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Nuclear Medicine in Pediatric Nephro-Urology: An Overview

Iosif Mendichovszky, MD, PhD, FRCR,* Bernardita Troncoso Solar, MD,† Naima Smeulders, MB, Chir MA, MD, FRCS (Paeds),† Marina Easty, MBBS, MRCP, FRCR,‡ and Lorenzo Biassoni, MSc, FRCP, FEBNM‡

In the context of ante-natally diagnosed hydronephrosis, the vast majority of children with a dilated renal pelvis do not need any surgical treatment, as the dilatation resolves spontaneously with time. Slow drainage demonstrated at Tc-99m-mercaptoacetyltriglycine (MAG3) renography does not necessarily mean obstruction. Obstruction is defined as resistance to urinary outflow with urinary stasis at the level of the pelvic-ureteric junction (PUJ) which, if left untreated, will damage the kidney. Unfortunately this definition is retrospective and not clinically helpful. Therefore, the identification of the kidney at risk of losing function in an asymptomatic patient is a major research goal. In the context of renovascular hypertension a DMSA scan can be useful before and after revascularisation procedures (angioplasty or surgery) to assess for gain in kidney function. Renal calculi are increasingly frequent in children. Whilst the vast majority of patients with renal stones do not need functional imaging, DMSA scans with SPECT and a low dose limited CT can be very helpful in the case of complex renal calculi. Congenital renal anomalies such as duplex kidneys, horseshoe kidneys, crossed-fused kidneys and multi-cystic dysplastic kidneys greatly benefit from functional imaging to identify regional parenchymal function, thus directing further management. Positron emission tomography (PET) is being actively tested in genito-urinary malignancies. Encouraging initial reports suggest that F-18-fluorodeoxyglucose (FDG) PET is more sensitive than CT in the assessment of lymph nodal metastases in patients with genito-urinary sarcomas; an increased sensitivity in comparison to isotope bone scans for skeletal metastatic disease has also been reported. Further evaluation is necessary, especially with the promising advent of PET/MRI scanners. Nuclear Medicine in paediatric nephro-urology has stood the test of time and is opening up to new exciting developments.
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Introduction

Nuclear Medicine has been a well-established component of the diagnostic workup of several pediatric nephro-urological clinical conditions for at least 40 years. Despite vast technological advances in radiology over the last half century, the functional information provided by radionuclide studies remains a cornerstone for the management of many pediatric diseases.

Nephro-urology constitutes the bulk of the workload of a pediatric nuclear medicine unit. This is due to the relative frequency of urinary tract infections (UTIs) and the variety of congenital renal anomalies, such as hydroureteronephrosis, nowadays detectable with antenatal ultrasound, and the increasing incidence of acquired conditions, such as renal calculi, which sometimes may require further evaluation with a functional study.

A major advantage for the use of Nuclear Medicine in pediatric nephro-urology is that these techniques do not require sophisticated pieces of equipment, a single-head

*Department of Radiology, University of Cambridge and NIHR Cambridge Biomedical Research Centre, Addenbrooke's Hospital, Cambridge, UK.
†Department of Urology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK.
‡Department of Radiology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK.
Address reprint requests to Lorenzo Biassoni, MSc, FRCP, FEBNM, Department of Radiology, Great Ormond Street Hospital for Children NHS Foundation Trust, London WC1N 3JH, UK. E-mail: Lorenzo.Biassoni@gosh.nhs.uk

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gamma camera being sufficient for almost the entirety of pediatric examinations. Sedation or general anesthesia is almost unnecessary and, in the case of dynamic renography, it can actually be detrimental due to its effect on diuresis. Central to successful pediatric radionuclide studies are human and environmental factors, in particular a team of child-friendly radiographers or technicians (specially trained in pediatric nuclear medicine practice), who know how to interact with the child and family, winning their trust and confidence and ensuring that the child is relaxed and cooperative on the gamma camera couch during the test. Special skills in venepuncture are also essential, as is an appropriately decorated nuclear medicine unit that helps relieve fear and anxiety in the child, often associated with hospital visits.

Radionuclide renal scintigraphy encompasses several nuclear medicine investigations: dimercaptosuccinic acid (Tc-99m-DMSA) renal scintigraphy, mercaptoacetyltriglycine (Tc-99m-MAG3), or diethylenetriaminepentaacetic acid (Tc-99m-DTPA) dynamic renal scintigraphy and radionuclide micturating cystography (direct and indirect radionuclide cystography). These techniques, together with ultrasonography (US), fluoroscopic micturating cystogram (MCUG) or MRI, and occasionally CT, of the renal tract, provide functional data for the diagnosis and management of children with suspected genitourinary tract problems, contributing to a holistic morphofunctional assessment of the pediatric urinary tract.

