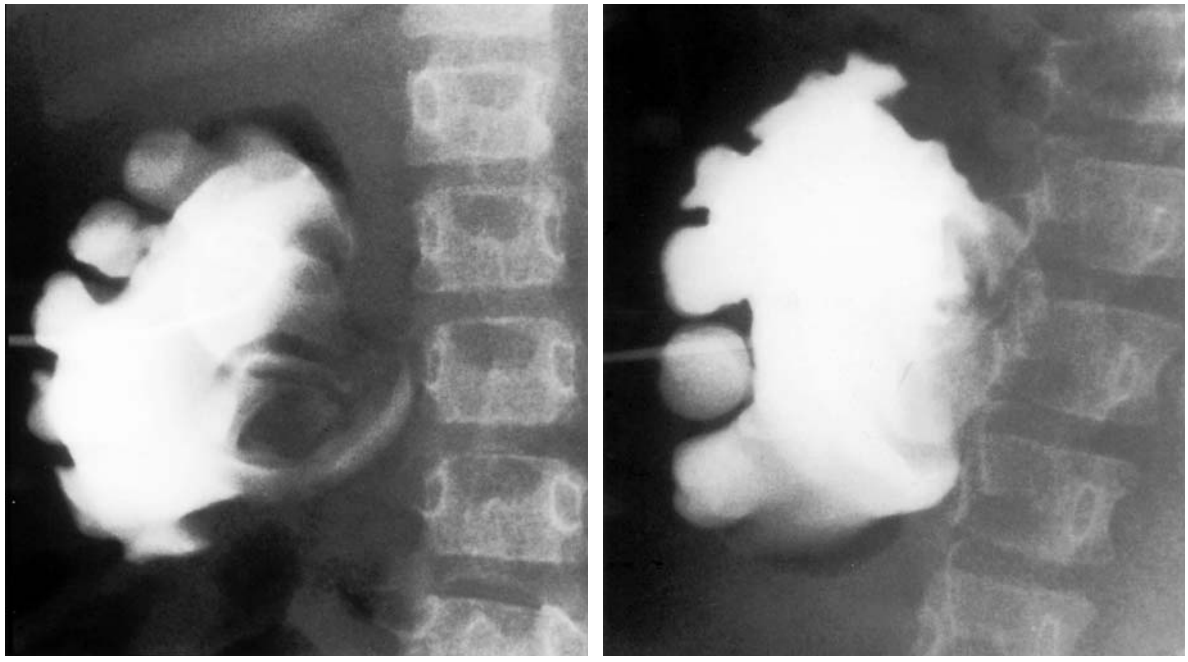


Fig. 26.3a,b. Neonate with complicated course developed UPJ obstruction secondary to a fungus ball. Nephrostomy drainage (5-French system) and amphotericin infusion eventually resolved the obstruction. **a** At diagnosis; **b** 2 weeks later shows partial resolution

may be the initial procedure required to gain access prior to other endourologic procedures. Examples of these include percutaneous stone removal and percutaneous endopyelotomy.

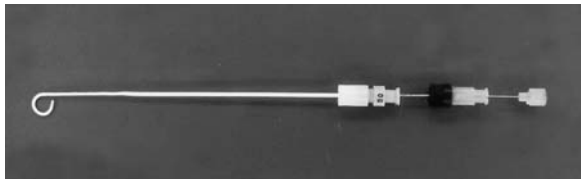
Contraindications to percutaneous nephrostomy are uncommon and include an uncorrectable coagulopathy and an unfavorable anatomy, making percutaneous access impossible or dangerous.

Properly sized equipment is essential to safely perform percutaneous nephrostomy in children. Equipment routinely used in adults may be ineffective or dangerous, especially in the perinate and young infant. For example, the Cope introducer system (Cook, Inc., Bloomington, Ind.), which facilitates exchanging a 0.035-inch or 0.038-inch guidewire for a 0.018-inch guidewire after puncture of the renal pelvis with a 22-gauge Chiba needle, is problematic in small infants. While this system works well in older children, its side port design (through which the 0.035-inch or 0.038-inch guidewire will exit) will often lie outside the renal pelvis making guidewire exchange difficult or impossible. Also, if the sheath is advanced, it likely will kink at the side port again, making guidewire exchange problematic. Thus, it is preferable to use an end hole coaxial dilator such as the Accustick system (Medi-Tech), the micro puncture set (Cook), or a sheathed needle to insert a 0.035-inch or 0.038-inch guidewire into a small renal pelvis.

It is important to consider carefully the guidewire selection. Standard and stiff guidewires are of value in both older children and adults. In perinates and small infants, a standard 0.035-inch or 0.038-inch standard guidewire may injure or lacerate the thin renal parenchyma. In the perinate, the thin skin, minimal paraspinal musculature, and the short distance from the flank to the renal pelvis offer little resistance to track dilation. The only barrier to catheter insertion is the renal capsule, which may be surprisingly tough. Thus, a guidewire that does not kink, such as a 0.018-inch angled guidewire or nitinol guidewire, is useful. If a 0.018-in. stainless steel mandril guidewire is used, one must be careful that the floppy tip does not kink, making wire withdrawal difficult. If one attempts to pull the guidewire back into the Chiba needle, the floppy tip may shear off. If a kink occurs it might be necessary to remove the entire system and repuncture the renal pelvis. As a result, this problematic guidewire is now rarely used. Regardless of the guidewire selected, it is important to maintain a straight catheter-guidewire course during tube placement to avoid buckling in the retroperitoneal soft tissues.

For insertion of standard drains (≥8 French) a variety of guidewires perform well, including the Newton, angled guidewire, nitinol, Rosen, and Amplatz guidewires. In patients who are muscular, obese, or those in whom catheter insertion is difficult, a stiff guidewire such as a nitinol, Amplatz, Rosen, or stiff guidewire provides greater stability and facilitates passage of the nephrostomy catheter.

Selection of the nephrostomy catheter depends upon the age and size of the patient, as well as the anticipated contents of the collecting system. The choice of catheter is usually determined by physician preference. In perinates and small children, a modified 5-French pigtail drain (Cook) or a 6-French pigtail catheter is used. In neonates, the 5-French pigtail drain has the advantage of a small distal loop (1 cm) and drainage holes positioned along the inner curve of the pigtail. This design prevents catheter occlusion resulting from contact with the wall of the renal pelvis. The operator can be confident that all drainage holes are satisfactorily positioned within the renal pelvis once the catheter reforms (Fig. 26.4).



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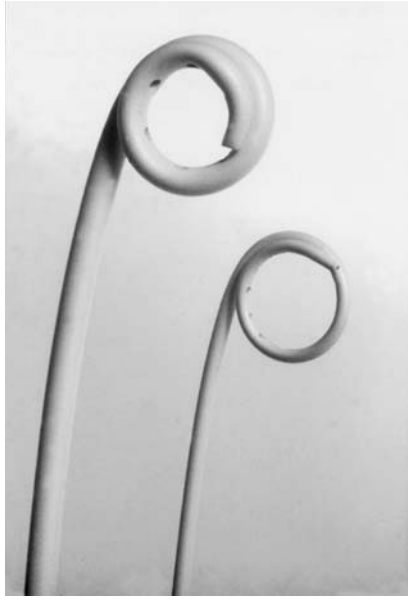


b

Fig. 26.4. a Modified 5-French neonatal nephrostomy drain. **b** Comparison of a 5-F (right) and standard 8-F (left) nephrostomy drains

Image guidance for percutaneous nephrostomy usually consists of a combination of fluoroscopy and ultrasound, although either modality can be used alone. The use of ultrasound obviates the need for opacification of the collecting system in most instances and is especially useful in patients with impaired renal function or contrast allergy. In the pediatric population, CT is rarely necessary for guidance and is only considered for children with unusual renal anatomy or when other guidance methods have failed. Patients with severe hydronephrosis may not require imaging guidance for puncture of the renal pelvis.

Local anesthetic and intravenous sedation are used in almost all cases for placement of a nephrostomy catheter. The patient is placed either in a prone or prone-oblique position. An entry site is selected on the flank using anatomic landmarks alone or with imaging. With ultrasound, an entry site is selected beneath the costal margin in approximately the mid-scapular line. The puncture site selected should allow for puncture into a middle or lower pole calyx. If a percutaneous surgical procedure is planned, it is usually best to enter the renal pelvis via a middle pole calyx. However, the best entry site depends on the procedure to be performed.

The skin is prepared and draped in a sterile fashion, and local anesthesia is injected into the skin and deep soft tissues at the entry site using a 30-gauge needle in the anticipated route. One percent lidocaine mixed with sodium bicarbonate (3 cc:2 cc) minimizes discomfort. Inadequate local anesthesia will result in pain that will awaken the child and make the procedure more difficult and time-consuming. A skin incision is then made with a no. 11 scalpel blade and enlarged with blunt dissection.

Puncture of the renal pelvis is made with a Chiba needle or a 19-gauge sheathed needle. A posterolateral approach angling the needle towards the costovertebral junction is used. Direct puncture of the renal pelvis is avoided to minimize the chance of injury to the posterior branch of the renal artery. In addition, the renal pelvis lacks supporting parenchyma to provide tamponade against bleeding or urine leakage or premature catheter loss. In contrast, direct puncture of the renal pelvis is used for Whitaker perfusion testing or if opacification of the collecting system is required for another procedure. After the kidney is punctured and a guidewire coiled within the renal pelvis, the tract may be dilated 2 French larger than the nephrostomy cath-

eter to ease insertion of the drain. Overdilation is especially helpful in some perinates.

In patients with renal transplants, the approach to percutaneous nephrostomy depends upon the surgical anatomy. Most transplants are extraperitoneal and located in the iliac fossa. Thus, the renal pelvis usually faces posteromedially. As a result, an anterolateral approach is usually best to avoid passage through the peritoneal cavity. In most cases, real time ultrasound is used to guide needle puncture. With intraperitoneal renal transplants, CT guidance may be necessary to avoid inadvertent injury to the bowel (Hunter et al. 1983).

Once in position, the nephrostomy tube is secured in position. Securing the catheter begins with placement of a 3–0 Ethicon suture that is tied tightly in a criss-cross pattern over the catheter shaft. This creates a locking stitch that tightens when outward tension is applied. A retention device is then adhered to the skin to secure the drainage catheter. Care is taken to avoid an excessively tight skin suture, which can cause discomfort and skin necrosis.

Major complications resulting from insertion of a percutaneous nephrostomy are unusual in children. Initially, percutaneous nephrostomy was considered less applicable to the pediatric population because of the need for general anesthetic. However, improvements in sedation techniques, monitoring equipment, catheters, and the widespread use of ultrasound for needle puncture guidance has helped percutaneous nephrostomy become a safe and effective procedure in the pediatric population (Ball et al. 1986; Pfister et al. 1981; Stanley 1986).

The two most serious complications of percutaneous nephrostomy are sepsis and bleeding. Overdistension of the collecting system at the time of catheter placement is likely the most significant factor leading to bacteremia. Decompressing the renal pelvis prior to performing an antegrade nephrostogram, especially in patients with pyonephrosis, is important to minimize this problem. For this reason, it is preferable to delay a diagnostic antegrade nephrostogram for 24–72 h to allow decompression of the obstructed system and sterilization of urine. Patients with suspected or documented pyonephrosis require antibiotic coverage before and after the procedure.

Transient mild hematuria is common after percutaneous nephrostomy and usually clears within 48 h. This can be ignored and should probably not be considered a complication. Severe bleeding at the time of catheter insertion or later is unusual and may indicate vascular injury, a clotting disorder, or an unsuspected vascular malformation. Occasionally blood clots will cause catheter obstruction. If significant bleeding occurs, arteriography may be required to establish the site and cause of bleeding, e.g., vessel laceration, pseudoaneurysm, and arteriovenous fistulas (Pode et al. 1982; Stanley and Diament 1986; Cope and Zeit 1982; Boddy et al. 1987). If a vascular injury is identified, it can be treated by selective embolization. The risk of vascular injury is reduced by using a posterolateral approach for renal pelvic access. Arterial injury and severe bleeding are minimized by parenchymal tamponade and using Brodel's plane of least vascularity.

Nephrostomy-related urinoma formation has been reported in the pediatric population. This complication is more likely when the renal parenchyma is thin, as in children with chronic reflux or where the free wall of the renal pelvis is punctured. If the urinoma is large or becomes infected, percutaneous drainage may be required (Gonzalez-Serva et al. 1977; Ball et al. 1986). While a small amount of urine leakage around the nephrostomy catheter can be considered normal, excessive leakage is usually due to catheter blockage, especially in patients with pyonephrosis or excessive bleeding.

With the use of ultrasound for guidance, misadventures due to needle malposition are unusual. Pneumothorax is now rarely reported as puncture above the 12th rib is usually avoided.

Conclusion

Nephrostomy tube insertion is the building block for a variety of interventions involving the urinary tract. Nephrostomy tube insertion is highly successful for treating urinary tract obstruction and pyonephrosis. Properly sized equipment is necessary for safe and effective treatment of urinary tract abnormalities.

26.3 Nephrostomy Tract Dilatation

This simple technique enlarges a nephrostomy tract so that larger equipment can be safety inserted into the renal pelvis or distal urinary tract for the purpose of an endourological procedure.

Dilatation of a nephrostomy puncture site or nephrostomy tube tract facilitates insertion of a stent or an angioplasty balloon or eases an endosurgical procedure. In the latter case, large diameter sheaths (12–24 French) are necessary. The contraindications for tracking dilatation are the same as those discussed for nephrostomy insertion. It is important to keep the child's size in mind when choosing the diameter of the sheath to be left in place. In general, the sheath size recommended is 2 French larger than the diameter of the largest instrument to be used. Overdilation of a track can lead to a renal injury.

Once access to the renal pelvis is achieved, either by direct puncture or by using an indwelling catheter, a non-kinkable guidewire is inserted and coiled within the renal pelvis or directed into the ureter or bladder. Using vascular dilators, the track is progressively enlarged at 2- to 4-French intervals to the predetermined diameter (Fig. 26.5). Alternatively, an angioplasty balloon can be used. At that point, a sheath is positioned in the renal pelvis. If endoscopy is to be used, a Rutner adapter (Cook, Inc.) is fitted into the sheath to make a water-tight connection. In many cases, the sheath needs to be shortened by cutting it with scissors. The shorter sheath is easier to work with and better fits the pediatric endoscope.

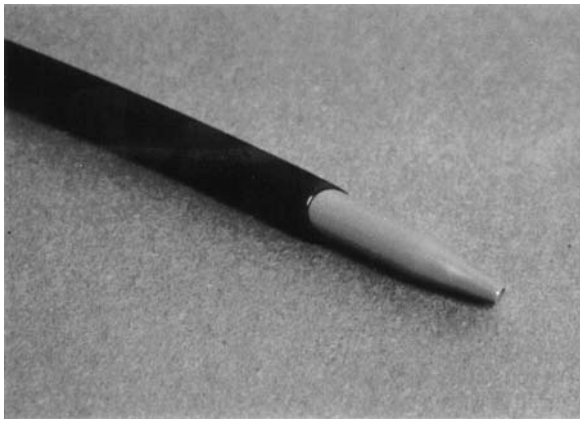


Fig. 26.5. Close-up of progressive dilator (*grey*) and outer sheath (*black*)

Conclusion

Nephrostomy tract dilatation is a procedure that translates a simple drainage entry procedure into percutaneous surgery and/or allows the introduction of stents or other devices.

26.4 Endurologic Techniques

Endurology is minimally invasive therapy involving the urinary tract. It is the natural evolution of techniques developed for treatment of renal obstruction using percutaneous access. Access to the collecting system is via a puncture identical to that used in placement of percutaneous nephrostomy. Sequential dilatation of the track allows for placement of an introducer sheath that allows for the endosurgical treatment of a variety of conditions. Endourologic procedures include ureteral dilatation, ureteral stenting, calculus removal (percutaneous nephrolithotomy), and endopyelotomy (percutaneous pyeloplasty).

26.4.1 Ureteral Dilatation and Stenting

Dilation of the ureter was initially reported by Doormashkin in 1926. It was not until the development of the percutaneous angioplasty balloon catheter that equipment effective for percutaneous dilatation became readily available. Subsequent research with animal models confirmed that ureteral strictures could be treated using a percutaneous approach (Barbaric et al. 1977). Percutaneous endourologic treatment of calculi and ureteropelvic junction strictures was initially described in adults and subsequently in children (Gedroyc et al. 1989; Kadir et al. 1982; Lee et al. 1988; Towbin et al. 1987). Since its introduction, ureteral stenting has become a well-established procedure for the management of ureteral obstruction of varying etiologies. As a result of continual improvements in technique and equipment, the percutaneous approach is currently utilized both as a primary therapy and as an adjunct to open and endourologic surgery.

Although permanent metallic stents are widely utilized in adults for treatment of malignant obstruction, they are not routinely used in the pediatric urinary tract. In almost all cases, temporary internal (double J) (Fig. 26.6) ureteral or internal-external nephroureterostomy stents (universal stent) (Fig. 26.7) are preferred to treat strictures in children.