The framework for each of the renal scintigraphy procedures has been published and revised by both the European and North American (NA) societies (EANM and SNMMI, respectively) in their corresponding guidelines.[1-7] Comprehensive highly informative reviews on different aspects of pediatric nuclear medicine have also been published in the past 10 years.[8-10]

Nuclear medicine examinations play a well-established role in the diagnostic algorithm of the different pediatric nephro-urological conditions. However, long-term studies on their prognostic value are desperately required. For example, we still do not know the risk of long-term complications (hypertension, chronic renal failure, and complications in pregnancy) of one, two, three, or multiple and bilateral renal scars. We can determine the function and drainage of a hydronephrotic kidney with a pelvic-ureteric junction (PUJ) anomaly and we currently know that less than 40% of these need surgery to prevent deterioration of renal function; however, we still need to find a reliable way to identify those kidneys at risk of losing function if left untreated. We can accurately perform an acute DMSA study during a febrile UTI to determine whether the renal parenchyma is involved, but we do not know whether it is possible to avoid a catheter cystogram in a child with a normal acute DMSA.

This article reviews the practice of dynamic and static renal scintigraphy and its clinical applications in the pediatric population. In addition, a section on the different clinical conditions has been added to present the scintigraphic techniques in clinical context, in comparison to the other available radiological examinations. This demonstrates how combining these imaging modalities can contribute to the patient's overall management.

Patient Preparation

Preparation for the procedure starts during the clinic appointment, where the reason for requesting the investigation and the examination itself are explained to the parents and child. Once a request form has been generated, a nuclear medicine practitioner assesses the clinical data supplied by the referrer and justifies the medical exposure to radiation (in the UK under the Ionizing Radiation [Medical Exposure] Regulations, IR(ME)R—Employer's Procedures). As part of the justification process, the clinical history (including information related to the structural renal abnormalities that may result in the need for additional views), ultrasound data, and previous radionuclide imaging should be reviewed. The importance of the justification process cannot be emphasized enough, as young children are much more sensitive to radiation than adults and all alternative diagnostic tests yielding equivalent information with less or no radiation burden should have been considered.

The parent and child should receive an appointment letter well in advance of the day of the examination containing detailed information on the procedure, including the waiting time between tracer injection and image acquisition, the probable duration of the scan and the need for adequate oral hydration of the child before getting to the department. Hydration should take into account that an increased oral intake of fluids might be needed in hot weather and this should also be briefly explained to the family in the clinic.[11,12]

A cooperative child should be encouraged to empty his or her bladder before the injection to reduce the need to void during the acquisition; this is essential for diuretic studies since a full bladder may delay upper tract emptying.[11-13] If the test involves administration of furosemide or bladder catheterization, these additional interventions should be fully explained as part of the informed consent process.

On the day of the test, as well as throughout and after completion of the examination, the parent(s) and child should feel that their emotional and physical needs have been considered in a friendly departmental environment and with the teamwork of trained staff, including booking staff, receptionists, nurses, and technicians or radiographers. The injection room and the gamma camera room should be uncluttered, welcoming, and give the impression of a safe environment for both child and parent. This can be achieved by mural and gamma camera decorations, the availability of toys for different age groups, small rewards (stickers) for cooperative behavior, books, warm lighting, music, and video projection capabilities that can be successfully used to distract the child and ensure his or her cooperation.[11] Departmental staff should have a positive and friendly attitude toward the child and parent, making them feel actively involved, reassured, and part of the team. The child should remain the central focus throughout the entire procedure, but the parent should be made aware that he or she offers the best form of

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comfort and security for the child and his or her cooperation can greatly contribute to the success of the examination.[11]