Stents may be placed either antegrade via a nephrostomy track or retrograde through the bladder using cytoscopy. Advantages of the antegrade

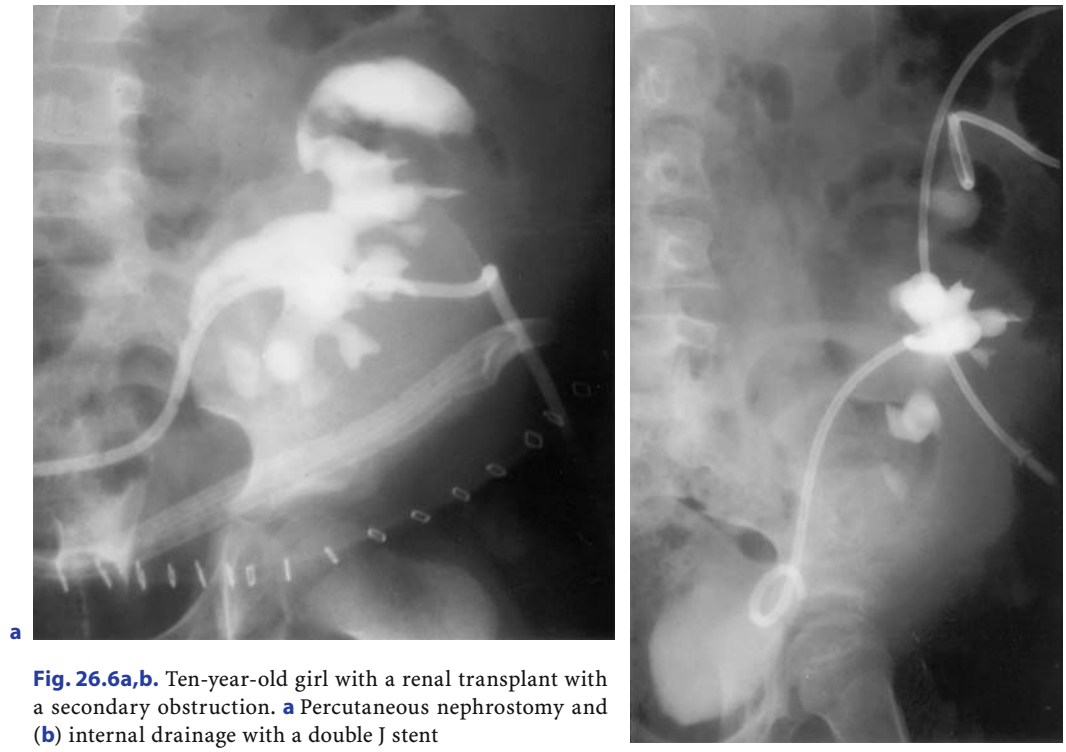


Fig. 26.6a,b. Ten-year-old girl with a renal transplant with a secondary obstruction. **a** Percutaneous nephrostomy and (**b**) internal drainage with a double J stent

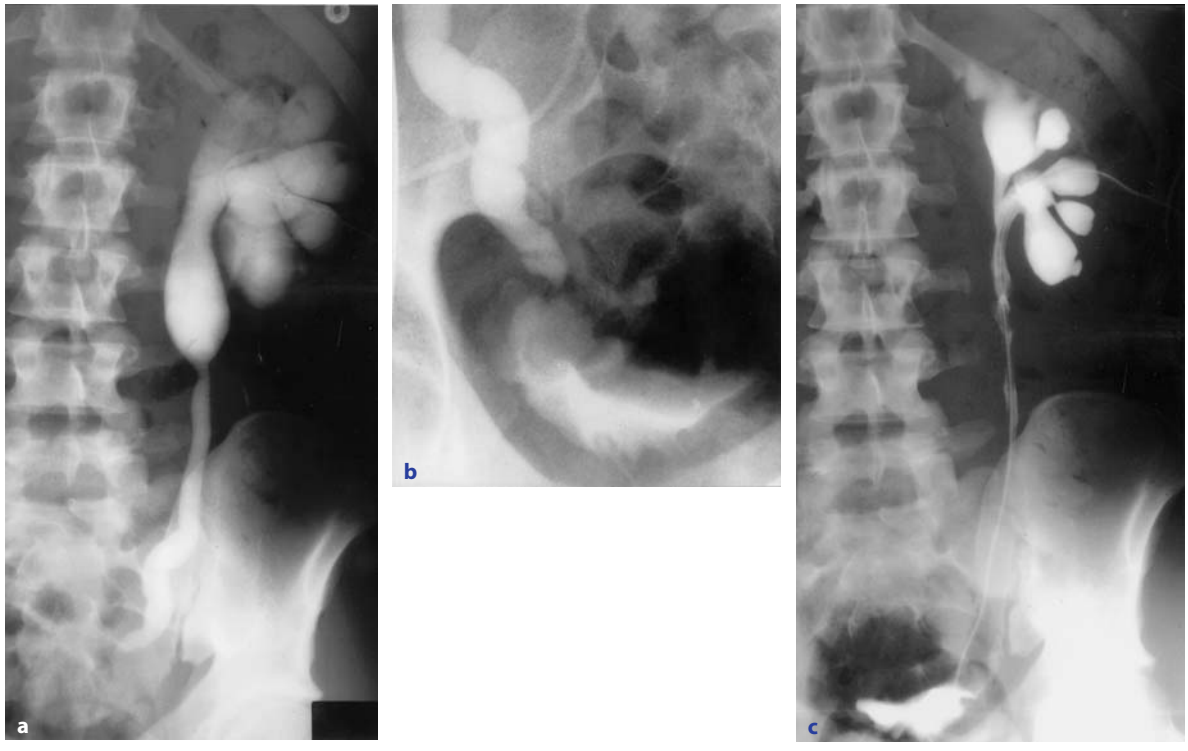


Fig. 26.7. a A 19-year-old patient with a UVJ obstruction and secondary hydronephrosis and hydroureter. **b** A coned-down view of the UVJ confirms the site of obstruction. **c** Treatment with a universal drain was effective

approach include the need for other percutaneous procedures of the urinary track, antegrade pyelography, and/or Whitaker perfusion testing, and children who have tortuous ureters or genitourinary track anomalies. A combined approach involving both the interventionalist and urologist may be valuable in children with an ileal loop who have a ureteroileal anastomotic stricture, or those with a UPJ obstruction needing an endopyelotomy, or to treat stone disease.

Percutaneous management of isolated ureteral stricture is often effective. Ureteral narrowing may result from intraluminal or extrinsic obstruction. The likelihood of successful dilatation of a stricture will depend upon the cause, length, and duration of the stricture. In the presence of impaired blood supply to the ureter, a successful result is uncertain, but strictures present for less than 3 months and postoperative strictures generally respond well to balloon dilatation. Location of a ureteral stricture does not appear to be of prognostic importance in predicting its response to balloon dilatation. However, for successful percutaneous therapy, one must be able to cross the stricture with a guidewire and catheter or other instruments.

Indications for ureteral stenting include relief of a ureteral obstruction from any cause, providing drainage while a ureteral injury heals, maintaining ureteral caliber until edema or mass effect subsides, stone removal, or surgery. The antegrade placement of a stent may be performed after failure of the endoscopic approach due to unfavorable anatomy.

Stent insertion should be avoided or delayed in the presence of significant hemorrhage or urinary tract infection. The presence of a stent can become the nidus for infection and may be obstructed by purulent material or blood clot. In patients with a ureteral fistula and nondilated upper tracks, retrograde stent insertion is the preferred route because of the ease of insertion.

Many interventionists prefer to perform ureteral dilatation and stent insertion under general anesthesia. However, a successful outcome can be regularly achieved with conscious sedation. A Foley catheter is inserted into the bladder once the child is asleep. The child is usually in the prone or prone-oblique position to allow optimal access to the collecting system and secured to the tabletop with Velcro straps. The skin entry site is selected so that the puncture is cephalad to the UPJ. This allows for an easier, more direct access to the UPJ and facilitates stent insertion. The intercostal approach is avoided to make tract dilatation and catheter insertion easier and to minimize the chance of hydrothorax and other thoracic complications.

After sedation is achieved, the flank is prepared and draped in a sterile fashion. One percent lidocaine buffered with bicarbonate (8:2 mixture) is *slowly* infiltrated into the skin and subcutaneous tissue with a 30-gauge, 1.5-inch needle in order to minimize discomfort.

After access to the renal pelvis is achieved, a guidewire is coiled within the renal pelvis or maneuvered into the ureter. The track is then progressively dilated to accommodate a peel-away sheath or valved introducer 2 French larger than the stent. A stiff guidewire (stiff guidewire, Rosen, Amplatz, etc.) is helpful to avoid buckling and/or telescoping of the stent as it is positioned across the stricture. A directional catheter (JB-1) and guidewire system are used to catheterize the ureter. Once the guidewire and catheter are within the proximal ureter, contrast is injected, and the location and extent of the stricture is identified. The length and diameter of the stricture are measured and the appropriate balloon is selected. The directional catheter and guidewire are then maneuvered into the bladder, if possible.

Strictures that are difficult to pass often require patience and various technical manipulations to cross. Opacification of the ureter can simplify the task of crossing a tight stricture. After the level of the stricture is determined, a radiographically dense marker is placed on the patient's skin or gown to aid crossing and dilatation of the stricture. Contrast is injected and the pathologic anatomy documented with a road map or digital image. The angled guidewire and directional catheter are manipulated until the guidewire and catheter are across the stricture. If necessary, a 0.018-inch guidewire can be substituted for the larger guidewire to initially cross the stricture. Once the catheter is within the bladder, the guidewire is exchanged for a stiff or superstiff guidewire.

Treatment of strictures may be carried out with a variety of balloons. Initially, the diameter and length of the stricture are measured. The PTA balloon selected is at least 1 cm longer than the stricture and equal to or slightly wider (1–2 mm) than the expected normal ureteral diameter as measured distal to the stricture. In all cases, the balloon with the highest bursting pressure is selected. After the balloon is centered across the stricture under fluoroscopic visualization, it is inflated with dilute contrast while balloon pressure is monitored with a

gauge. Under fluoroscopic guidance, balloon inflation progresses until the stricture waist disappears. If the stricture persists, the process is repeated. If the postdilation ureterogram still shows obstruction with no significant change in the stricture diameter, a ureteral incision (by the urologist), with a blade or electrocautery, may be considered if technically feasible.

After dilatation of a stricture has been completed, placement of a stent is needed to maintain the enlarged lumen. Stent selection depends upon a number of factors including personal preference, available equipment, and the duration of the stenting. Each stent type has its advantages and disadvantages. Internal double J stents have a higher patient satisfaction rate because they are not visible, are less apt to be inadvertently pulled out, require no maintenance, and probably have a lower infection rate. They have a number of disadvantages in that they are more difficult to insert, special sizes (shorter lengths) must be stocked, they are more difficult to remove, and gross hematuria and infection limit their use. The internal-external (universal) stent is more flexible, easier to tailor to length, and easier to remove. Removal of the drain is performed on an outpatient basis without sedation or anesthesia in most instances. In spite of its disadvantages, the internal double J stent is usually preferred since it has greater stability and easier postprocedural care.

Placement of an internal stent is performed under fluoroscopic guidance. Prior to beginning ureteral stent placement, a second (safety) guidewire is inserted through the peel-away sheath and coiled in the renal pelvis. This guidewire is then secured to the drape with a hemostat and covered with a sterile towel. After a stiff guidewire has been maneuvered into the bladder, a 5-French catheter is positioned over the guidewire with the tip just distal to the ureterovesical junction (UVJ). The length of the ureter is measured so that the proper stent length can be selected. Ureteral length can be obtained using a calibrated catheter or guidewire, or the bent guidewire technique. Ureteral length is determined by positioning the tip of the guidewire under fluoroscopic guidance at a point just distal to the UVJ. The guidewire is then bent at the catheter hub. Alternatively, a hemostat may be clipped to the guidewire at this point and left in position. Next, the guidewire is pulled back so that the tip is at the UPJ and again bent or clipped with a hemostat. The distance between the bends or hemostats is the length of the ureter internal stent. Depending on the age and height of the child, stent length usually varies between 8–24 cm.

Once an internal stent has been measured, a suture is inserted through the distal end-hole and used as a safety to pull the stent back into the renal pelvis if it is pushed out of the renal pelvis. The stent is then fed over the guidewire and pushed through the peel-away sheath into the renal pelvis and ureter. To maneuver the distal end of the stent into the renal pelvis, a pusher catheter is used. The pusher catheter is advanced onto the guidewire and used to advance the stent into its final position. Catheter positioning is intermittently monitored with fluoroscopy. Once the stent is in a satisfactory position, the pusher catheter is kept abutted to the stent and counter-pressure applied while the safety suture is removed. If the stent is not in the appropriate position, it may be repositioned before the suture is removed. In order to complete the procedure, the guidewire must be removed. This step is crucial to the success of the procedure and although technically easy, often leads to problems. Again, the stent is maintained in a satisfactory position by applying counter-pressure with the pusher catheter while the guidewire is slowly removed. If a safety guidewire is in position, the guidewire can be completely removed. If not, the guidewire is withdrawn until it exits the stent, but is still within the renal pelvis. At this point the guidewire is advanced and coiled in the renal pelvis to assist placement of the nephrostomy catheter. If this maneuver fails, the renal pelvis can be recatheterized via the peel-away sheath.

Next, a nephrostomy catheter is inserted and secured to the skin. The nephrostomy catheter should be equal to the diameter of the track to prevent leakage of urine. The nephrostomy tube may be left in place as long as is clinically indicated. If another procedure is necessary, the nephrostomy is left in place for access. If no procedure is planned and no problem has occurred, the nephrostomy tube is removed after 24–72 h. Prior to removal, a nephrostogram is obtained to confirm satisfactory position and functioning of the stent. If the ureter drains well, the nephrostomy is removed and covered with a dry, sterile dressing. The child is usually followed clinically, and when the ureteral stent is no longer needed, it is removed cystoscopically from the bladder. In rare cases, the stent may be removed from above after a nephrostomy track has been re-established.

Regardless of the stent used, duration of stent placement will vary according to the underlying

etiology of the stricture. Short-term placement (3–5 days) is required for treatment of ureteral edema, while 10–15 days is usually needed after ureteral surgery. Longer time periods (6–8 weeks) are usually needed to maintain ureteral caliber after endopyelotomy.

In the immediate postprocedural period, care centers around recovery of the child from sedation or general anesthesia and treatment of complications. Children awakening from sedation have their vital signs continually monitored and recorded every 5–15 min for the first 30–60 min and every 30–60 min until discharge. When the child is awake and alert, he/she is given clear liquids to drink. If tolerated, the diet is advanced to solids. If the child tolerates the clear liquids, he/she is considered for discharge to home. In addition to monitoring the vital signs, the nephrostomy site and drainage are checked for bleeding. If no hematuria is identified, the Foley catheter is removed before the child awakens. Any complication identified is immediately treated, and the appropriate clinical service and referring physician are notified.

When the child is discharged to home, careful and detailed verbal and written instructions are given by the interventional nurse and, if necessary, the physician. Written instructions include a list of the more common delayed complications and appropriate telephone numbers to contact the interventionalist on call. If necessary, a prescription is given for antibiotics or analgesics to treat discomfort. In general, mild analgesics such as acetaminophen, ibuprofen, or acetaminophen with codeine will be recommended. Occasionally, oral toradol will be prescribed if significant flank pain is encountered. If this approach does not suffice, the child will be taken back to the hospital and re-examined by the interventionalist or referring services, since this level of discomfort is unexpected.

Any reported complication resulting from nephrostomy insertion such as bleeding, sepsis, or urine extravasation secondary to a leak or laceration may also be noted after a percutaneous surgical procedure. Complications specific to percutaneous stricture dilatation include ureteral perforation or rupture and intraluminal or submucosal hematoma. Surprisingly, these problems have rarely been reported in either adults or children. Untoward effects related to stent placement are more common, but still unusual in the pediatric population (Woodside et al. 1985). Stent occlusion is probably most common and occurs secondary to encrustation, bleeding, or rarely, infection. An encrusted stent is prone to secondary infection, which may lead to sepsis. Therefore, it is important to keep the urine diluted and infection free. Stent occlusion can be detected by cystography, antegrade pyelography, excretory urography, or, if present, nephrostomy injection. In most instances, cystography is performed: stent patency is inferred if vesicoureteral reflux occurs. The ideal timing for stent removal or replacement remains controversial. Twelve weeks is the preferable limit of time the stent is left in situ. With high-risk children, such as those with renal transplant on immune suppression, shorter intervals are recommended.

Stent migration occurs if the stent is not adequately positioned or if it is not the correct length. This problem is avoided by careful technique and accurate measurement of ureteral length and selection of a stent of appropriate diameter and length. When stents are too long, bladder irritation will occur. If unavoidable, bladder spasm can be treated with urinary anesthetics such as pyridium.

Conclusion

Ureteral dilatation with stenting is an effective method for treating ureteral strictures.
Either internal or external drainage may be effective for treating strictures.
Ureteral dilatation and stenting can be safely performed under sedation or general anesthesia.

26.4.2 Percutaneous Nephrolithotomy

The fundamental techniques of nephrostomy insertion, track dilatation, and stent insertion have led to the development of more sophisticated endourologic procedures. The initial percutaneous technique developed was for removal of renal calculi. Within a short time, techniques for treatment of ureteropelvic junction and ureteral strictures were developed. Today percutaneous nephrolithotomy has been replaced in many situations by extracorporeal shock wave lithotripsy (ESWL) and ureteroscopic techniques. However, nonoperative management of staghorn calculi, infected lower pole calculi, or cystine stones via percutaneous nephrolithotomy and lithotripsy is still indicated.

In industrialized countries, urinary calculi are uncommon in the pediatric population. When stones

occur, they are often metabolic or infectious in origin. Prior to the advent of percutaneous nephrostomy and ESWL, surgical procedures were required for treatment of recurrent stone disease. Current management of renal calculi in both adults and children may require a combination of techniques. Either alone or in combination with ESWL, percutaneous nephrolithotomy and ureteroscopy may be helpful for management of calculi without surgery. Chemical dissolution of calculi is an alternative to surgery in adults, but has not been used in the treatment of children. Both ESWL and endoscopic techniques have had a profound impact on management of renal calculi and now limit the use of percutaneous techniques. Prior to the availability of ESWL, percutaneous techniques were considered superior to open surgery because of reduced cost, decreased morbidity, and shortened convalescence and hospital stay. In addition, the presence of a nephrostomy track enabled subsequent removal of any residual stone fragments. Although its role has changed, the need for percutaneous stone removal persists.

Indications for calculus removal include pain, urinary track infection, and obstruction. Percutaneous nephrolithotomy is preferable for patients with large stone volumes such as staghorn or branched calculi which, if fragmented, are likely to cause obstruction (Shepard et al. 1988). Percutaneous evacuation of the stone material, combined with fragmentation using ESWL, laser energy, or percutaneous ultrasonic lithotripsy offers a safe alternative. Renal calculi associated with obstruction either at the UPJ or in the ureter may be better managed percutaneously. ESWL is also precluded when spinal stabilization hardware is present as in children with myelodysplasias, a group making up a significant proportion of the pediatric renal calculi population.

Contraindications to percutaneous nephrolithotomy are infrequent, but include a child with an uncorrectable coagulopathy. Children with a small renal pelvis cause technical problems. Renal access may be difficult, and there may be insufficient room to maneuver instruments if the collecting system is not large enough. Also, in small children, the size of the kidneys may make dilation to greater than 10–12 French dangerous for fear of a renal fracture.

Percutaneous nephrolithotomy is performed under fluoroscopic guidance. In most cases, single plane, C-arm fluoroscopy is adequate. However, in some instances, biplane fluoroscopy is useful.

Nephrolithotomy requires establishing a nephrostomy track from 12 to 24 French depending on the size of nephroscope used. A pediatric nephroscope (≤12 French) is used whenever possible to minimize potential complications. Stone removal can be performed in one or two stages. Some operators prefer the two-stage approach where on the first day a track is established, followed by track enlargement and stone removal at a later date. A single-stage procedure is preferred, whenever possible, since it can be performed under a single general anesthesia. Bleeding is not a problem as has been suggested.

The location and size of the renal calculi are initially determined by excretory urography, US, or CT. Prior to the procedure, an abdominal radiograph is obtained to confirm the presence of the stone. The most important factor for successful percutaneous nephrolithotomy is appropriate placement of the nephrostomy track. A posterolateral puncture of a middle calyx is preferred so that a direct route to the ureter is obtained and an effective tamponade achieved to limit bleeding. The target calyx depends on the location of the calculus.

After access to the renal pelvis has been achieved, a 0.035- or 0.038-inch guidewire is advanced into the ureter or preferably to the bladder. The presence of a long, stiff guidewire makes later manipulations easier. If the guidewire cannot be passed through the UPJ into the ureter, it is initially coiled in the renal pelvis or upper pole calyx. A directional catheter (JB-1) is used if traversing the UPJ proves difficult. In many cases, retrograde insertion of a guidewire via the bladder is best. Prior to track dilation a generous skin incision is made. Track enlargement is accomplished with either progressive dilators or an angioplasty balloon of appropriate size. Final track size is predetermined by the diameter of the endoscope selected. The sheath acts to tamponade the fresh track to prevent bleeding, reduce renal injury, and maintain access to the renal pelvis for insertion of instruments and catheters.