Anesthetic cream can be applied to relieve the discomfort of the tracer injection, and the 60-minute wait for the cream to have its effect can be used to ensure good hydration. When necessary, an ultrasound can be performed during this interval. Tracer injection can be performed either through a cannula (which also allows the administration of furosemide during dynamic renal scintigraphy) or a fine butterfly needle (gauge 23-25 according to child's age). Regardless of the chosen access method, great care should be taken when injecting the tracer to avoid extravasation. Administration of radioactivity beyond what is essential should be avoided and the amount of radiopharmaceutical to be injected should be optimized to give the desired diagnostic information at the cost of minimal radiation burden. Recommendations on administered activities for a number of pediatric nuclear medicine examinations have recently undergone harmonization by the European and NA societies. Calculation of the injected activity is now straightforward either through the EANM or SNMMI website or the EANM Dosage Card Calculator.[14,15]

Drug sedation is very rarely used, as adequate preparation, analgesia, environmental distractions, and team communication with the parent(s) and child help reduce anxiety and assist in obtaining adequate immobilization of the child during the procedure.[13,16] Sandbags, Velcro straps on either side of the child or a vacuum cushion can also be used as external aids for comfortable, yet effective, immobilization. Many of the pitfalls and limitations encountered in pediatric radionuclide studies can be avoided by gaining the patient's and family's cooperation, limiting the child's movements (by employing distraction techniques and immobilization devices) and using an optimal technical setup for image acquisition.[17]

These factors, combined with the full integration of the radionuclide study with complementary radiological investigations, will result in a complete morphofunctional assessment of the pediatric renal tract, thus aiding clinical management.

Static Cortical Renal Scintigraphy

The European procedure guidelines for Tc-99m-DMSA renal scintigraphy were initially published in 2001 and updated in 2011, whereas similar NA guidelines were initially published in 1997 and updated in 2003 (currently version 3.0).[5,7] Tc-99m-DMSA scintigraphy is currently the investigation of choice in the assessment of renal parenchymal integrity, and provides the most reliable information on differential renal function (DRF). Tc-99m-DMSA is used for the detection of focal renal parenchymal abnormalities, acute pyelonephritis, postinfective renal sequelae, renal congenital anomalies (duplex kidney, hypoplastic or dysplastic kidney, horseshoe kidney and crossed fused renal ectopia), and for confirmation of a nonfunctional kidney, such as the multicystic dysplastic kidney.[5,18,19]

Tc-99m-DMSA is bound to plasma proteins, cleared from the blood stream by tubular absorption and retained by the renal cortex. Renal uptake is dependent on renal blood flow, glomerular filtration, and megalin- and cubilin-mediated endocytosis in the proximal tubule from the glomerular filtrate.[20,21] The NA and European dose harmonization process recommends a minimum administered activity of 18 MBq (0.49 mCi), gradually increasing it in older children according to body weight (EANM Dosage Card Calculator).[14,15]

Optimum quality images are acquired at 2-3 hours after tracer injection, when the renal cortex has taken up 40%-65% of the injected radiopharmaceutical. Late images (between 4 and 24 hours) may be useful for quantitation of split renal function when some tracer still remains within a dysplastic renal collecting system, thus interfering with the evaluation of the split renal function. Images should be acquired with the child in a supine position, as close to the collimator surface as possible (ideally on a customized perspex table), to improve image quality. Posterior and posterior oblique views (additional anterior views for horseshoe or ectopic pelvic kidneys) should be acquired using a low-energy, high-resolution or ultra-high-resolution (± pinhole) collimators. Pinhole collimators can improve image resolution and contribute to better detection of renal scarring; however, they can distort anatomy and lengthen acquisition time, with the potential of image degradation by motion artefacts.

In an older and cooperative child, the European and NA guidelines recommend acquiring at least 300,000-500,000 counts (or a 600-second image) for the posterior view, and at least 350,000 counts (or a 600-second image) for the posterior oblique views. For younger and less cooperative children, the count number can be reduced, with at least 250,000 counts (or a 600-second image) acquired for the posterior view and 200,000 counts (or a 600-second image) for the posterior oblique views. The acquisition matrix should be 128 × 128 or 256 × 256. If pinhole views are required, the guidelines advocate 100,000-150,000 counts for better detection of small cortical defects. In most cases, high-quality static planar images are sufficient for an accurate diagnostic assessment, but a SPECT acquisition, with the possible addition of a low-dose CT (where such a scanner is available), can be useful in complex cases, such as crossed fused renal ectopia and complex renal stones.[22,23] Recent studies have suggested Tc-99m-DMSA scintigraphy for predicting dilating vesicoureteral reflux (VUR) in young children with febrile UTI; but so far, only limited (and sometimes conflicting) data are available in the literature.[24-29]

Data processing and reporting steps are generally straightforward, but can sometimes be challenging in duplex or horseshoe kidneys. Regions of interest (ROIs) are drawn around each kidney, with a further ROI defined for background subtraction. In children with normal kidney size and position, a reliable background-corrected DRF is calculated using the arithmetic mean from the posterior view; whereas in children with ectopic or very large kidneys, the differential function has to be calculated with the geometric mean. Horseshoe kidneys are better defined when imaged anteriorly to detect the connecting bridge or isthmus of renal tissue anterior to the spine; however, a posterior view should also be acquired.

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Image interpretation should consider several pitfalls, such as normal variants (pear-shaped kidney, fetal lobulation, and kidney axis rotation), ectopic kidneys, crossed fused ectopia, the influence of motion, high background activity, activity in the renal collecting system, and tracer contamination.[17] The DMSA images should ideally be assessed with the benefit of renal ultrasound images, if available.

Dynamic Renal Scintigraphy

Over its more than 40-year history, dynamic radionuclide renography has become an indispensable technique in the functional assessment of both adult and pediatric patients with nephro-urological conditions. Although initially suffering from significant local variability, the technique has been standardized and it has become increasingly popular in the clinical assessment of patients with hydronephrosis. The technique and interpretation have been summarized in recent guidelines and reviews.[1,30,31] The most recent (2011) guideline gives recommendations for estimating two indicators of renal function: the relative renal clearance (DRF) and the renal excretion of the tracer.[1] It recommends that DRF estimation should be undertaken between 1 and 2 minutes after tracer injection (with appropriate corrections for background and intrarenal and extrarenal vascular components), whereas renal excretion can simply be evaluated by inspecting the dynamic renal images and with tracer transit quantification techniques.[32-34]

Dynamic radionuclide renography is performed using tubular extraction tracers (I-123-hippuran), Tc-99m-MAG3 and Tc-99m-ethylenedicysteine (Tc-99m-EC), or Tc-99m-DTPA, the only glomerular filtration–dependent radiopharmaceutical. As tubular tracers have greater renal extraction than Tc-99m-DTPA (resulting in improved kidney-to-background ratio), they are preferred for DRF estimation and indirect cystography in children. Tc-99m-DTPA is preferred when glomerular filtration rate estimation (with blood sample analysis) is required.[1]

The most commonly used radiopharmaceutical is Tc-99m-MAG3, a highly protein-bound agent that is removed from the plasma by uptake in the proximal renal tubules.[35-37] Its renal extraction fraction is 40%-50%, more than twice that of Tc-99m-DTPA, making it an excellent clearance agent for patients with suspected obstruction and impaired renal function.[21,37] The clinical indications for the procedure include all uropathies that require evaluation of drainage (pelviureteric and vesicoureteric stenosis, bladder outlet obstruction, bladder dysfunction, complicated duplex kidneys, renal functional assessment posttrauma, asymmetrical renal function, chronic pyelonephritis—with an indirect cystogram performed at the end of the renogram, and renal transplantation).[1,2] The recommended administered activities have not been fully harmonized—although the EANM Dosage Card Calculator recommends 15 MBq (0.41 mCi) minimum injected Tc-99m-MAG3, the NA guidelines suggest a minimum of 19 MBq (0.5 mCi) or, in some practices, 37 MBq (1 mCi).[2,14] The effective dose to a 5-year-old child is <1 mSv (0.54-0.82 mSv for Tc-99m-DTPA, 0.20-0.38 mSv for Tc-99m-MAG3, and 0.41-0.7 mSv for I-123-hippuran) and reduction of injected activity is advocated if renal function is impaired.[38-40]

Good hydration is essentially for a good-quality dynamic study. Some guidelines recommend intravenous hydration[2]; whereas in other parts of the world, oral hydration, starting a few hours before the renogram, is considered sufficient.[1]

Image acquisition is performed with a constant 10- or 20-second frame rate (10 second frames for quantification), upfacing low-energy general-purpose collimator, 128 ×128 and word (or byte) mode, with zoom adjusted to patient size and including the heart for processing purposes. Postmicturition views (at the end of the study and 50-60 minutes after tracer injection) are essential and they will help distinguish between a dilated nonobstructed and an obstructed renal tract. Although widely used in NA centers, bladder catheterization is not advocated by the European guidelines.[2] The minimum recommended duration of the study is 20 minutes.