There are multiple techniques that can be used alone or in combination to remove renal calculi. Small stones may be removed under direct vision or fluoroscopic guidance with a stone basket or forceps (Fig. 26.8). Irrigation and aspiration with saline may be successful in removing stones or fragments smaller than the diameter of the sheath. Occlusion balloon catheters inflated in the ureter distal to the stone may be helpful in preventing dislodgment and passage of fragments into the ureter. Stones larger than 1.5 cm usually require fragmentation prior to removal. Calculi can be crushed mechanically or

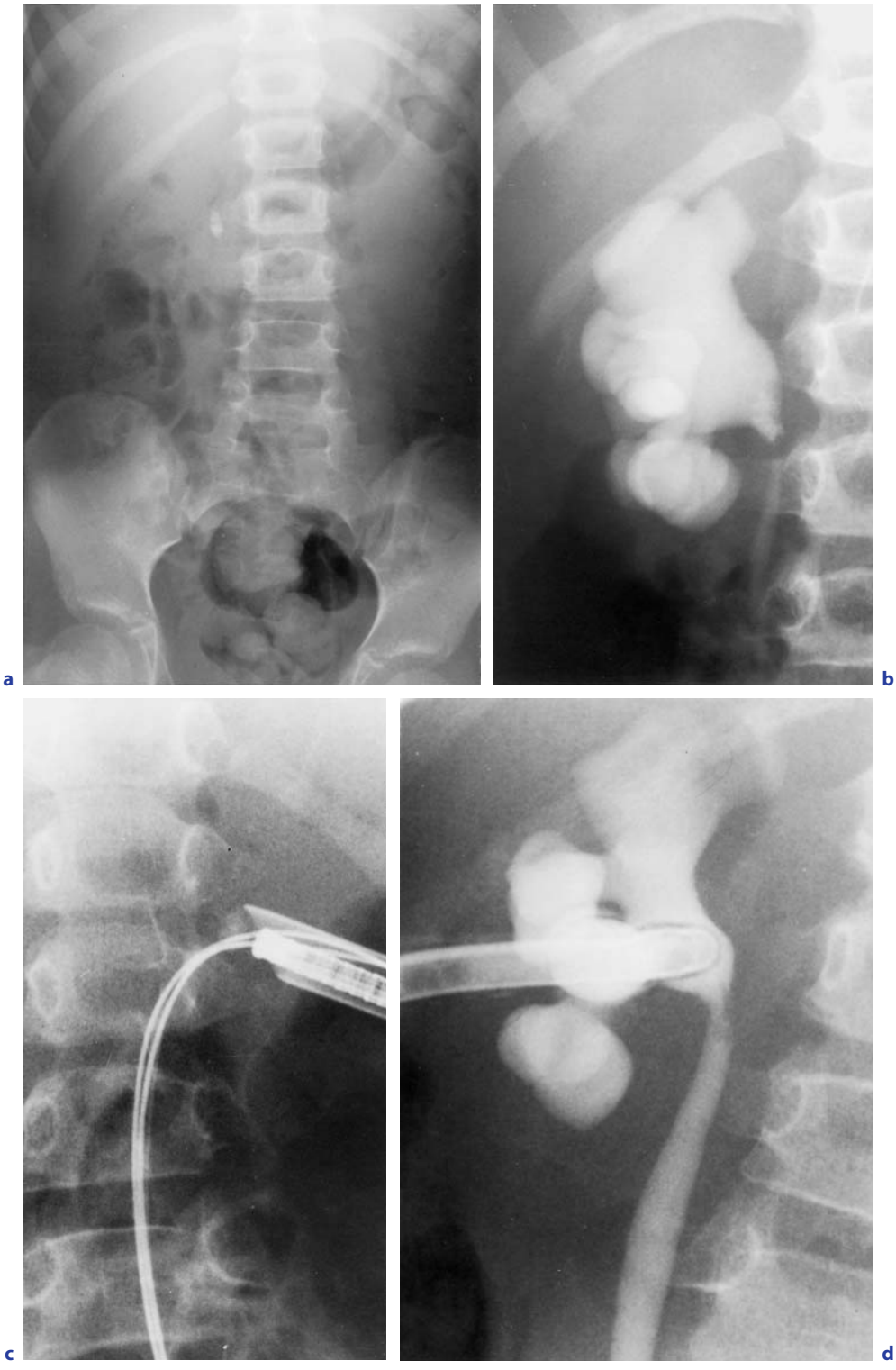


Fig. 26.8. a An 8-year-old boy presenting with renal colic secondary to a stone obstruction to the right UPJ. **b** Excretory urogram confirms stone position and demonstrates moderate hydronephrosis. **c** After puncture of the middle pole calyx, tract dilation, and insertion of guidewires and a sheath, the stone was removed endoscopically. **d** A council tube was inserted at the completion of the procedure for drainage and to maintain renal access

fragmented by using a laser fiber ≥200 micra or with an ultrasonic lithotriptor.

At the conclusion of the procedure, a plain radiograph is obtained to look for residual fragments not visible fluoroscopically. With a guidewire in place, the sheath is removed, and a council catheter (end-hole Foley) or pigtail catheter, measuring the same diameter as the track, is inserted to provide access to the renal pelvis if needed and to provide continued tamponade. At 48 h a repeat abdominal radiograph is obtained to look for residual stones or fragments. If no residual is found, a nephrostogram is performed to confirm patency of the ureter. If the ureter is normal, the nephrostomy tube is clamped for 24–48 h, and if no problems occur, the tube is removed.

The excellent results with nephrolithotomy in adults (Ball et al. 1986; Boddy et al. 1987; Hulbert et al. 1985) led to its application in children. While in the reported pediatric series most children were over 5 years of age, percutaneous stone removal in younger children has been successful (Ball et al. 1986). The percutaneous approach has been especially useful in managing recurrent renal calculi in children who have had multiple open surgical procedures.

Bleeding and sepsis are the most frequent complications of percutaneous nephrolithotomy (Lee et al. 1985; LeRoy and Segura 1986). Some degree of hematuria occurs in most patients, and although it is usually not of clinical significance, on occasion transfusion is needed. Delayed bleeding due to a leaking pseudoaneurysm or arteriovenous fistula has been reported in adult series, but not in children. Infection resulting from assessing an infected urinary track or infected calculus may also occur. Using antibiotics before the procedure, avoiding overdistension of the renal pelvis or collecting system, and draining adequately minimize this risk.

Perforation of the renal pelvis or ureter may occur. These tears usually seal spontaneously within 72 h if adequate drainage is provided. Renal pelvic and ureteral edema requiring prolonged nephrostomy drainage is uncommon, and delayed ureteral or ureteropelvic stricture has not been reported in children. A potential complication is extravasation of irrigation fluid from the percutaneous track producing fluid overload, pleural effusion, and retroperitoneal collections. A postprocedural chest radiograph is routinely obtained when an intercostal approach has been used to exclude hydrothorax.

Conclusion

Renal stones can be safely and effectively removed using percutaneous surgical techniques.
An interventionalist working with urologists makes a good team for treatment of renal stones.
Procedures are usually performed under general anesthesia.

26.4.3 Percutaneous Endopyelotomy (Percutaneous Pyeloplasty)

In 1943, Davis described the intubated ureterostomy for treatment of ureteral and UPJ strictures (David 1943). In this procedure the ureter was incised from the outside and stented. He showed that the ureter would heal and maintain a larger diameter, thereby resolving the obstruction. Forty years later, the endoscopic counterpart to the Davis intubated ureterostomy was described (Wickham and Kellett 1983; Whitfield et al. 1983). Using a nephroscope, UPJ obstruction was treated by incising the stricture under direct vision using a cold knife. The work of these pioneers and others provided the foundation for developing percutaneous surgical treatment of ureteral strictures in children. Badlini and Smith (1986) later popularized the endopyelotomy technique. Their results and those of other investigators compared favorably to those achieved by open pyeloplasty. In 1987, Towbin and colleagues proved that the percutaneous approach could be successfully performed on children with congenital UPJ obstruction. Dismembered pyeloplasty remains the mainstay for treating children with strictures of the UPJ. However, with the development of percutaneous surgical techniques, percutaneous endopyelotomy (PE) has become an acceptable alternative. PE can be performed as a one- or two-step procedure, as is the case for nephrolithotomy; the one-step approach is preferable.

The indications for an endopyelotomy are similar to those for an open surgical procedure. Children with congenital or acquired strictures of the ureteropelvic junction or ureteral strictures elsewhere are candidates for endopyelotomy (Fig. 26.9a). Although there are few absolute contraindications to either the precautions (antegrade) or endoscopic (retrograde) approaches, children with long (>2 cm) strictures respond poorly to endopyelotomy and should likely go directly to an open procedure. Very

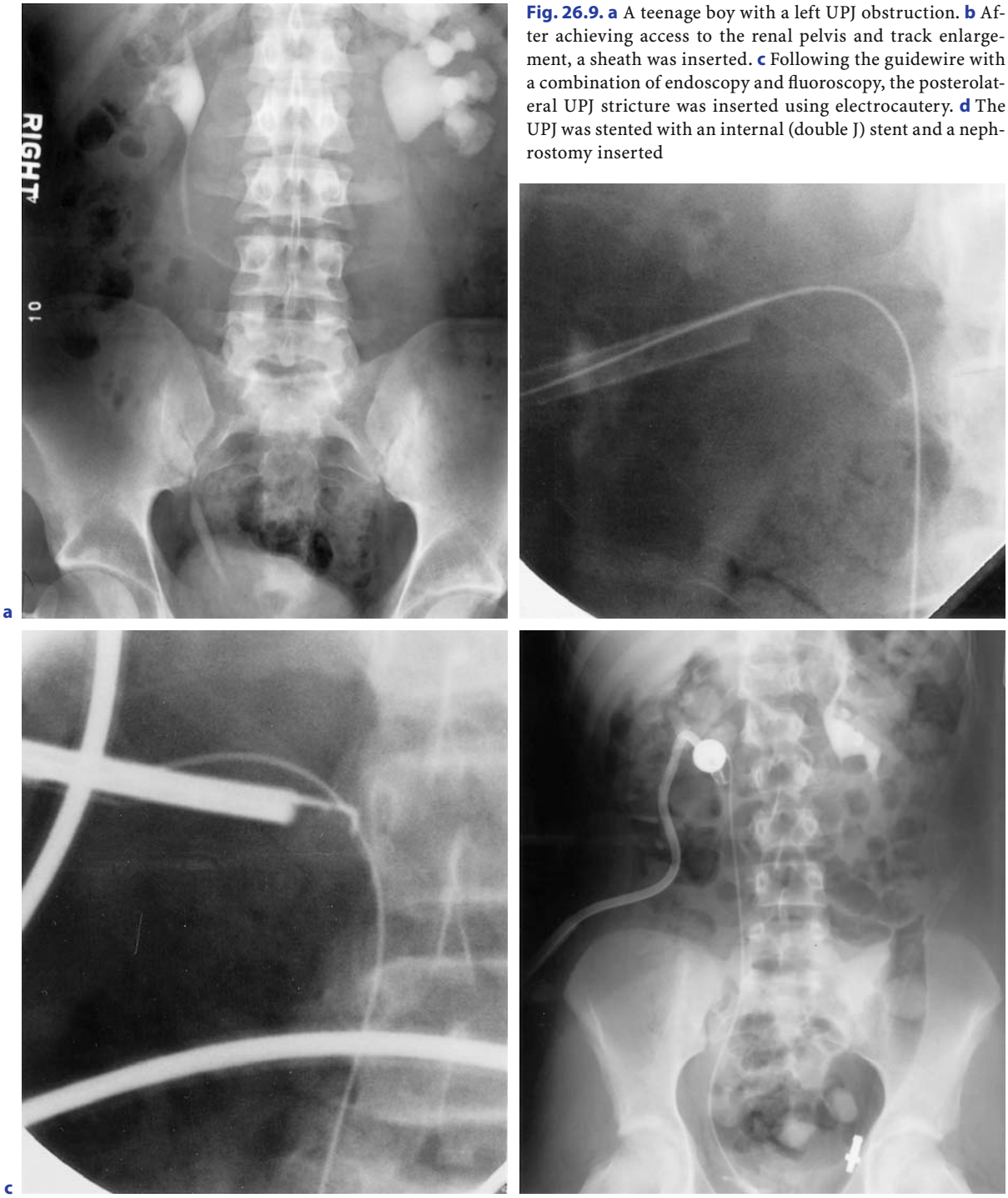


Fig. 26.9. a A teenage boy with a left UPJ obstruction. **b** After achieving access to the renal pelvis and track enlargement, a sheath was inserted. **c** Following the guidewire with a combination of endoscopy and fluoroscopy, the posterolateral UPJ stricture was inserted using electrocautery. **d** The UPJ was stented with an internal (double J) stent and a nephrostomy inserted

small children may also benefit from open surgery. As is true for other genitourinary interventions, children with uncorrectable coagulopathy, those who are medically unstable, and those with inaccessible anatomy are not candidates for percutaneous endopyelotomy.

An endopyelotomy is begun with a guidewire inserted into the renal pelvis in retrograde fashion. Retrograde guidewire placement is often easier, especially in patients with an eccentric stenosis of the UPJ. If difficulty passing the guidewire is encountered, the antegrade approach may be uti-

lized. A directional catheter and guidewire are used to probe until the guidewire is directed past the stricture into the bladder.

The child is positioned prone or prone-oblique, and a nephrostomy is performed. Once renal access has been obtained, the tract is dilated to the predetermined size. A sheath 2 French larger in size is left in place. After the stenosis has been crossed with a guidewire, it is retrieved and pulled out of the urethra or renal pelvis depending on the site of insertion. A hemostat is fastened to the distal end (urethral side) so that the guidewire cannot be inadvertently removed during the procedure. In this circumstance, a second guidewire (safety wire) is not necessary. A Rutner valve (Cook, Inc.) is connected to the sheath so that an endoscope can be used without using large volumes of water while maintaining a dry field. Using a combination of direct vision and fluoroscopy, the endoscope is maneuvered to the UPJ, and an incision is made with electrocautery (Fig. 26.9b), a knife blade, laser, or an Acucise cutting balloon (Applied Medical Resource Company, Laguna Hills, CA), through the posterolateral wall of the UPJ. The posterolateral wall is selected for site of incision since this is an unlikely site for vessels to course. Regardless of the instrument used, the incision is made through the full thickness of the UPJ until periureteric fat is identified. The procedure is completed by insertion of a 5- or 6-French internal stent and nephrostomy tube (Figs. 26.9c,d).

The best results with percutaneous endopyelotomy have been achieved in children with a stricture occurring within a few months of an injury or surgery. In addition to postoperative strictures, congenital UPJ narrowing, strictures associated with stones, and those secondary to tumors have all been successfully managed with percutaneous therapy. Variable results have been seen with long ureteral strictures, e.g., UPJ strictures after ureteral reimplantation and ureteroenterostomy strictures. Results with balloon dilation of congenital and acquired UPJ strictures have been mixed. Percutaneous pyeloplasty has been an effective method of treatment in children with congenital UPJ strictures and is a good alternative for children who have contraindications to surgery or those families who prefer the percutaneous approach.

Following PE, the child is admitted to the recovery room and observed for 6–8 h. Generally, the child is admitted overnight for monitoring of vital signs and observation in case of untoward effects. Most children require analgesia for mild to moderate discomfort. After discharge, the child is instructed to resume normal activity as tolerated. Two weeks after the percutaneous endopyelotomy, the child is brought to the radiology department, and a nephrostogram is obtained. If there is prompt antegrade flow of contrast and no extravasation or other complication is identified, the nephrostomy tube is removed. The internal stent is kept in place for 6–8 weeks to allow the UPJ incision to heal. The stent is then removed cystoscopically.

The success rate of an endopyelotomy for treatment of strictures at the ureteropelvic junction is about 85% with a range of 57%–100% (Towbin et al. 1987; Badlani et al. 1986; Capulicchio et al. 1997; Khan et al. 1997; Kavoussi et al. 1993; Motola et al. 1993). It appears that a failed endopyelotomy does not jeopardize the success of a subsequently performed open surgical procedure. The success rates achieved for endoscopic and percutaneous endopyelotomy are similar (Kavoussi et al. 1993; Brooks et al. 1995).

The complication rate is low with endopyelotomy. The exact rate and type of complications depend somewhat upon the technical approach selected and the indication for therapy. Major complications have been reported and include hemorrhage requiring transfusion or occasionally embolization, ureteral necrosis, and ureteral avulsion. However, minor problems occur more frequently (10%–23%) and include stent or nephrostomy-related problems. Minor complications include stent repositioning, retroperitoneal hematoma, dysuria, flank pain, and stenoses in the ureter, UVJ, or urethra. The incidence of minor complication is about 20%. The incidence and type of complications occurring using the Acucise devise appear to be similar to the other methods. It is important to realize that it is possible to lacerate adjacent blood vessels and cause major hemorrhage. Fortunately, vascular injury is uncommon and occurs in less than 1% of cases (Gerber and Lyon 1994; Bogaert et al. 1996; Figenshau et al. 1996). Other possible untoward effects include congestive heart failure, oliguria, hematuria, intrarenal clots, recurrent strictures, and hydrothorax or pneumothorax. The latter two problems can occur when the pleural space is transgressed at the time of renal access. Therefore, it is imperative that the operator be aware of the possible position of the pulmonary sulcus.

Percutaneous endopyelotomy appears to be a safe and effective method for the treatment of both primary and secondary strictures of the ureter and ure-

teropelvic junction. Each approach appears to result in a successful outcome with a low complication rate and good long-term patency. Open surgery still remains the gold standard for the treatment of either primary or secondary UPJ obstruction in most institutions. Proponents of endopyelotomy suggest that the reduced overall morbidity, decreased postoperative analgesic requirements, the shortened hospital stay, and a more rapid return to normal activity favor the endourologic approach.

Minimally invasive diagnostic and therapeutic procedures are well-suited for the pediatric urinary tract. It seems that the advantages of the percutaneous approach may be ideal for treating children and are especially cost-effective. Thus, one can expect that the interventional approach will continue to grow with a broadening of indications.

Conclusion

Percutaneous surgery is best performed under general anesthesia. Incision of the ureteropelvic junction can be achieved using a variety of methods including a cold knife, electrocautery, or a laser. Percutaneous endopyelotomy is an acceptable alternative for treating congenital UPJ stenosis.