Evaluation of Split Renal Function

The evaluation of split renal function has been standardized.[32] In the processing step, the ROIs should be generous, drawn on a summed image, and encompassing the entire kidney to avoid excluding some renal activity.[41-43] Background correction using rectangular, elliptical, or perirenal ROIs should be performed on all images or renogram curves, and the cardiac ROI, needed for quantification, should cover the hottest pixels over the heart on the very first two or three frames.[1] A 2-3 minute summed image of all the frames during the clearance or uptake phase should be created and the DRF assessed visually on the images and uptake curves, as well as calculated using either the integral method or the Patlak-Rutland plot method.[32,41,44-48]

The integral method calculates the mean value of the area under the background-subtracted renogram curves during a 1-2-minute period. This method has been shown reproducible and accurate in normal volunteers, with a difference of more than 5% representing a significant change.[41]

The Rutland-Patlak plot is a graphic representation of the split renal function; the slope of the fit curve represents the relative function of each kidney. In theory, this method is more accurate than the integral method because of the added correction of the intrarenal vascular component. However, it is also more prone to statistical errors in conditions with increased background activity, such as infants with immature renal function and patients with chronic kidney disease.

The evaluation of the split renal function using two independent methods constitutes a good quality control; both methods should give the same result (within 5% difference).

Evaluation of Drainage

The furosemide test was introduced in the late 1970s to help in differentiating between urinary outflow obstruction and urinary stasis due to a baggy collecting system.[49] Furosemide is injected at 20 minutes if the dynamic images show slow drainage: a dilated nonobstructed renal pelvis usually shows response with significant drainage, whereas an obstructed renal pelvis shows poor response to the diuretic. More

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recently, the "F0" technique has been introduced, with the diuretic injected together with the radiotracer: this shortens the time of acquisition and results in better drainage at the end of the renogram. Administration of furosemide 15 minutes before tracer injection is another possible technique, which allows starting the renogram under the full effect of furosemide.[50-54] Recommended furosemide doses are 1 mg/kg i.v. in infants and 0.5 mg/kg in children older than 1 year (20 mg maximum dose). One of the pitfalls related to drainage is the presence of a full bladder at the end of the renogram. Therefore, the insertion of a bladder catheter during the test has been recommended, especially in North America.[55] The European guidelines recommend instead the acquisition of a postmicturition view, after the child has been in upright position for at least 15 minutes and has emptied the bladder, acquired in the same way as the dynamic renography, so that it can be compared with it.[1]

The evaluation of drainage has been standardized, with several functional parameters being proposed. The output efficiency represents the amount of activity that has left the kidney, expressed in a percentage of what has entered the kidney.[56] The normalized residual activity is a parameter inversely correlated with output efficiency and describes the amount of activity remaining in the kidney at the end of the renogram.[57] These parameters are independent on the level of differential function and can be calculated at the end of the renogram as well as on the delayed postmicturition views.

For a long time, drainage has been estimated on the basis of the slope of the furosemide curve, a long T-half reflecting obstruction and a short T-half indicating good urinary outflow. This method is accurate only when drainage is good, but fails to differentiate poor drainage due to obstruction from poor drainage due to a dilated nonobstructed collecting system.

Lack of protocol standardization (especially for postmicturition images), tracer extravasation, motion, high background activity, bladder status, poor renal function, and degree of renal pelvic dilatation can all pose interpretation challenges.[17]

Renal Immaturity

When evaluating newborns and infants, nuclear medicine practitioners should recognize normal renal immaturity and its effect on the renal handling of radiotracers.[58] The glomerular filtration rate per unit of surface area in the newborn is approximately 30% of the adult rate. Depending on renal maturation, renal uptake of tracers may be lower in newborns than in older children and adults. In addition, intrarenal transit time and excretion of these tracers may be slow at this age. Background may be high throughout the study, reflecting slow plasma clearance of the tracer.

Radionuclide Micturating Cystography

Direct radionuclide cystography (DRC) is a catheter cystogram that entails administration of a small amount of Tc-99m-pertechnetate together with saline into the bladder. It is indicated in non–toilet-trained boys (usually less than 3 years of age), when a reassessment to look for persistent VUR after endoscopic or surgical treatment is required, once a baseline radiological MCUG has excluded posterior urethral valves. In girls, less than 3 years of age, it is used when the DMSA scan is abnormal and an US shows either a dilated ureter or pelvis. It can also be used in the diagnosis of familial reflux or in the serial evaluation of bladder dysfunction (neuropathic bladder) for VUR.[3,4,6]

As VUR is an intermittent phenomenon and it may only occur in the filling phase of the bladder, the advantage of DRC is that both the filling and micturition phases can be studied, increasing the chances of detecting VUR.[59-61] DRC may be undertaken in any child, but it has a limited role in low-lying or ectopic kidneys with ureteric dilatation. The main disadvantage is that it requires bladder catheterization (with all its associated risks and discomforts): this should be performed by an experienced operator under strict aseptic conditions and antibiotic prophylaxis.[3]

Imaging acquisition requires the administration of 20-40 MBq of Tc-99m-pertechnetate in 500 mL saline through the catheter for more than 10 minutes until full bladder capacity is reached and then the child is allowed to void. Dynamic posterior view frames are acquired at maximum 5 seconds per frame using a general-purpose collimator and 64 × 64 or 128 × 128 matrix. The radiation burden from the procedure is favorable compared to MCUG, although a recent publication has reported a lower radiation exposure from the fluoroscopic procedure when using state-of-the-art equipment and frame grab techniques.[62]

Indirect isotope cystography (IRC) is a completely physiological test in toilet-trained children used for the detection and follow-up of VUR and for the assessment of the effect of a full and empty bladder on the drainage from dilated upper tracts.[4] The advantage of this technique is that it allows a complete functional assessment of the urinary tract (including renal parenchymal integrity, split renal function, drainage, timing, and completeness of bladder emptying), it has a low radiation burden and it does not require bladder catheterization, which can be physically and emotionally traumatic for the patient.

The patient sits on a commode with the gamma camera centered posteriorly over the region of the bladder and kidneys. The patient voids into a urinal, a bedpan, or a jug. Precautions to reduce contamination of the equipment and the room must be taken. Recording is begun when the patient is ready to void and continues until the end of voiding. If the child has failed to void on the first attempt, or has voided incompletely, another cystogram can be acquired later on, until the bladder is empty, or VUR has been demonstrated. Repeated acquisitions increase the sensitivity for VUR.

The most common pitfalls in radionuclide micturating cystography are too early micturition, before the radiographer has commenced images acquisition (often because the child is not really toilet-trained), and a dilated renal collecting system with persisting urinary stasis from the immediately previous dynamic renography.[17] These can be mitigated by performing IRC in children who are continent and by furosemide administration before the start of the first IRC to clear the

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upper tracts.[17] Knowledge of the expected functional bladder capacity is useful for evaluation of VUR in children.

In the absence of bladder pathology such as bladder exstrophy-epispadias complex, the expected bladder capacity for age can be estimated by the formula 30 + (30 × age in years) for children older than 2 years[63] and 38 + (2.5 × age in months) for children younger than 2 years.[64]

Clinical Applications of Nuclear Medicine in Pediatric Nephro-Urology

UTIs and VUR

Background

Approximately 2% of men and 8% of women will develop a UTI at some point. Most UTIs in men occur at <3 months of age with prevalence 10 times less in circumcised men vs uncircumcised men in this age group. After 1 year of age, most UTIs occur in women.

Symptomatic UTI must be differentiated into upper tract infections, with lesions of the kidneys (acute pyelonephritis and pyelitis), and lower tract infections (acute cystitis). Upper UTI usually presents with high fever, flank pain or tenderness, malaise, irritability, leukocytosis, and bacteriuria, but there may be no clear indication that there is renal parenchymal infection. Lower UTI presents with voiding symptoms. However, it is often impossible to differentiate them or even to diagnose UTI, particularly in babies.[65]

Primary goal in the diagnosis of UTI and in the subsequent evaluation of the predisposing factors is to reduce the incidence of recurrent UTI and prevent acquired renal damage.

Imaging in UTI

The purpose of imaging is to detect pathologic malformations or risk factors that, if not diagnosed and managed appropriately, might lead to additional infections and ongoing parenchymal damage. Ultrasound, MCUG, and Tc-99m-DMSA scan are the core imaging examinations used. However, the use of these imaging techniques is variable with different approaches.

Ultrasound. Renal ultrasound can define kidney shape, length, echogenicity, and the presence of dilatations. US can also describe the bladder volume, bladder wall thickness and renal and bladder calculi, ureteric abnormalities, and adjacent pathology (such as collections). The disadvantages are the poor detection rate of parenchymal defects and VUR. In a series of children with their first febrile UTI,[66] 88% of patients had normal US findings (11.5% had dilated urinary tract and 0.3% renal calculi).