26.4.4 Percutaneous Renal Angioplasty

Renovascular hypertension continues to be a diagnostic and therapeutic challenge in the pediatric population. Up to 2% of children suffer from systemic hypertension and in as many as 20% of these individuals the underlying pathology involves the renal arteries (Haas et al. 2002). Treatment of this subgroup of children depends largely on the location and underlying pathology of the renal artery stenosis (RAS). Fortunately, the most common etiology of main or branch renal artery stenosis in children is fibromuscular dysplasia (FMD) that is amenable to percutaneous transluminal renal angioplasty (PTRA) and has a high technical and clinical success rate. PTRA is currently considered the treatment of choice for RAS due to FMD (Levy et al. 2000). Ostial or aortorenal narrowing is often associated with syndromes such as neurofibromatosis, William's syndrome, or an arteriitis or mid-aortic syndrome (Courtel et al. 1998; Lund et al. 1984; Booth et al. 2002; Robinson et al. 1991; Kurien et al. 1997; Haas et al. 2002; Shroff et al. 2006; Panayiotopoulos et al. 1996; Daniels et al. 1987; Mali et al. 1987; Ellis et al. 1995; Arora et al. 1995; Fostera et al. 2000; Cura et al. 2002; Hughes et al. 2004). These lesions are often resistant to PTA and in the past have required surgical revascularization when medical therapy failed.

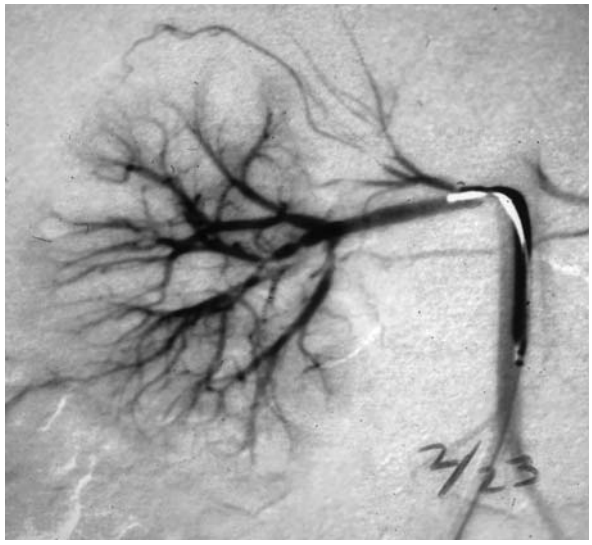
In a prospective study in 35 children with renovascular hypertension, Tyagi and colleagues (1997) found PTRA to have a beneficial effect on blood pressure in 93.1% of these children. Unfortunately, re-stenosis occurred in 25.8% of lesions treated percutaneously. In adults, renal artery stenting is commonplace for lesions not responding to PTRA. However, renal artery stenting (Ing et al. 1995) has been avoided in children whenever possible due to technical issues (McLaren et al. 2003) related to the size of the vessels and concerns that stents may limit arterial growth, make subsequent surgical revascularization more complicated, and predispose to renal artery thrombosis.

The equipment necessary to perform a PTRA in a child is generally available today and should be tailored to the size and weight of the child. The first step in a child with hypertension suspected of having main or branch renal artery narrowing is to do cross-sectional imaging. Although non-invasive imaging cannot definitively rule out renal artery stenosis, it is important to evaluate the child for non-renal causes of hypertension as well as renal arterial disease. Cross-sectional imaging is also valuable for planning of an interventional procedure. In some patients renal vein renins may be collected to help localize a lesion. At the same time diagnostic abdominal aortography and selective renal angiography are performed to define the pathologic anatomy. In most children AP and oblique injections are performed to best evaluate the renal vascular tree. The most common site for stenosis is the main renal artery. However, the most challenging area for diagnosis is the branch renal arteries. Often the angiographer needs to look carefully and have a high level of suspicion to find these subtle lesions. If necessary, selective injections in a variety of obliquities may be required to confirm the diagnosis.

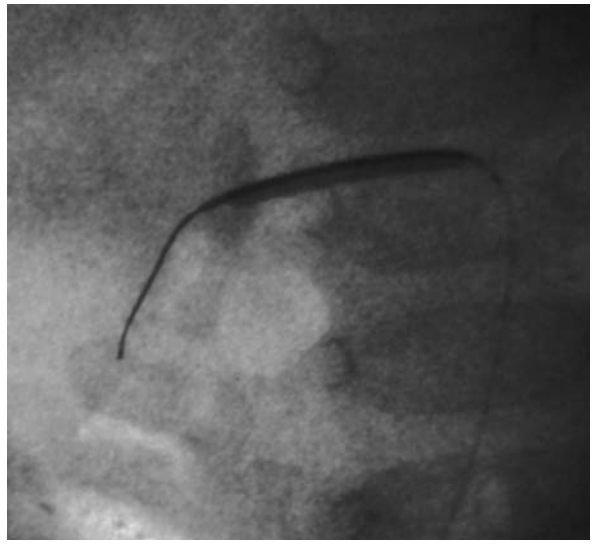
Our approach to the angiographic examination of these children is to begin with an abdominal aortogram in frontal projection to evaluate the aorto-renal junction and main renal arteries. The examination begins with puncture of the right femoral artery. In all children >10 kg a sheath with hemostasis valve is inserted into the vessel. The sheath must be large enough to accept an angioplasty catheter. Initially,

a 3F–5F pigtail catheter is inserted and positioned across from the origins of the renal arteries and approximately 1.0–1.5 cc/kg of contrast is power injected in 1–2 s, and images are obtained at 3/s. In selected instances (rapid heart rates, high flow lesions) faster film rates (up to 6/s) are utilized. Next, a selective catheter (RIM, C-1, JB-1) is positioned in the proximal renal artery. With the child positioned obliquely, a selective injection of contrast over 2 s is performed using 0.5–1.0 cc/s of contrast, e.g., 2 ccs for a total of 4 ccs. Again images are obtained at a minimum of 3 frames/s. When possible, pressure measurements are obtained across the area of stenosis.

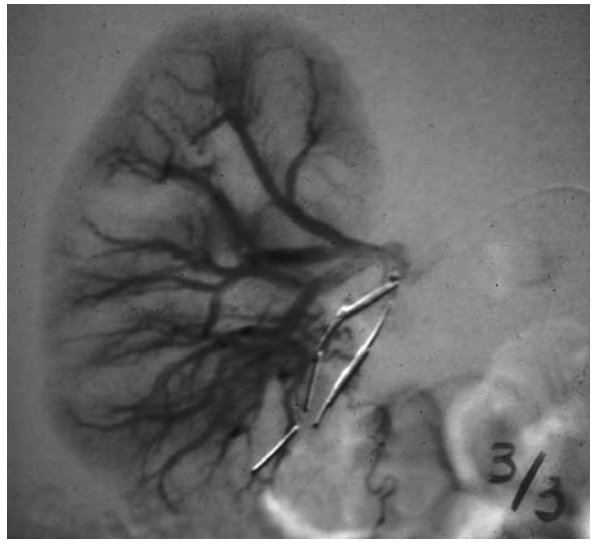
If an area of stenosis >50% is identified, the child is considered for PTRA after consultation with the primary physician. In preparation for PTRA, the narrowest diameter and length of stenosis are measured in an adjacent area of normal arterial diameter. We prefer to select the angioplasty balloon that most closely approximates the normal arterial size and will not dilate the artery to greater than 10% more than the predicted normal diameter. In addition, the balloon selected will generally be the one with the highest inflation pressure. Our goal is to dilate the artery to the measured level on the initial attempt. Before PTRA the child is heparinized to reduce the incidence of renal artery thrombosis and renal loss. A successful PTRA is often signaled by elimination of the "waist' as the balloon inflates to size and improvement in the pressure measurements across the lesion (Fig. 26.10). At the comple-



a



b



c

Fig. 26.10a–c. A 4-year-old girl with severe hypertension that failed medical therapy. **a** Abdominal aortography (not shown) and selective right renal arteriography (1A) demonstrated branch renal artery stenosis with the presumed diagnosis of fibromuscular dysplasia. PTRA was of limited help and with the use of a microangioplasty balloon (**b**) the lower middle pole segmental renal artery branch was dilated. However, the stenotic lower pole segmental artery could not be catheterized and dilated. Therefore, the effected branches were embolized with Hilal microcoils (**c**). Post-angioplasty the hypertension was treated with fewer drugs, but not cured

tion of the angioplasty, a follow-up angiogram is performed to assess outcome and identify complications if present. If there is significant post PTRA improvement, no further treatment is performed. If there is significant residual stenosis, repeat angioplasty with a larger balloon or stenting may be considered. Since there may be clinical improvement even in children with disappointing visual results, a conservative approach is taken. The procedure is concluded if the visual result suggests less than 50% narrowing, there is a reduction in the measured gradient across the stenosis, the collateral vessels are no longer seen, or if the operator is uncomfortable with additional treatment. At the conclusion of the procedure, the child is taken to the intensive care unit for observation and continuous monitoring of blood pressure and vital signs. Heparin is continued and until discharge or conversion to oral medications, which are continued for several months.

If, upon clinical follow-up, there is improvement in the blood pressure, no additional intervention may be needed. However, if the hypertension persists, repeat US, CTA, or MRA can be performed to evaluate renal artery anatomy and flow. If further vascular intervention is considered, repeat angiography is performed. If re-treatment is needed, repeat PTRA, stenting, or a recently developed technology, cutting balloon angioplasty (CBA), may be considered.

In 1991, Barath and colleagues (1991) introduced the cutting balloon, a device consisting of three or four metal blades mounted on the surface of the balloon catheter parallel with the long axis of the catheter (Fig. 26.11). Upon inflation of the balloon, the blades are exposed and create radially distributed longitudinal atherotome incisions into the intimal and medial layers of the artery. Unterberg et al. (1993) reported the first clinical use of the cutting balloon for the treatment of a coronary artery stenosis. Since than, the use of the cutting balloon in children has been reported for the treatment of peripheral pulmonary artery stenosis (Rhodes et al. 2002) and in a small number of adolescents and young adults (Haas et al. 2002; Lupatteli et al. 2005; Oguzkurt et al. 2005; Tanemoto et al. 2005) and in children (Caramella et al. 2005; Towbin et al. 2007) with resistant renal artery stenosis. This new technology may allow treatment of resistant stenosis, especially in children with syndromes and arteriities that result in renal artery stenoses. In the past, these lesions responded poorly to PTRA and usually required open surgery. In these conditions there is typically aorto-renal or proximal renal artery involvement. This pattern of involvement makes treatment with PTRA less effective with a high rate of failure (Booth et al. 2002; Ing et al. 1995). In patients with syndromic causes, renal artery lesions are more often bilateral and are usually localized to the ostia of the renal arteries (Ing et al. 1995).

Since its introduction, indications for cutting balloon angioplasty CBA have included treatment of vascular stenoses that are resistant to conventional balloon angioplasty, such as arterial stenoses, principally in the coronary arteries (Unterberg et al. 1993) and pulmonary arteries (Rhodes et al. 2002; Schneider et al. 1999), venous stenoses (Vorwerk et al. 1995), and in-stent stenosis (Miyamoto et al. 2001). More recently, CBA has been used to treat peripheral arterial stenoses that are not amenable to conventional balloon angioplasty, including arch vessels (Rath et al. 2004; Henry et al. 2004), and for treatment of hypertension due to resistant RAS (Haas et al. 2002) (Fig. 26.12). Cutting balloons are now available in a wider variety of diameters

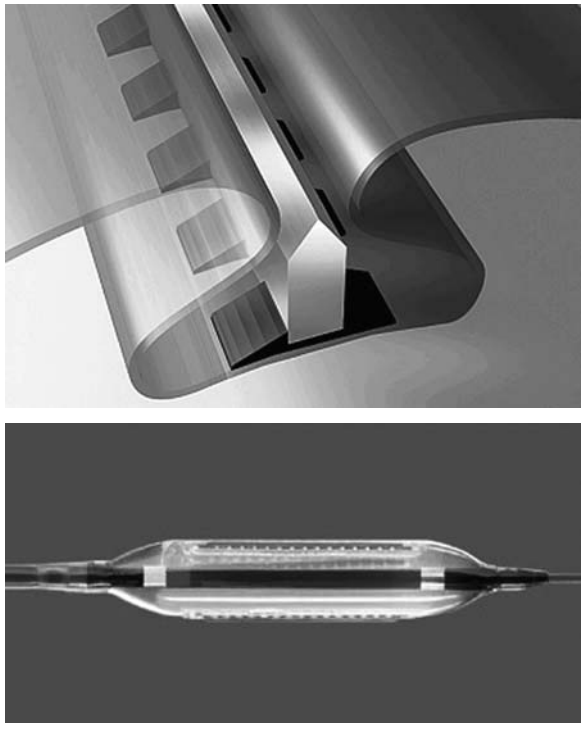
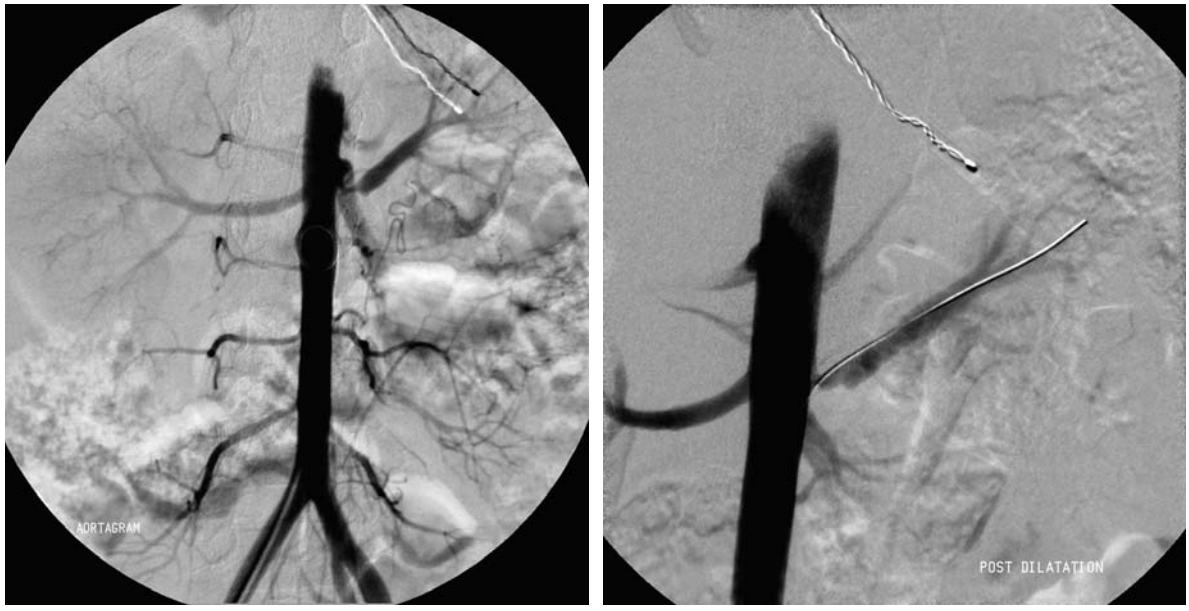


Fig. 26.11a,b. A diagram (**a**) of a cutting balloon blade and cutting balloon catheter (**b**) that is used to treat resistant stenoses



a b

Fig. 26.12a,b. A 9-year-old, 26.6-kg male with type 1 neurofibromatosis and a past medical history of a left optic nerve glioma. Hypertension (140/100) discovered during a routine school screening examination. Medical therapy inadequately controlled blood pressure. Three days before referral to the interventional radiology service, a diagnosis of renal artery stenosis (RAS) was suggested near the origin of the left renal artery demonstrated on abdominal CT with CT angiography. **a** Pre-treatment imaging included abdominal aortography and bilateral renal arteriography confirming severe stenosis at the origin of the left renal artery with associated post-stenotic dilatation. **b** Prior to PTRA an intravenous heparin bolus of 2,000 IU was given. PTRA was attempted using 3- and 4-mm high-atmosphere (15 ATM) balloons without success. A residual pressure gradient of 45 mmHg remained. A 4×10-mm cutting balloon (Interventional Technologies, San Diego, CA) was positioned across the lesion and the balloon was inflated to approximately 6 ATM. A follow-up arteriogram (not shown) revealed mild residual stenosis. Therefore, a PTRA using a 5×2-cm balloon was performed. An arteriogram after angioplasty showed no significant residual stenosis, and the systolic pressure gradient was now less than 15 mmHg. The patient is normotensive on no anti-hypertensive medications 2 years and 9 months after treatment

and lengths with a range suitable for treatment of pediatric lesions. In addition, CBA has the potential to reduce the rate of re-stenosis by avoiding the random disruption of the arterial wall created by conventional balloon angioplasty that can lead to neointimal proliferation (Tsetis et al. 2006).

The complications associated with use of cutting balloons for treatment of hypertension related to resistant RAS are similar to those described for PTRA, including dissection, rupture, and thrombosis of the renal artery. In a study of 110 patients who were treated with CBA, the incidence of significant dissection was 3.6%, and the incidence of coronary artery perforation was 0.9% (Safian and Textor 2001). In one case, arterial dissection resulted from a fracture of one of the microsurgical blades (Haridas et al. 2003). The arterial injury complicating CBA in patient 3 was similar to that described by Caramella and colleagues (2005), with delayed pseudoaneurysm formation leading to recurrence of hypertension. The possibility of arterial injury should be communicated during informed consent, and specific surveillance should be employed to exclude this complication at the conclusion of the CBA procedure.

In the rare instance of arterial rupture with associated hemorrhage, balloon tamponade of arterial extravasation (Towbin et al. 2007) offers at least one salvage strategy that may preserve a successful final outcome. Additional recommendations that may increase safety include pre-procedure imaging of the arterial wall, such as with intravascular ultrasound (Lupatteli et al. 2005), to place the cutting balloon in the safest position. We agree with Tanemoto and colleagues (2005) that it may be a safer strategy to limit the cutting balloon diameter to no more than the normal vessel diameter in the incisional phase. Then, if necessary, the lumen can be further enlarged with PTRA.

Conclusion

PTRA has long been an option for the minimally invasive treatment of children with renovascular hypertension. Angioplasty is especially effective in children with fibromuscular dysplasia. Unfortunately, children with lesions resistant to PTRA have generally required open surgery because other minimally invasive options have not been available. With the advent of the cutting balloon, children with lesions resistant to traditional angioplasty, such as those with syndromes and arteritis, can now be considered for therapy. Additional experience and long-term follow-up are needed to determine if CBA is a useful addition to the interventionalist's therapeutic arsenal.