Renal Cortical Scintigraphy

"Acute" DMSA. A DMSA scan performed during the acute phase of a UTI can confirm the presence of acute pyelonephritis. The diminished uptake of Tc-99m-DMSA in areas of acute inflammation probably reflects both focal tubular cell dysfunction and ischemia.[67] DMSA scanning does not differentiate old from new lesions unless a previous examination exists. Acute DMSA imaging will confirm the diagnosis of acute pyelonephritis in patients with equivocal symptoms. The advantage of this approach is that in patients with normal acute DMSA, there is no probability of developing renal scarring. The sensitivity of Tc-99m-DMSA scintigraphy for the early diagnosis and localization of acute pyelonephritis reaches more than 90%.[68]

"Late" DMSA. If treated appropriately within 48 hours, acute pyelonephritis may resolve completely and scintigraphic images typically would become normal within 4-6 months. Alternatively, without adequate and early antibiotic treatment, a permanent cortical scar may develop. A mature cortical scar is usually associated with contraction and apparent loss of volume of the involved cortex. This may manifest as cortical thinning on ultrasound, flattening of the renal contour, or a wedge-shaped defect. The scintigraphic pattern of a maturing scar on DMSA varies according to the severity of the UTI, the location of the lesion, the age of the patient, as well as the rate of growth of the surrounding normal renal tissue. The guidelines issued by the National Institute for Health and Clinical Excellence (NICE) recommend a DMSA scan in children with recurrent or atypical UTIs, 4-6 months after the infection.[69] Some investigators recommend renal scintigraphy 6-12 months after the first febrile UTI to detect the formation of scarring, which would require follow-up.[70,71]

The prognostic value of renal scars needs to be further evaluated. A study from Sweden showed that a cohort of children with renal scarring followed up for 1-26 years had no increased likelihood of developing hypertension in comparison to the general population.[72] However, a recent study showed increased blood pressure in a cohort of patients with normal renal function and UTI associated renal damage.[73] Other studies have reported a significantly increased risk of hypertension and chronic kidney disease in children with bilateral scarring.[73-75]

Although ultrasound is the favoured imaging method in children, MRI, and occasionally CT, may have a role when intrarenal abscesses are suspected or when there is a delayed response to antibiotic treatment.[76,77]

Vesicoureteral Reflux

VUR refers to the retrograde flow of urine from the bladder into the ureter and, usually, into the collecting system of the kidney. In most individuals, VUR results from a congenital anomaly of the vesicoureteric junction (VUJ); whereas in others, it results from high-pressure voiding secondary to posterior urethral valves, neuropathic bladder, or voiding dysfunction. Its management is one of the most controversial topics in pediatric urology.

The clinical importance of VUR consists in its association with pyelonephritis and its contribution to reflux-related renal scarring. VUR is a not an uncommon urological anomaly in children, with an incidence of nearly 1%. However, the incidence of VUR is much higher among children with UTIs (30%-50%, depending on age). Among all children with UTIs, boys are more likely to have VUR than girls (29% vs 14%);

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boys also tend to have higher grades of VUR diagnosed at younger ages, although their VUR is more likely to resolve.[78]

Grading of reflux is based on the work of the International Reflux Study Group and includes VUR from grade I-V (Fig. 1). Not all types of VUR carry the same risk of contributing to renal scarring. For example, dilating VUR will increase the risk of developing acute pyelonephritis and renal scarring. A significant percentage (10%-40%) of children with symptomatic VUR have evidence of renal scarring, resulting from either congenital dysplasia or acquired postinfectious damage, which may have a negative effect on growth and general well-being.[79]

High-grade VUR is associated with a higher risk of renal scarring and recurrent UTIs.[80] Lower grade VUR is associated with a lower risk of renal scarring and may vary from examination to examination. VUR varies also with bladder volume, voiding or filling, patient position, and level of anxiety. Renal scarring occurs in approximately 10% of children with prenatal hydronephrosis and VUR[81,82]; whereas in patients with lower urinary tract dysfunction (LUTD), scar rate may increase up to 30%.[83] Renal scarring may adversely affect renal growth and function, with bilateral scarring increasing the risk of chronic kidney disease. Follow-up studies have shown that 10%-20% of children with chronic pyelonephritis and VUR develop hypertension or end-stage renal disease.[84]