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Clinical Management of Common Nephrourologic Disorders (Guidelines and Beyond)

27

Ekkehard Ring, Michael Riccabona, Christoph J. Mache and Richard Fotter

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E. Ring, MD,
Professor, Department of Pediatrics, Division of General Pediatrics, University Hospital Graz, Auenbruggerplatz 30, 8036 Graz, Austria
M. Riccabona, MD
Professor, Department of Radiology, Division of Pediatric Radiology, University Hospital Graz, Auenbruggerplatz 34, 8036 Graz, Austria
C. J. Mache, MD
Department of Pediatrics, Division of General Pediatrics, University Hospital Graz, Auenbruggerplatz 30, 8036 Graz, Austria
R. Fotter, MD
Professor and Chairman, Department of Radiology, Head Division of Pediatric Radiology, University Hospital Graz, Auenbruggerplatz 34, 8036 Graz, Austria

27.1 Introduction

It is not the aim and is beyond the scope of this chapter to show and to discuss all issues concerning treating nephro-urological disorders. In some aspects, we can refer to other chapters of this book. Basically, pediatric radiologists are responsible for imaging, clinicians (pediatric nephrologists, pediatric urologists, general pediatricians, etc.) for treatment. This strict separation is valid, but somewhat questionable for optimal diagnosis and treatment. The task of preserving renal parenchyma, to the best of our knowledge, can be achieved only by cooperation and an interdisciplinary approach in many situations. The partners need to know about each other's thinking, intentions, and expectations. Interdisciplinary discussions with an exchange of knowledge are of value. This chapter is dedicated to discussing the cooperation between sub-specialties and to showing aspects of the treatment of disorders. The discussion will include the dilemma of guidelines in general and in the daily routine of single centers. Disorders with minimal or no contribution of imaging to clinical decisions (e.g., dosage or duration of steroid treatment in glomerular disorders) are excluded. Some aspects of this clinical management are shown in Chapters 19 and 21. The overlap with other parts of this book is desired as this chapter provides a more clinically oriented approach.

27.2 What Clinicians Should Know

Basically, one could recommend clinicians to read this book entirely. Yet this is not realistic as, conversely, radiologists will not read a textbook of pedi-

atric nephrology as well. Clinicians referring a child to imaging procedures – especially when working in a center for pediatric nephrology/urology – must have a basic knowledge about the imaging procedures, radiation burden, and the impact of the different investigations. Aside from reviewing the literature, personal communication is of importance for quick information about trends in imaging, changes in the performance of established investigations, and indications for new imaging procedures. Renal ultrasound (US) is the basic and often single investigation and frequently guides further imaging. It is wrong to rely exclusively upon US for answering all questions; this would be giving too much credit to US. No other imaging technique is more investigator-dependent and prone to errors and pitfalls if not performed correctly. This should be kept in mind as the use of US has partially shifted to other specialists such as general pediatricians, pediatric urologists, and pediatric nephrologists, or to obstetricians in the case of fetal imaging. Particularly fetal US is part of the daily obstetrical routine. It may be that some special issues of imaging can be discussed with the pediatric radiologist. After birth, pediatric radiologists should know the results of previous imaging in order to plan and perform further radiological imaging properly.

27.3 What Clinicians Expect from Imaging

Clinicians expect the investigations to give clear answers to their questions. It would be optimal to perform just one or two investigations – as minimally invasively as possible – to know all about the patient's disorder (Ring et al. 2002). The daily routine is as follows: the families get a sheet of paper with hopefully sufficient information about the disease and the questions for the current investigation. They come back to the clinician with a preliminary result of the investigation to clarify and discuss the results and to plan the treatment including further investigations and the next outpatient visit. This situation requires several basic conditions to function. The clinical information must be sufficient, the ordered investigation must be capable of answering the questions, and the setting must be appropriate. The preliminary result should not be different from the final result of the investigation. This way probably is appropriate for most routine situations, but requires modifications in special and emergency situations. Important initial results or major changes during follow-up need a rapid personal communication for properly planning the immediate treatment or urgent additional investigations. Basically, a few images are superior to a thousand words. Thus, radiological documentation programs must include rapid access to images for clinicians. If requested, pediatric radiologists should find enough time to participate in interdisciplinary conferences on special patients to demonstrate the results of imaging. These discussions are time consuming and seem to be unnecessary in most routine situations as clinicians are capable of interpreting imaging. Local interdisciplinary meetings focusing on the current knowledge and future aspects of imaging in renal disorders seem to be of value. Here pediatric radiologists can clarify why, e.g., IVU nowadays is no longer the routine investigation in urinary obstruction if new investigations such as MRI are available or why echo-enhanced cystosonography, if locally available, should replace conventional VCU in certain clinical settings. This should lead to an improvement of imaging settings, to prevention of invalid performances, and to a better understanding of each other, consecutively enabling an optimal management of our children.

27.4 What Pediatric Radiologists Should Know about Treatment

27.4.1 Urinary Tract Infection

Urinary tract infection (UTI) is the second most frequent bacterial infection during childhood defined by the presence of bacteria within the kidneys and/or the urinary tract. Demographic data on UTI have remained unchanged during the last decades with an overall female predominance, an equal gender distribution during infancy, and with infant boys having UTI earlier than girls (Ring and Zobel 1988; Hansson et al. 1999). UTI in boys aged more than 2 years is exceptional. Many factors are involved in the pathogenesis of UTI. We are on the way to a better understanding of the innate and adaptive immunity of the urinary tract and the impact of Toll-like

receptors or cytokines on host defense mechanisms. Detection of immunologic disturbances or of genetic polymorphisms could contribute to the identification of children susceptible to recurrent UTI and to renal scarring (Saemann et al. 2005; Mak and Kuo 2006). So far, no single clinical or laboratory factor can identify children at risk. Determination of procalcitonin (PCT), an indicator of systemic bacterial infection, could be of value to define special groups of patients as significantly higher PCT levels were found in patients with renal lesions on DMSA scan and in those with VUR (Pecile et al. 2004; Leroy et al. 2005, Leroy et al. 2007). Nevertheless, it is no longer accepted nowadays that renal damage following UTI is predominantly the consequence of VUR as there seems to be an equal distribution of renal scarring in refluxing and non-refluxing renal units (Hellerstein 2006; Moorthy et al. 2005). Sometimes VUR is found contralateral to a severely compromised kidney (Fig. 27.1). Aside from looking

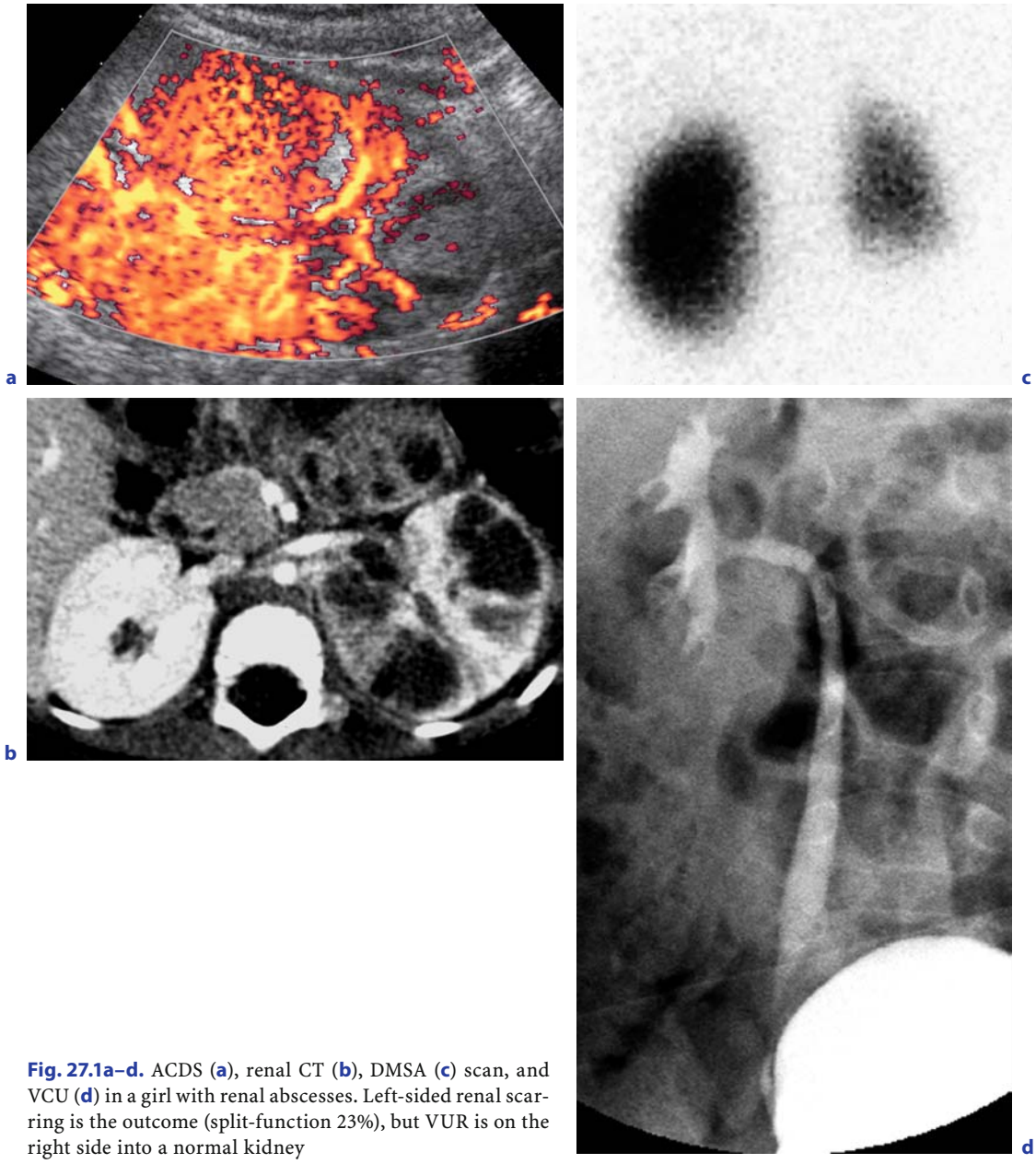

Fig. 27.1a–d. ACDS (**a**), renal CT (**b**), DMSA (**c**) scan, and VCU (**d**) in a girl with renal abscesses. Left-sided renal scarring is the outcome (split-function 23%), but VUR is on the right side into a normal kidney

for UT malformations, functional disturbances of the bladder must be addressed especially in children with recurrent UTI. Appropriate treatment of non-neurogenic bladder-sphincter dysfunction with drugs such as anticholinergics and/or behavioral therapy and treatment of constipation are of importance in reducing the number of recurrent UTIs (see Chap. 14). Selected cases need imaging to exclude neurological deficits such as occult dysraphia, lipoma, or a tethered cord. It is well recognized that circumcision is associated with a significantly reduced risk of UTI in infant boys (Schoen et al. 2005). This could be of value in boys with severe UT malformations. From a European view, there is no benefit of circumcision to prevent UTI in the general male population (Malone et al. 2005).

Symptomatic UTI needs immediate antibiotic treatment, and a delay of diagnosis and treatment may be associated with renal scarring (Jodal 1987). Therapy needs to be appropriate for the severity of infection shown by clinical symptoms such as vomiting, fever, or shock. Treatment for lower UTI can be shorter than treatment of febrile upper UTI where an antibiotic course of 10 days is adequate. Bacteria can persist within the bladder tissue in a quiescent state and may serve as a reservoir for recurrent infections (Mulvey et al. 2000). Antibiotic prophylaxis for a few weeks, especially after severe infections, could be the consequence. But what about long-term prophylaxis? For decades, long-term prophylaxis–even for many years–was an accepted treatment for children with recurrent UTI in preventing renal scarring, but this effect is questioned nowadays (Williams 2001; Beetz 2006). Nevertheless, prophylaxis can be recommended in children with a normal urinary tract and problems such as recurrent pyelonephritis, infection stones, or functional bladder disorders as adjunct to bladder therapy. The most frequently used substances are trimethoprim, co-trimoxazole, and nitrofurantoin. Cephalosporines are a reasonable alternative as the number of bacterial strains resistant to trimethoprim is increasing (Kaneko et al. 2003). Each center or region separately must decide on the best drug according to the local bacteriological findings.

27.4.2 Vesicoureteral Reflux

No other clinical entity of pediatric nephrology and urology causes more interdisciplinary discussions than VUR, and the most frequent clinical situations associated with VUR are shown in Table 27.1. A reorientation concerning diagnosis, treatment, and outcome of VUR took place during the past years and is going on still. The International Reflux Study in Children gave the final report after 10 years of follow-up. There were no differences in the outcome (scarring, renal growth, UTI recurrence rate) under medical or surgical management except that medically treated children more often had febrile UTI. The importance of continuous surveillance of VUR patients was emphasized (Jodal et al. 2006). Children with VUR do not necessarily suffer from recurrent UTI. Consequently, the need and the duration of antibiotic prophylaxis have to be questioned. There is evidence that VUR grade 3–5 (international classification) is a risk factor for UTI, but not so VUR grade 1–2 (Nuutinen and Uhari 2001; Hellerstein and Nickell 2002). Stopping long-term prophylaxis in children with persisting VUR was found to be safe without an increased risk for UTI or renal scarring, mostly in school-aged children with non-dilating VUR (Cooper et al. 2000; Thompson et al. 2001; Al-Sayyad et al. 2005; Garin et al. 2006). The above-mentioned gender differences in UTI could influence the decision to stop prophylaxis, being earlier in boys than in girls. Discontinuing or not even starting prophylaxis in cases with VUR (no prophylaxis in VUR grade 1–2; stopping prophylaxis in persisting VUR grade 3–4 after 1 year, at least in boys) is more often accepted in Europe and was proposed as an alternative much earlier than in North America (Jodal and Lindberg 1999).

The American Urological Association recommended continuous antibiotic prophylaxis as initial treatment for most children with VUR. Surgery (mostly open surgery) was recommended in children with persistent dilating VUR (Elder et al. 1997). Nowadays, surgically oriented institutions mostly emphasize endoscopic treatment (subureteral injection) not only as an alternative to prophylaxis and

Table 27.1. Clinical situations with an increased probability of VUR

- Urinary tract infection
- Fetal hydroureteronephrosis
- Family member with VUR (sibling, parents)
- Unilateral multicystic dysplasia or renal agenesis
- Neurogenic and nonneurogenic bladder-sphincter dysfunction

to open surgery, but sometimes also as the first-line treatment for most children with VUR (Puri et al. 2006; Capozza and Caione 2007).

What is our ultimate goal? Is it prevention of renal damage or is it cure of VUR? Treatment options for children with VUR are shown in Table 27.2. We are obliged to inform families about all treatment options. Parental preferences have to be respected and need to be incorporated into ultimate decisions. A recent questionnaire study showed that the majority of parents favored antibiotic prophylaxis over surgery as initial treatment. If a long-term treatment course was predicted, surgery and especially endoscopic treatment were preferred (Ogan et al. 2001). Information given to parents for decisions should be objective, but certainly are biased by center preferences. This has to be considered in interpreting a questionnaire study of a surgical center showing an 80% parental preference of endoscopic treatment (Capozza et al. 2003). Whatever the individual situation, spontaneous resolution or surgical repair of VUR is not the endpoint of treatment and observation. Long-term studies showed that UTI is independent from VUR, and it was found in up to 74% of patients 20 years even after successful antireflux surgery (Beetz et al. 2002; Mor et al. 2003). Women with or without reflux nephropathy (RN) are prone to UTI during pregnancy, abortion may occur in 37% of pregnancies, and chronic renal failure will deteriorate in approximately 20% of cases (Jungers et al. 1996). Arterial hypertension is found in 10–20% of all patients with RN. Patients with chronic renal failure (CRF) due to bilateral RN or to RN in a single kidney are especially prone to these long-term sequelae (Smellie et al. 2001).

It is well recognized that particularly boys with bilateral high-grade VUR present with renal hypodysplasia, also called congenital RN (Ring et al.

Table 27.2. Treatment options for children with primary VUR. Supportive measures such as awareness of UTI, treatment of non-neurogenic bladder-sphincter dysfunction, constipation, vulvitis, and phimosis are mandatory in all. RTx renal transplantation, CRF chronic renal failure

1. Observation without continuous medication
a) Frequent urinalysis (partially at home)
b) Immediate treatment of UTI
2. Antibiotic prophylaxis (Px)
a) Px until VUR resolves
b) Stopping Px despite VUR persistence and observation as in option 1
c) Px for a defined period without re-evaluation. Observation as in option 1
3. Primary surgical treatment (with or without postoperative Px)
a) Subureteral injection
b) Open surgery
4. Combined conservative and surgical approach
a) Elective primary surgery (e.g., paraostial diverticulum)
b) Surgery following conservative treatment
– Recurrent UTI with options 1 or 2
– New scarring
– Preservation of bladder function (e.g., megacystis-megaureter syndrome)
c) Failure of surgery–with second surgery and/or options 1 or 2
– Invalid technique
– Not recognized non-neurogenic bladder-sphincter dysfunction or neurogenic bladder
5. Proceeding based on parental preferences and compliance to treatment

1993; Yeung et al. 1997; Wennerström et al. 2000; Marra et al. 2004). Hypodysplasia with VUR is the most frequent single cause of CRF during childhood, accounting for 25.8% of cases (Ardissino et al. 2003). Future end-stage renal failure cannot be prevented in these children, but the progression of CRF can be delayed. Proper nephrological treatment is essential to avoid complications such as hypertension, renal anemia, or renal osteodystrophy and must start early in CRF.

Statements such as "... it is not clear whether any intervention for children with primary vesicoureteric reflux does more good than harm" or "it is uncertain whether the identification and treatment of children with VUR confers clinically important benefit" are questionable (Wheeler et al. 2003). The presence of renal hypodysplasia cannot be changed by any treatment. However, early identification of children with congenital renal compromise, particularly those with CRF, is essential for adequate nephrological treatment. The rationale for treatment of VUR can only be the prevention of acquired renal scarring. Scars may cause renal morbidity in patients born with normal kidneys or can accelerate the progression of CRF in patients with renal hypodysplasia. Therefore, we need identification, observation, and probably treatment of VUR patients at risk for renal scarring. As a negative example, a study of 115 adults (99 females)–all born before 1968–with VUR detected in adulthood and without diagnosis of VUR during childhood showed that 88% of patients had RN, 34% were hypertensive, and 19% suffered from CRF. Females more often had UTI, while CRF was predominant in males (Köhler et al. 1997). These data of a special group of adults indicate that we should not leave our children without long-term care and surveillance. Gender differences of VUR and of RN have to be considered as they may influence management significantly (Fanos and Cataldi 2004). In addition, developing countries strongly await our decisions and our support (Xhepa et al. 2004).

Decisions about treatment are influenced by guidelines – commonly accepted or not – which are discussed below. Clinically oriented decisions, individually influenced by our knowledge about the family situation, the estimated compliance with medical treatment, and the adherence to follow-up investigations, seem to be of equal importance. Aside from patients being involved in multicenter studies with strict protocols, treatment of many children with VUR is based on individual experience, local attitudes, and the specialization of the center. Our current knowledge seems to raise more questions than solutions concerning evidence-based treatment of children with VUR.

27.4.3 Fetal Hydronephrosis

Formerly, the term "hydronephrosis" indicated obstructive uropathy with severe compromise of the renal parenchyma. Nowadays, this term refers to different grades of renal pelvic dilatation on ultrasound investigation (prenatally and after birth) mostly classified as proposed by the Society for Fetal Urology (Fernbach et al. 1993). Different grading systems exist. A major point of discussion is what extent of fetal HN at which gestational age reliably predicts significant postpartum renal and urinary tract disease (Toiviainen-Salo et al. 2004). Recent publications could show that severe degrees of HN (SFU grades 3–4) and an anterior-posterior renal pelvic diameter of >12 mm on a third trimester US are highly predictive for significant postpartum pathology (Lee et al 2006; Sidhu et al. 2006). HN per se does not necessarily indicate a special disease, and a correct final diagnosis is warranted. US devices applicable to small fetuses enabling diagnosis of renal disease in early pregnancy are welcome. Yet the actual diagnostic potential during fetal life is limited, and the correct postpartum diagnosis cannot be obtained in many cases.

The diagnosis of fetal renal failure is based on US findings of the kidneys (no kidneys present, a single dysplastic kidney, renal cysts, hyperechogenic renal parenchyma), the calculation of the amount of amniotic fluid as oligohydramnios indicating renal failure, and the measurement of electrolytes in fetal urine. Sometimes repeated US and analyses of fetal urine indicate an adverse outcome justifying elective termination of pregnancy. MRI of the fetal kidneys and urinary tract sometimes may clarify inconclusive findings on US and may serve as a valuable future tool (Hörmann et al. 2006; Cassart et al. 2004). The impact of MRI on fetal and postpartum management has not yet been established. Fetal interventions nowadays are mostly restricted to boys with oligohydramnios and bilateral urinary tract obstruction caused by posterior urethral valves. Fetal rupture within the urinary tract may cause concern on postpartum renal and pulmonary function (Fig. 27.2). Fetal interventions must be dis-

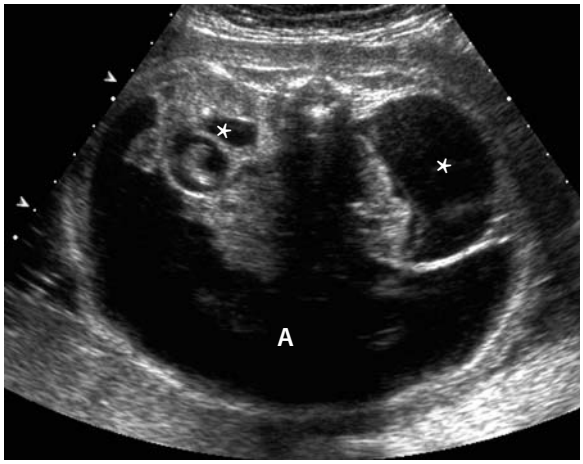

Fig. 27.2. Oligohydramnios, fetal urinary ascites (*A*), and bilateral urinoma (*asterisks*) in a boy with posterior urethral valve recognized in the 32nd week of gestation

cussed interdisciplinary in these rare but important situations. If not indicated or performed, early imaging and emergency treatment immediately after birth are mandatory, and the long-term renal outcome may be poor.

Most fetuses with isolated HN survive and are asymptomatic neonates after birth. Further imaging is needed frequently to clarify the fetal findings. Sometimes the parents may not know enough about the significance of prenatal findings and their postpartum diagnostic and therapeutic management. Such a situation leads to a long period of uncertainty and anxiety for the parents who have been worried about their child's renal outcome since the first recognition of fetal HN. Correct information for the parents from the obstetricians is therefore mandatory, with pediatric radiologists eventually being helpful in interpreting US. Especially in severe findings on fetal US, the direct contact to neonatologists, pediatricians, or preferably to pediatric nephrologists already during pregnancy is of utmost importance. They should inform the parents what will happen after birth and which investigations (mostly imaging) should be performed at which postpartum age. Appropriate information about prognosis and therapeutic options (antibiotic prophylaxis, indications for surgery, etc.) should be provided in time. In strictly unilateral renal compromise with a normal contralateral kidney showing compensatory hypertrophy, the global renal outcome will be favorable.

Fetal HN is found in up to 5% of pregnancies. It is transient or physiological without renal compromise in approximately 60% of cases. Nearly half of the neonates with significant pathology suffer from UPJO and one third from VUR. In the early years of US, most of us were deeply impressed by the magnitude of neonatal HN and probably too many children had early operations. A recent retrospective survey carried out for 19 years showed that prenatal diagnosis led to earlier detection of UPJO and to earlier surgical repair. The total number of operations remained unchanged (Capello et al. 2005). The "wait and see" strategy, nowadays successfully applied in many centers, may reduce the number of surgically treated neonates and infants significantly. Dilatation is not necessarily equal to obstruction. Obstruction basically means development of renal damage if left untreated and is a retrospective assessment. However, acquired irreversible renal damage should not be the rationale for therapeutic decisions. In this dilemma of operating only on children with proven obstruction and not losing renal parenchyma, we must accept investigations felt to be somewhat invalid (e.g., MAG3 isotope washout curves) or rely on repeated US and split renal function on isotope investigation with deterioration being an indication for surgery. Permanent loss of renal parenchyma may occur within few months (Dejter and Gibbons 1989), is accepted to occur in some studies (Dhillon 1998; Thorup et al. 2003), and a close follow-up can prevent this irreversible renal damage (Ulman et al. 2000; Onen et al. 2002). A survey of French-speaking European pediatric nephrologists and urologists showed that about 61% rely on 99m Tc-MAG3 curves to recommend surgery or not (Ismaïli et al. 2004).

The long-term outcome of children with prenatally recognized UPJO is favorable in general. Deterioration on long-term surveillance seems to be rare, and the outcome of the affected kidney mostly is determined at birth. Children with a moderate reduction of neonatal split renal function may benefit from pyeloplasty, while poorly functioning kidneys mostly will not recover despite surgery (Thorup et al 2003; Ylinen et al. 2004). In the latter cases, pelvic dilatation on US may be moderate due to the decreased urine output. Increased parenchymal echogenicity, cortical cysts, and a reduced perfusion indicate a congenital lesion already in neonates (Fig. 27.3).

Although performed frequently, it is unclear whether all neonates with fetal HN should receive an antibiotic prophylaxis starting at birth. Infants with urinary tract obstruction had an increased

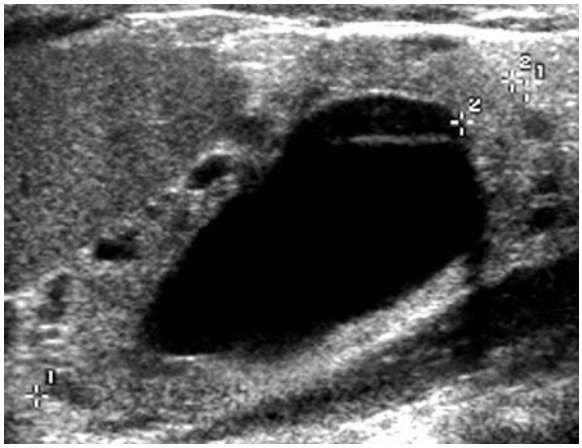

Fig. 27.3. Neonatal US in ureteropelvic obstruction with moderate renal pelvic dilatation. Increased echogenicity and cortical cysts indicate severe obstructive dysplasia and poor renal function

incidence of UTI in an early study (Ring and Zobel 1988). A 36% incidence of UTI–predominantly during the first 6 months of life–in infants with severe obstructive HN and left without antibiotic prophylaxis was reported recently. UTI was more frequent in infants with ureterovesical obstruction than with UPJO (Song et al. 2007). Prophylaxis given to all neonates with all grades of fetal HN and starting with birth may be a prerequisite for large prospective multicenter trials, but otherwise is not timely. Just 23% of pediatric nephrologists and 31% of pediatric urologists would recommend prophylaxis immediately after birth, more often in VUR than in urinary tract obstruction (Ismaïli et al. 2004). Table 27.3 shows possible indications for antibiotic prophylaxis in neonates depending on the severity of fetal and neonatal findings. If prophylaxis is questioned in cases with low grade VUR, indications for VCU in asymptomatic neonates with mild to moderate fetal and neonatal HN and a normal appearance of renal parenchyma should be modified (Ismaïli et al. 2006; Lidefelt et al. 2006). VCU should be selectively used with the knowledge that some neonates with predominantly mild VUR may be missed. Renal parenchymal lesions on US, known to be associated with severe VUR, and indirect signs of dilating VUR, such as ureteral distension or a changing ureteral or renal pelvic width, are in favor of immediate or delayed VCU.

Table 27.3. Indications for antibiotic prophylaxis in neonates with fetal HN

- Neonates after fetal interventions
- Severe fetal findings leading to immediate neonatal investigations
- Suspicion of posterior urethral valves
- Complex obstructive uropathy (e.g., duplication with ureterocele)
- Uni- or bilateral severe supravesical HN
- Dilating VUR (grades 3–5, international classification)
- Single functioning kidney with severe HN

27.5 Guidelines and Beyond

27.5.1 General Considerations

Guidelines permanently accompany our work in the daily routine. Young colleagues eagerly follow the proposals of the local specialists, making the daily work much easier. Specialists themselves are involved in the interdisciplinary approach to special disorders within their own countries or in the setting of international cooperation or societies. Consequently, clinical and basic research continuously modifies our approach to disorders (Marks 2006). The resulting guidelines influence the clinical management and represent a continuum to better care for our children. But are our guidelines always followed? A recent study showed that less than half of infants with UTI received the recommended care including diagnostic imaging. Hospitalized infants were more likely to get imaging (Cohen et al. 2005). Another point of concern is the practicability of a given guideline. Adequacy for a tertiary center may be a challenge for primary or secondary care or for countries with limited resources. We have to accept that not all can follow new concepts. Modifications according to local circumstances or adherence to previous proposals are the consequence.

It is the current attitude to question approved approaches to diagnosis and therapy and to ask for evidence-based medicine. If the treatment of special disorders is not evidence based, prospective, multicenter, randomized trials are proposed and "further decisions strongly will depend on these findings." Meanwhile and for the years up to the first results of

ongoing or planned studies, we are in a vacuum, not knowing what should be done. But our patients and their disorders cannot wait years for such suggestions as treatment has to be done immediately.

Meta-analyses showing that current approaches are not evidence based and proposing studies to clarify these issues are of importance. Yet there is no proof that omitting all current imaging and treatment protocols is better and does not harm our children. Timely individual management, partially influenced by personal experience and local preferences, and sometimes being different from proposed guidelines, must parallel clinical research. Guidelines are as good as they allow modifications for the individual patient. It is not our intention to give new proposals or algorithms with the presumption of being superior to previous recommendations. The impact of investigations in disease entities will be discussed from a clinically oriented view. This hopefully will contribute to the best decision on imaging in children with UTI, VUR, and fetal HN where doctors from several sub-specialties are involved.

27.5.2 Urinary Tract Infection and Vesicoureteral Reflux

It is almost universally accepted that all infants and children with UTI should undergo imaging starting with US. Yet one prospective study found US to be of limited value if performed at the time of acute UTI as the impact on treatment is low (Hoberman et al. 2003). No other imaging procedure is more investigator-dependent than US. But high-quality modern US including DS and ACDS has the potential to influence and to guide further imaging, thereby reducing the total radiation burden. This is to some extent a local decision. If local clinicians rely on the results of US, recommended subsequent imaging eventually can be delayed, performed just in selective cases, or be omitted. Inconsistencies and failures need re-evaluation of such an approach mostly going back to an imaging protocol following generally recommended guidelines.

Discussion on imaging following UTI is based on the correlation of UTI with renal scarring, VUR, other malformations of the kidneys and the urinary tract, and nonneurogenic bladder-sphincter dysfunction. Voiding cystourethrography (VCU) is the central point of discussion and is an invasive investigation with radiation burden, discomfort, and a small risk of causing a UTI. The American Academy of Pediatrics and a Swedish state-of-the-art conference recommended US and VCU in all infants and young children up to 2 years of age with UTI to detect VUR (American Academy of Pediatrics 1999; Jodal and Lindberg 1999). This is a widely accepted imaging policy even nowadays, but there is ongoing research to reduce the number of investigations or even to replace VCU. Radionuclide cystography (RNC) with low-dose radiation or voiding urosonography (VUS) without radiation are alternatives to conventional fluoroscopic VCU, but both also require catheterization of the bladder. As stated above, it is our ultimate goal to recognize and to prevent renal damage. Renal scarring without VUR is frequent. Conversely, detecting VUR is not a good predictor of renal damage after UTI and cannot serve as a screening investigation for renal damage (Gordon et al. 2003).

Siblings of an index patient more often have VUR, mostly low-grade VUR, and the mean incidence is 32% (Hollowell 2002). Scarring is infrequent in this special, mostly asymptomatic population, and no increased risk for UTI has been reported. Performing a VCU seems to be advisable in siblings with UTI or with proven renal damage. Elective screening with RNC was recommended recently (Lee et al. 2006), but close surveillance including repeated US and immediate urinalysis in febrile states could be an alternative.

VCU in children older than 2 years is a matter of debate. A DMSA scan–if available–was recommended 6–12 months after an upper UTI, and VCU was performed only if a renal lesion was recognized (Jodal and Lindberg 1999). In contrast, others recommended VCU in all prepubertal children (Lee et al. 2006). There is increasing evidence that an imaging policy using US and DMSA scan could be a reasonable alternative to strict adherence to VCU in all cases (Riccabona and Fotter 2004). Two recent studies with this approach could reduce the number of VCUs by 49% and 30%, respectively (Hansson et al. 2004; Tseng et al. 2007). It is important to note that–taking these two studies with 445 patients together–a small number of children with VUR grade 1–2 and just 1 child with a renal lesion were missed. This is acceptable, especially if we feel that some children with VUR can be left without prophylaxis.

Looking for alternatives to VCU for diagnosing VUR, a recent study determined serum procalcitonin (PCT) and found high PCT to be a predictor of VUR

with a 75% sensitivity (Leroy et al. 2007). One third of VCUs could be avoided, but unfortunately a DMSA scan was not included in the study design. Another point of concern is the timing of repeated VCU once VUR is detected. Most centers probably would accept VCU in yearly intervals while children are on prophylaxis. A recent study analyzed a schedule of delaying VCU, thereby taking into account the resolution rates of different VUR grades. A delay of 2 years in children with mild VUR and of 3 years with severe VUR would have reduced the number of VCUs by 19% with a moderate prolongation of giving prophylactic antibiotics (Thompson et al. 2005). In cases in which prophylaxis is stopped despite persisting VUR, the need for a repeated VCU basically has to be questioned in an uneventful course without UTI.

There is a significant change in the approach to children with VUR concerning treatment and imaging. The central point of concern is the renal parenchyma and not VUR itself. If we can accept that all children with renal compromise, but not all children with VUR have to be detected, a significant reduction of radiation seems to be possible.

27.5.3 Fetal Hydronephrosis

Imaging protocols following fetal hydronephrosis should be dedicated to identifying neonates with renal dysplasia, complex uropathies, obstructive uropathy, single functioning kidneys, or severe VUR with or without congenital RN. Fetal findings do not necessarily equal postpartum findings. High-quality fetal US is not performed in all pregnancies, and some renal or urinary tract malformations can be missed including VUR. Consequently, a recently reported approach not to perform renal US in children with UTI and a reportedly normal fetal US has to be questioned (Hoberman et al. 2003).

Severe fetal findings suggesting important diagnoses such as posterior urethral valves are a neonatal emergency, and US is needed immediately after birth. Otherwise, neonatal US can be delayed up to the end of the first week of life. Timely imaging algorithms basically including VCU were shown recently (Riccabona and Fotter 2004; Lee et al. 2006). Neonatal US is the first investigation, but VCU in all neonates even with unilateral, severe fetal HN, but without hydroureter has to be questioned nowadays. Antibiotic prophylaxis is prescribed in most of these neonates, obviating the need for immediate VCU that can be performed later and electively. Modern US can guide further imaging in a more individually based fashion. Preservation of renal parenchyma is the ultimate task in cases with fetal HN, but the radiation burden can be lowered with modified imaging protocols.

Conclusion

Interdisciplinary communication and cooperation are necessary for optimal treatment of children with renal disorders where imaging significantly contributes to management.

Infants and children with UTI need appropriate treatment. Antibiotic prophylaxis is recommended in selected cases, but imaging is required in all. Renal scarring following UTI is equally found in patients with and without VUR.

Prospective studies eventually modifying the current treatment of infants and children with VUR are welcome. Long-term renal morbidity is significant, and prevention of renal damage is the ultimate goal. It is not an option to reduce all imaging to detect VUR nearly to zero. Not to identify children with dilating VUR and a high risk for renal compromise may increase long-term renal morbidity.

Fetal hydronephrosis frequently is a transient feature, but postpartum renal US is needed in all. The majority of infants with significant postpartum findings have ureteropelvic obstruction. Follow-up studies with renal US and isotope investigations decide between the more frequently applied "wait and see strategy" and surgery.

Guidelines are important for the daily routine and are permanently influenced by the results of new research. They should be appropriate for most countries and centers. Modifications according to preferences of single centers are acceptable unless the timely treatment and long-term prognosis of our infants and children are not challenged.

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Normal Values

28

Ekkehard Ring, Michael Riccabona, and Richard Fotter

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28.1 Introduction

Correct interpretation of different data in disease states requires comparison with data obtained in a normal situation. This is valid especially during childhood as, for example, a given value may be normal for an adolescent, but is pathologic for an infant. Selected data important for daily routine are discussed in this chapter. For some data, the reader is referred to other chapters of this book. Comments are added where appropriate.

E. Ring, MD
Professor, Department of Pediatrics, Division of General Pediatrics, University Hospital Graz, Auenbruggerplatz 30, 8036 Graz, Austria
M. Riccabona, MD
Professor, Department of Radiology, Division of Pediatric Radiology, University Hospital Graz, Auenbruggerplatz 34, 8036 Graz, Austria
R. Fotter, MD
Professor and Chairman, Department of Radiology, Head Division of Pediatric Radiology, University Hospital Graz, Auenbruggerplatz 34, 8036 Graz, Austria

28.2 Physiologic Data

Percentiles for body length and body weight, as well as normograms to calculate body surface area (BSA), are found in most pediatric textbooks or as charts in every pediatric department. Some basic data are shown in Tables 28.1, 28.2 and in Figure 28.1.

A simple estimation of BSA is possible with an empirically derived formula.

$$\text{BSA } (m^2) = \text{square root of [body weight (kg)} \times \text{body length (cm)} : 3{,}600]$$

Table 28.1. Heart rate in children

Age	Mean heart rate (bpm)	Range
Neonates	123	(88–168)
1–3 weeks	148	(96–188)
1–12 months	137	(100–176)
1–2 years	119	(68–165)
3–4 years	108	(68–145)
5–7 years	100	(60–139)
8–11 years	91	(51–145)
12–15 years	85	(51–133)

Comment: Many factors can influence the heart rate of a child (e.g., sleep, excitement, hypovolemia, and cardiac failure). Heart rate is of importance for correct interpretation of values obtained by Doppler sonography such as the resistive index (RI)

Table 28.2. Mean systolic blood pressure during the first week of life

Gestational age	Mean systolic blood pressure
<29 weeks	45–57 mmHg
29–32 weeks	50–62 mmHg
33–36 weeks	58–69 mmHg
>37 weeks	66–77 mmHg

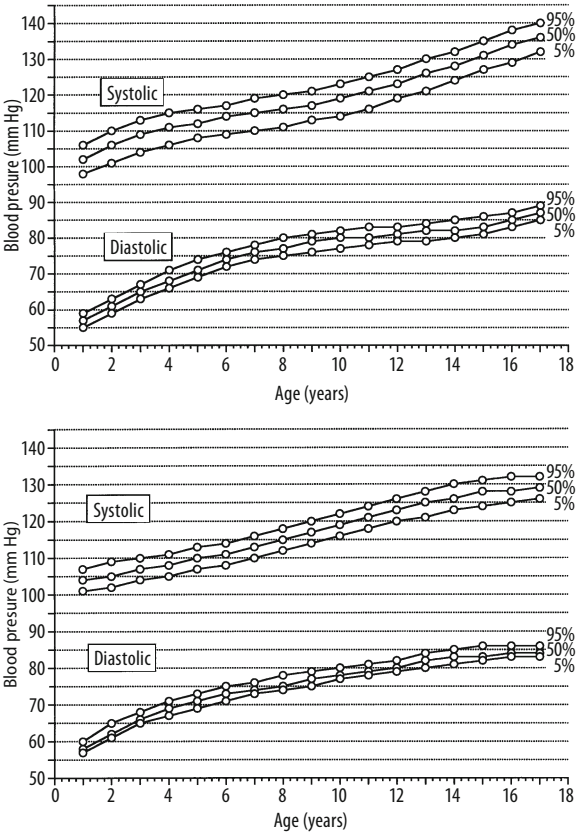

Fig. 28.1a,b. Normograms for systolic and diastolic blood pressure in boys (**a**) and girls (**b**). The upper limit of normal blood pressure (95th percentile) is shown according to age and percentile for body length (5th, 50th, and 95th percentiles are shown). Adapted from National High Blood Pressure Education Program (1996)

28.3 Laboratory Values

28.3.1 Serum Creatinine

Determining serum creatinine is of utmost importance in calculating renal function. Normal values vary with age, and this is shown in two illustrations (Table 28.3, Fig. 28.2).

Further important laboratory values are shown in Tables 28.4–28.9.

Table 28.3. Serum creatinine values in preterm and term neonates during the first 3 weeks of life[a] (adapted from Bueva and Guignard 1994)

Weight	Age			
	1–2 days	1 week	2 weeks	3 weeks
Preterm 1,000–1,500 g	1.10	0.72	0.55	0.40
Preterm 1,500–2,000 g	1.00	0.65	0.56	0.34
Preterm 2,000–2,500 g	0.94	0.53	0.43	0.34
Full term	0.75	0.45	0.34	0.31

[a]Mean values, mg/dl

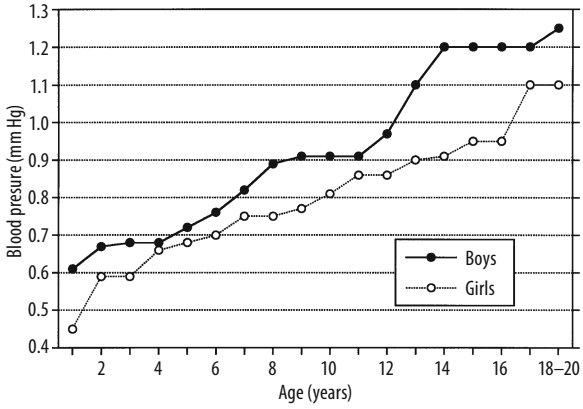

Fig. 28.2. Serum creatinine values (upper limit of normal) during childhood and adolescence. Adapted from Schwartz et al. (1976)

28.3.2 Combined Serum and Urinary Values

Combined determination of serum and urinary values of markers makes it possible to refine the determination of different renal functions. Calculating clearance and excretion values is possible. These calculations are extremely dependent on urine collection, which may be inappropriate. Formulas have been derived to overcome this problem (Tables 28.10, 28.11).

Table 28.4. Selected blood values at different ages

	Neonates	Infants	Age 1–6 years	Age 7–16 years
Leukocytes/mm^3	9,000–30,000	6,000–17,500	5,000–15,000	4,500–13,000
Erythrocytes (10^6/mm^3)	4.2–5.8	3.1–4.6	3.7–5.1	3.9–5.3
Hemoglobin (g/dl)	14.0–20.0	11.0–13.5	11.5–13.5	11.5–15.5
Platelet count (10^3/mm^3)	150–350	–	140–440	–

Table 28.5. Selected serum values at different ages

	Neonates	Infants	Age 1–6 years	Age 7–16 years
Sodium (mmol/l)	130–143	–	135–145	–
Potassium (mmol/l)	3.7–5.9	3.9–5.5	3.5–5.0	–
Calcium (mmol/l)	1.9–2.9	–	2.2–2.7	–
Phosphorus (mmol/l)	1.3–2.3	1.25–2.0	1.1–1.75	1.0–1.7
Urea (mg/dl)	10–30	–	10–40	–
Uric acid (mg/dl)	3.6–6.0	–	3.0–6.4	–
Total protein (g/dl)	5.6–8.0	5.6–7.4	5.8–8.0	6.4–8.2

Table 28.6. Urine values

	Normal	Questionable	Pathologic
Leucocytes/mm^3	<20	20–50	>50
Erythrocytes/mm^3	<5	5–10	>10
	Normal		**Pathologic**
Bacteriuria (bacterial count/ml urine)			
Bag urine specimen	10^5		10^6
Mid-stream collection	10^4		10^5
Bladder catheterization	10^3		10^4
Suprapubic aspiration	No bacteria		Each count

Table 28.7. Proteinuria

Level of proteinuria	Values
24-h collection	
Normal	<4 mg/m^2 per hour
Significant proteinuria	4–40 mg/m^2 per hour
Nephrotic range proteinuria	>40 mg/m^2 per hour
Spot urine (urine protein/creatinine ratio)	
Normal	<0.2 mg/mg
Minimal proteinuria	0.2–0.5 mg/mg
Moderate proteinuria	0.5–2.0 mg/mg
Nephrotic range proteinuria	>2.0 mg/mg

Table 28.8. Urinary excretion of electrolytes

Electrolytes	Values
Sodium	2–4 mmol/kg per day
Potassium	1–2 mmol/kg per day
Calcium	< 0.1 mmol/kg per day
Calcium in spot urine	
<1 year	< 1.0 mmol/mmol creatinine
>1 year	< 0.6 mmol/mmol creatinine

Table 28.9. Conversion table to standard international (SI) units

Component	Present unit	Conversion factor	SI unit
Erythrocytes	Per mm^3	1	10^6/l
Leucocytes	Per mm^3	1	10^6/l
Platelet count	$10^3/mm^3$	1	10^9/l
Calcium	mg/dl	0.2495	mmol/l
Phosphorus	mg/dl	0.3229	mmol/l
Creatinine	mg/dl	88.4	µmol/l
Urea nitrogen	mg/dl	0.357	mmol/l
Uric acid	mg/dl	59.48	mmol/l

Table 28.10. Normal values of creatinine clearance

Age group	Values	
Neonates	10–20	ml/min per 1.73 m^2
Infants	20–40–60	ml/min per 1.73 m^2
1–18 years	80–140	ml/min per 1.73 m^2

Table 28.11. The Schwartz formula

$$\text{GFR (ml/min/1.73 m}^2) = \frac{\text{Body length (cm)} \times k}{\text{Serum creatinine (mg/dl)}}$$

Table of k	
Low birth weight infants <1 year	0.33
Term infants <1 year	0.45
Children 2–12 years	0.55
Girls 13–18 years	0.55
Boys 13–18 years	0.70

Comment: The Schwartz formula enables simple and rapid estimation of GFR without urine collection. It is established in pediatric nephrology and widely used for daily routine (see Chap. 21)

28.3.3 Clearance (C)

The general clearance formula is U/P×V, where U and P indicate urinary and plasma (serum) concentrations of a substance, and V is urinary volume. Determination of creatinine (crea) clearance is important and roughly equals the glomerular filtration rate (GFR):

$$C_{crea}(\text{ml/min/1.73m}^2) = \frac{U_{crea} \times V(\text{ml in 24 h}) \times 1.73}{P_{crea} \times 24{\times}60 \times BSA(m^2)}$$

28.3.4 Fractional Excretion

Calculation of fractional excretion (FE) makes it possible to study certain tubular functions. "Fractional" means relative to creatinine. Most frequently, the FE of sodium (FE_{Na}) is calculated. For calculation, simultaneous determination of creatinine and of sodium in the serum and in spot urine is needed. FE_{Na} is helpful to distinguish prerenal failure from intrinsic renal failure.

$$FENa(\%) = \frac{Una \times Pcrea \times 100}{Pna \times Ucrea}$$

28.4 Radiologic Data

28.4.1 Sonography

Body height and body weight influence renal size and volume. In addition, as characteristics of a population may be of value, the data depicted here are valid in most situations, but some populations may require special growth charts (Kasiske and Umen 1986). The kidney volume is calculated using the formula:

$$\text{Kidney volume (ml)} = L \times W \times [(D1 + D2):2] \times 0.523$$

where L is bipolar length, W is width, D1 is longitudinal depth, and D2 is transverse depth. Tables 28.12–28.13 and Figures 28.3–28.7 show important measures on sonography.

28.4.2 Voiding Cystourethrography and Intravenous Urography

A formula-derived estimation of bladder capacity (BC) is shown in Table 28.14. Data of BC obtained during VCUG are compared with formula-derived BC in Figure 28.8. The normogram for renal measurements on intravenous urography is shown in Figure 28.9.

Table 28.12. Urinary bladder wall thickness

Bladder volume (ml) = L × W × [(D1 + D2) : 2] × K	
Bladder wall thickness (upper limit of normal)	
Almost empty bladder	5.0 mm
Full bladder	3.0 mm

(L = length, W = width, D1 = longitudinal depth, D2 = transversal depth, K = correction factor). The factor K ranges from 0.5 to 1.1 depending on the form of the bladder (Knorr et al. 1990)
Comment: Bladder volume measured on ultrasound evaluation reflects the current filling of the bladder, which does not necessarily equal the maximal or functional bladder capacity. Measurement of residual urine after voiding seems to be appropriate and 3D US can significantly improve the accuracy of the results (Riccabona et al. 1996). Bladder wall thickness should be measured at a significant filling of the bladder. There is a linear relationship between bladder filling and bladder wall thickness. The cut-off point of 3–5 mm seems to be independent of age and gender and is also valid in adults (Jéquier and Rousseau 1987; Manieri et al. 1998)

Table 28.13. Resistive index (RI)[a]

Age (years)	Mean RI (upper limit of normal)
1–3	0.68 (0.80)
3–6	0.66 (0.75)
6–13	0.64 (0.72)
13–16	0.64 (0.70)

[a] RI is calculated by the formula RI= $(V_s–V_d)/V_s$, where V_s is maximal systolic flow velocity and V_d is end-diastolic flow velocity.
Comment: Determination of RI is the most common measure giving information on renal perfusion and on vascular resistance. Several renal arteries must be checked for correct interpretation. RI is angle-independent, but influenced by factors such as heart rate, cardiac output, blood viscosity, and medications such as vasopressor support. Thus, pathologic values should be compared to values of other arteries to exclude systemic changes. A side difference of RI may indicate unilateral renal disease

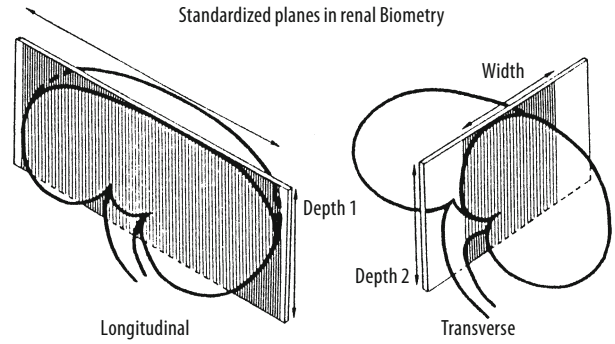

Fig. 28.3. Correct planes for measurement of renal size. According to Dinkel et al. (1985).
Comment: Exact measurement of real maximal length and diameters of the kidneys is of utmost importance. Most inaccuracies derive from measurements taken in a slightly oblique or displaced section

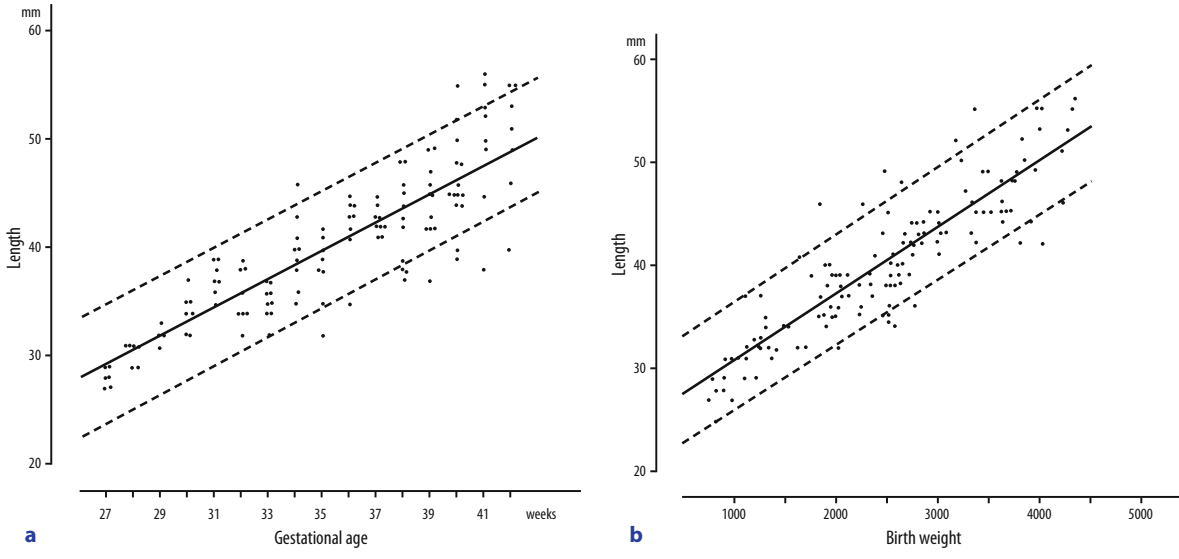

Fig. 28.4. Kidney length related to (**a**) gestational age and (**b**) birth weight in term and preterm neonates. From Chiara et al. (1989)

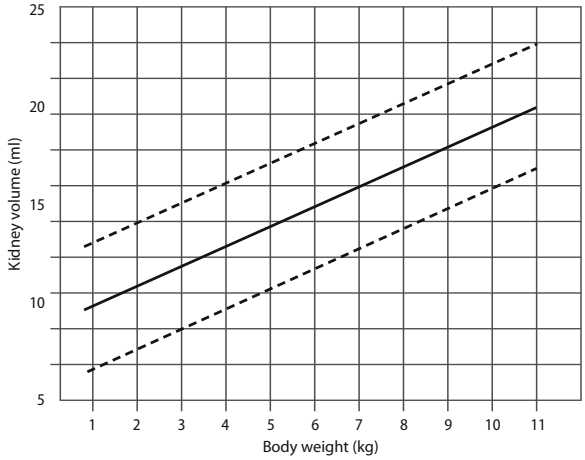

Fig. 28.5. Kidney volume of neonates and infants related to body weight (mean±2 SD is shown). Modified from Peters et al. (1986)

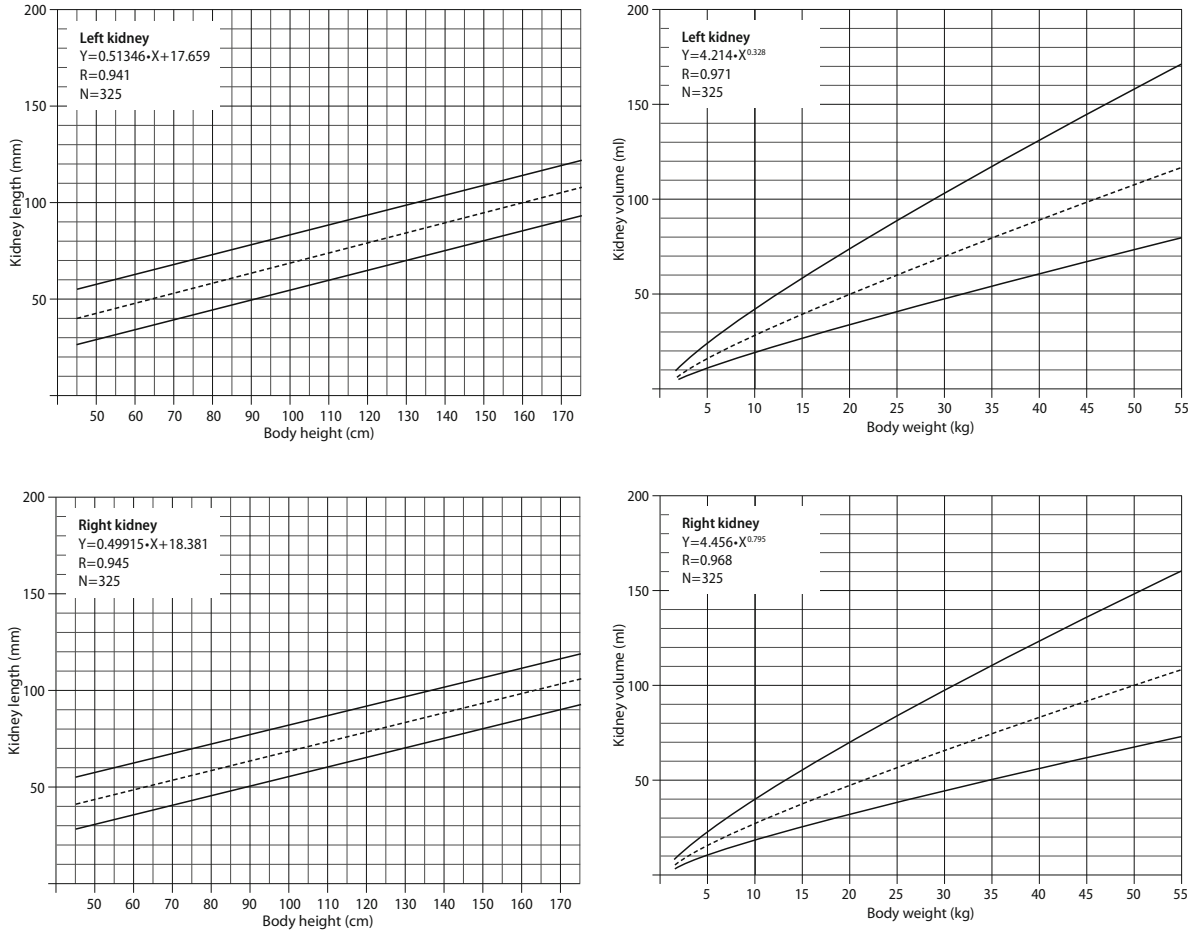

Fig. 28.6. Growth charts for kidney length and volume. From Dinkel et al.

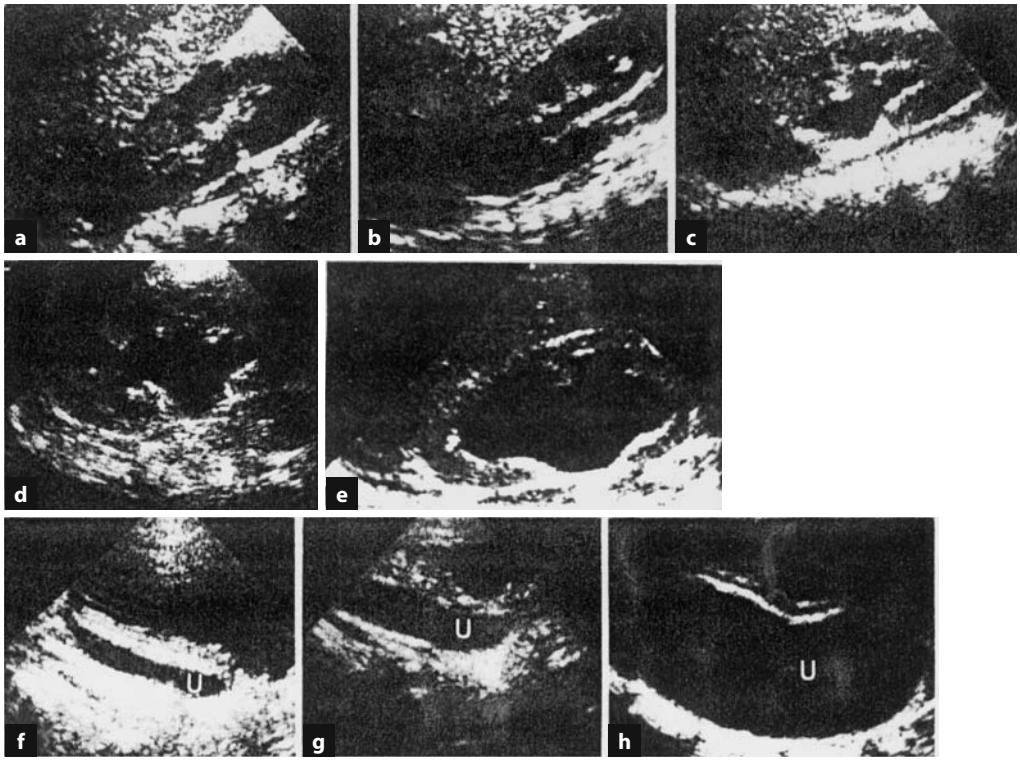

Fig. 28.7a–h. Grading system for hydronephrosis: **a** grade 0: closely apposed central renal echo complex; **b** grade 1: slight separation of the central renal echo complex; **c** grade 2: further dilatation of the renal pelvis, a single or a few calices are visible; **d** grade 3: dilated renal pelvis, all calices are fluid filled, normal thickness of renal parenchyma; **e** grade 4: as in grade 3, but thinning of the renal parenchyma over the calices. **f–h** Grading system for hydroureter: **f** grade 1: ureter dilated less than 7 mm; **g** grade 2: ureter 7–10 mm; **h** grade 3: ureter greater than 10 mm (from Fernbach et al. 1993).
Comment: This grading system was introduced to standardize the degree of hydronephrosis primarily in neonates with prenatally recognized hydronephrosis and to allow comparison between institutions. As calyceal distention depends on urine production, standardized and optimized hydration is crucial. In addition to the grading, accurate measurement of pelvic, calyceal, and ureteral diameters is mandatory and must be given with a precise description of calyceal and forniceal morphology

Table 28.14. Bladder capacity (BC)

BC (ml) = (age in years + 2) × 30
BC (ml) = (30 × age in years) + 60
(Both formulas are identical)
Bladder capacity in children with myelodysplasia
BC (ml) = (24.5 × age in years) + 62

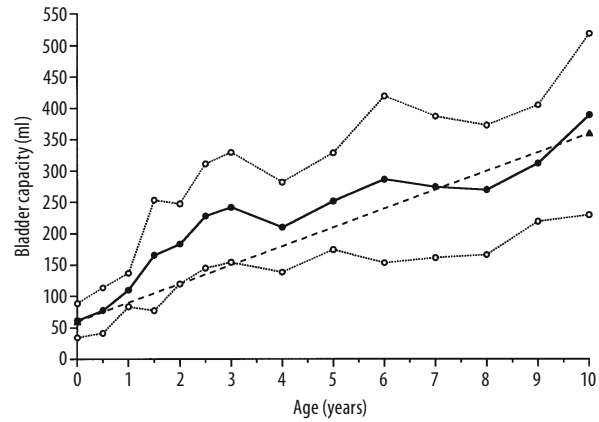

Fig. 28.8. Bladder capacity (*BC*) (mean ±1 SD) during childhood. The *dotted line* represents the formula-derived estimation of BC. Data obtained from Zerin et al. (1993).
Comment: The above-mentioned formula seems to underestimate mean BC during the first few years of life. This may reflect the normal development of BC, but could be influenced by bladder training to reach continence. Children with myelodysplasia seem to have a BC approximately 20%–25% lower than neurologically intact children (Palmer et al. 1997)

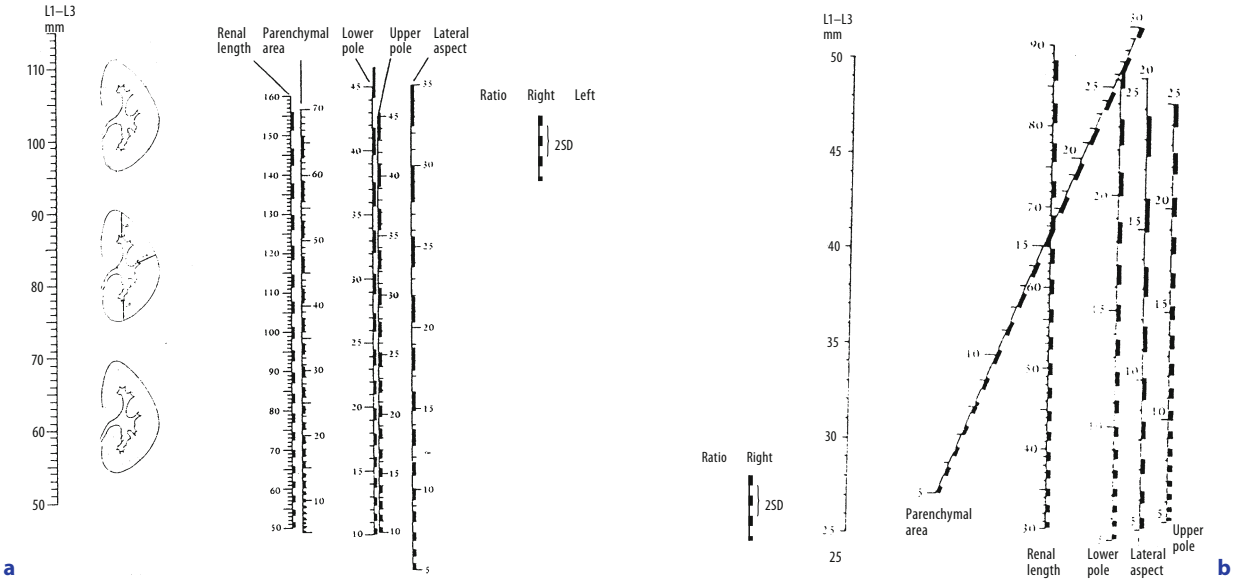

Fig. 28.9a,b. Normogram for renal measurements on intravenous urography (*IVU*). **a** L1–L3 distance between 50 and 115 mm; **b** L1–L3 distance between 25 and 50 mm (from Claesson et al. 1981).
Comment: For decades IVU was the single reliable method to detect renal scarring and has proven its value even in international studies. Nowadays, DMSA (and ultrasound) seems to have replaced IVU for this purpose (Stokland et al. 1998). Yet both investigations are reported to be rather complementary and not competitive in detecting renal scarring (Smellie 1995). MR urography could replace IVU in the future, but standardization is not yet available (Borthne et al. 1999). Despite these considerations, IVU remains a reliable and inexpensive investigation for small institutions or for countries with limited resources. Therefore, the Claesson normogram is of value even nowadays

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Gadolinium and Nephrogenic Systemic Fibrosis

29

Michael Riccabona, Øystein Erlend Olsen, Michael Claudon, Jean-Nicolas Dacher, and Richard Fotter

There is a new and important disease that needs to be considered for MR imaging of the paediatric urogenital tract: nephrogenic systemic fibrosis (NSF). This entity, also known as nephrogenic fibrosing dermopathy or scleromyxedema-like illness of renal disease, is a recently defined condition with potentially deleterious outcome; its aetiology is not completely understood yet. A common factor is a kidney disease with renal insufficiency (on dialysis) or patients with liver transplants. Another factor observed in the majority of cases is gadolinium (Gd) administration, though there are patients suffering from NSF without previous known Gd exposure. Additional risk factors are metabolic acidosis and inflammatory and post-operative conditions.

This recently discovered and described association caused reconsideration of our use of Gd-based MR contrast material in general and particularly in children. It furthermore induced a series of investigations and observations that showed other risk factors in addition to renal insufficiency defined as decreasing glomerular filtration rate (GFR) and in particular with a GFR less than 30 units (ml/min/1.73m^2): repeated and/or high Gd dose, and linear Gd compounds such as Omniscan® and Magnevist®. However, there are a few reports of patients developing NSF after exposure to cyclic Gd derivates, too. Though most affected patients are adults, a few cases of NSF in children have been described – at present these are only partly linked with Gd exposure. This new insight urges the paediatric radiology community to consider NSF when performing MRI and MRU in children. Consecutively, recom-0mendations on how to proceed with this issue are frequently discussed.

The FDA, pharmaceutical groups and companies, as well as a number of major hospitals have issued recommendations that suggest a careful use of Gd-based contrast agents, particularly in infants (due to the physiological immature kidney in the first weeks of life). Additionally, some drugs (i.e. Magnevist® and Omniscan®, both linear Gd compounds) have had their approval for use in the first year of life withdrawn. Thus, in order to address the potential risk of Gd administration in children and considering present knowledge and the current discourse, some precautions and measures have been recommended.

- Reconsider the need of MR. Sophisticated ultrasound investigations can probably solve a number of problems answering the therapeutically relevant questions, thus making MR unnecessary. Therefore particular interest should be taken in establishing a high-standard paediatric ultrasound service with dedicated and well-educated examiners and adequate equipment, available 24 h on all 7 days of every week.
- There are situations where the use of contrast-enhanced MR should be reconsidered; sometimes unenhanced MR scans using new techniques can solve the problem. Some queries may be answered by (even un-enhanced) CT, but with

M. Riccabona, MD
Professor, Department of Radiology, Division of Pediatric Radiology, University Hospital Graz, Auenbruggerplatz 34, 8036 Graz, Austria
J.-N. Dacher, MD, PhD
Professor, Department of Radiology, University Hospital of Rouen, 1, Rue de Germont , 76031 Rouen, France
Ø. E. Olsen, PhD
Consultant Paediatric Radiologist, Great Ormond Street Hospital for Children NHS Trust, London WC1N 3JH, UK
M. Claudon, MD
Professor, Department of Radiology, Children's Hospital, Centre Hospitalier Univ. de Nancy Brabois, Rue du Morvan, 54511 Vandoeurvre Les Nancy, France
R. Fotter, MD
Professor and Chairman, Department of Radiology, Head Division of Pediatric Radiology, University Hospital, Medical University Graz, Auenbruggerplatz 34, 8036 Graz, Austria

this technique the significant radiation burden as well as the risk of contrast-induced nephropathy (CIN) has to be considered carefully.

- Precautions have to be taken to identify patients at increased risk for NSF, i.e. patients with renal disease and patients after or expecting liver transplantation. Some centres primarily rely on patient history and clinical data; other centres ask for a recent blood sample to prove normal creatinine (as often also done for contrast-enhanced CT). Estimated GFR in children may be calculated as: the height of the child (cm) × 33/serum-creatinine (μg/l).
- In all patients with a potential renal disease or impaired renal function as well as in patients with inflammatory conditions and acidosis, GFR measurements or estimates should be performed and – if below 30 – the indication for contrast-enhanced MR should be reconsidered and discussed on an individual level. Tight collaboration with the attending nephrologists is advisable in patients with increased NSF risk. If (estimated) GFR is between 30 and 60, Gd should be administered with caution. In any case, patients and their parents have to be informed about the potential risk, and an informed consent should be obtained prior to the investigation.
- Particularly in infants and children with an increased risk for NSF, only macro-cyclic Gd compounds should be used as they are more stable and presently are considered to have a lower risk of inducing NSF.
- As repetitive applications potentially leading to a high cumulative systemic Gd dose appear to be an important risk factor, reduction of repeated investigations and basically single-dose techniques should be promoted. The cumulative Gd dose of a patient should be recorded and noted, e.g. in the patient's file, and a thorough follow-up – particularly in risk patients – over a longer period of time should be established.
- Supportive measures for preventing NSF are balancing acidosis, hydration and improvement of renal function prior to administration. However, all of these measures – particularly dialysis – do not guarantee full protection.
- However, all this should not lead to an "overcautious" behaviour. We believe that one should never deny a child a well-indicated examination with relevant therapeutic or prognostic value.

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List of Contributors

Fred E. Avni, MD, PhD
Professor and Chairman
Department of Medical Imaging
Erasme Hospital
808 Route de Lennik
1070 Brussels
Belgium

Gabriele Benz-Bohm, MD
Professor
Birresborner Strasse 40
50935 Cologne
Germany
formerly
Department of Radiology
Division of Pediatric Radiology
University of Cologne
Kerpenerstrasse 62
50924 Cologne
Germany

Hervé Brisse, MD
Department of Radiology
Institut Curie
Service de Radiodiagnostic
26, Rue d'Ulm
75005 Paris
France

Ann Marie Cahill, MD
Head, Division of Interventional Radiology
The Children's Hospital of Philadelphia
34th Street & Civic Center Boulevard
Philadelphia, PA 19104
USA

Marie Cassart, MD, PhD
Department of Medical Imaging
Erasme Hospital
808 Route de Lennik
1070 Brussels
Belgium

Cécile Cellier, MD
Department of Pediatric Radiology
University Hospital of Rouen
1, Rue de Germont
76031 Rouen
France

Michael Claudon, MD
Professor, Department of Radiology
Children's Hospital
Centre Hospitalier Univ. de Nancy Brabois
Rue du Morvan
54511 Vandoeurvre Les Nancy
France

Frank Collier, MD
Department of Urology
University Children's Hospital Queen Fabiola
Avenue JJ Crocq 15
1020 Brussels
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Department of Radiology
Institut Gustave Roussy
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94800 Villejuif
France

Jean-Nicolas Dacher, MD, PhD
Professor, Department of Radiology
University Hospital of Rouen
1, Rue de Germont
76031 Rouen
France

Nash Damry, MD
Department of Medical Imaging
Children's Hospital Queen Fabiola
Avenue JJ Crocq 15
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Belgium

Veronica Donoghue, FRCR, FFR, RCSI
Consultant Pediatric Radiologist
Department of Radiology
Children's University Hospital
Temple Street
Dublin 1
Ireland
and
National Maternity Hospital
Holles Street
Dublin 2
Ireland

Richard Fotter, MD
Professor and Chairman
Department of Radiology
Head of Division of Pediatric Radiology
University Hospital
Medical University Graz
Auenbruggerplatz 34
8036 Graz
Austria

Ingmar Gassner, MD
Section of Pediatric Radiology
University of Innsbruck
Medical School
Anichstrasse 35
6020 Innsbruck
Austria

Theresa E. Geley, MD
Section of Pediatric Radiology
University of Innsbruck
Medical School
Anichstrasse 35
6020 Innsbruck
Austria

Isky Gordon, FRCP, FRCR, FRCPaed
Professor of Paediatric Imaging
Institute of Child Health
30 Guilford Street
London, WC1N 1EH
UK
and
Honorary Consultant Radiologist
Child Health Consultant Radiologist
Great Ormond Street Hospital for Children
London, WC1N 3JH
UK

J. Damien Grattan-Smith, MBBS
Department of Radiology
Children's Healthcare of Atlanta
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Atlanta, GA 30342
USA
and
Department of Radiology
Emory University School of Medicine
Atlanta, Georgia
USA

Michelle Hall, MD
Department of Nephrology
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Melanie P. Hiorns, MBBS, MRCP, FRCR
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NHS Trust
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UK

Michael E. Höllwarth, MD
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Department of Pediatric Surgery
University Hospital Graz
Auenbruggerplatz 34
8036 Graz
Austria

Bernd Hoppe, MD
Professor, Department of Pediatrics
Division of Pediatric Nephrology
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Kerpenerstrasse 62
50924 Cologne
Germany

Khalid Ismaïli, MD, PhD
Department of Pediatric Nephrology
University Children's Hospital Queen Fabiola
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Richard A. Jones, PhD
Department of Radiology
Children's Healthcare of Atlanta
1001 Johnson Ferry Road
Atlanta, GA 30342
USA
and
Department of Radiology
Emory University School of Medicine
Atlanta, Georgia
USA

Christopher Kuhn, MD
Department of Radiology
Mercy Hospital
144 State Street
Portland ME 04101
USA

Christoph J. Mache, MD
Department of Pediatrics
Division of General Pediatrics
University Hospital Graz
Auenbruggerplatz 30
8036 Graz
Austria

Anne Massez, MD
Department of Medical Imaging
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1070 Brussels
Belgium

Clare A. McLaren, DCR(R)
Clinical Specialist Radiographer
(Interventional Radiology and Cardiology)
Great Ormond Street Hospital for Children
London, WC1N 3JH
UK

Sylvia Neuenschwander, MD
Department of Radiology
Institut Curie
26, Rue d'Ulm
75005 Paris
France

Øystein Erlend Olsen, PhD
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Great Ormond Street Hospital for Children
NHS Trust
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UK

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Loschgestrasse 15
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Germany

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Division of Pediatric Radiology
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8036 Graz
Austria

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Division of General Pediatrics
University Hospital Graz
Auenbruggerplatz 30
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Austria

Sabine Rudnik-Schöneborn, MD
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der RWTH Aachen
Pauwelstrasse 30
52074 Aachen
Germany

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Department of Urology
Erasme Hospital
808 route de Lennick
1070 Brussels
Belgium

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Department of Pediatric Nephrology
University Children's Hospital Queen Fabiola
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1020 Brussels
Belgium

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Professor, Department of Radiology
Division of Pediatric Radiology
University Hospital Graz
Auenbruggerplatz 34
8036 Graz
Austria

Gundula Staatz, MD
Professor, Department of Radiology
Division of Pediatric Radiology
University of Erlangen-Nürnberg
Loschgestrasse 15
91054 Erlangen
Germany

Richard B. Towbin, MD
Radiologist–in–Chief
Phoenix Children's Hospital
1919 East Thomas Road
Phoenix, Arizona 85016
USA

Klaus Zerres, MD
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