The spontaneous resolution of VUR is dependent on age at presentation, sex, grade, laterality, mode of clinical presentation, and renal tract anatomy.[85] In several Scandinavian studies, the complete resolution rate for high-grade VUR has been reported in excess of 25%, which is higher than the resolution rate for VUR detected after infancy.[86]

High-grade VUR, age at diagnosis, and male sex have been shown to be risk factors for renal parenchymal damage. In this group of patients, it is mandatory to discover reflux early to prevent renal damage.[87]

Management of a Patient With VUR. Controversy persists over the optimal management of VUR, particularly the choice of treatment (observational, medical, endoscopic, or open or laparoscopic surgical), and the timing of treatment. The main goal in management is the preservation of kidney function by minimizing the risk of pyelonephritis. By defining and analyzing the risk factors for each patient (ie, age, sex, reflux grade, LUTD, anatomical abnormalities, and kidney status), it is possible to identify those patients with a potential risk of UTIs and renal scarring.

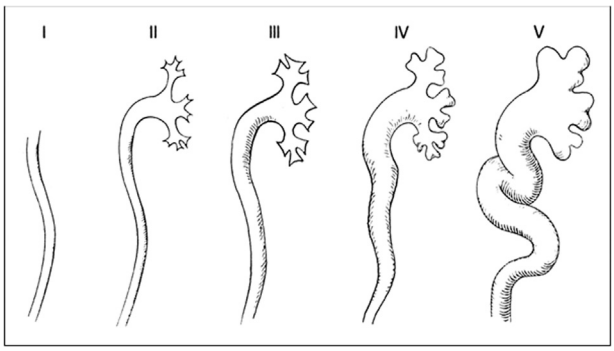

Figure 1 The International Reflux Grading System. Grade I: Contrast only refluxes into a normal caliber ureter. Grade II: The contrast fills a non-dilated ureter and pelvicalyceal system. Grade III: Mild dilation of ureter and pelvis. The sharp angles on the fornix of the calyx are blunted. Grade IV: There is moderate dilation of the ureter and pelvis, with distortion of the calyceal anatomy. Grade V: There is severe dilation and tortuosity of the ureter, severe dilation of the pelvis, and clubbed calyces.

There are two main approaches to the management of VUR: conservative and surgical. In all patients with secondary VUR, management of the underlying anomaly should be considered before treating the VUR.[88,89]

Conservative Approach. The conservative approach includes watchful waiting, intermittent or continuous antibiotic prophylaxis, and bladder rehabilitation in those with LUTD. The objective of conservative therapy is prevention of febrile UTI and it is based on the understanding that VUR resolves spontaneously, mostly in young patients with low-grade reflux. Resolution is nearly 80% in VUR grades I and II and 30%-50% in VUR grades III-V within 4-5 years of follow-up.[85] Furthermore, VUR does not damage the kidney when patients are free of infection and have normal lower urinary tract function. There is no evidence that small scars can cause hypertension, renal insufficiency, or problems during pregnancy.[72] Circumcision during early infancy may be considered as part of the conservative approach as it is effective in reducing the risk of infection in normal children.[90]

Regular follow-up with ultrasound imaging is part of the conservative management. In all cases of febrile breakthrough infections despite prophylaxis, intervention should be considered.

Recent prospective randomized controlled trials have shown that the role of prophylaxis in children with no VUR or with grade I or II VUR is questionable, as the rate of recurrent symptomatic UTIs was similar in the group with prophylaxis and in the group with no therapy.[80,91-93] For children with VUR grade III-V, who have a much higher rate of recurrent UTI[80,94-96] prophylaxis would be appropriate, particularly in girls. There are no data on the optimal duration of prophylaxis.

Surgical Correction of VUR

Endoscopic Treatment. VUR can be corrected by endoscopic injection of a bulking agent at the VUJ or by surgical reimplantation.

The subureteric injection of bulking materials is currently the first therapeutic option in children with VUR and recurrent infections. The injected agent elevates the ureteral orifice and the distal ureter, so that coaptation is increased. This results in narrowing of the lumen, which prevents reflux of urine into the ureter while still allowing its antegrade flow. With the availability of biodegradable substances, endoscopic subureteric injection has become an alternative to long-term antibiotic prophylaxis and surgical intervention.

The reported resolution rate is 83% for endoscopic therapy after a single injection (American Urological Association guidelines).[97] Imaging with a MAG3 dynamic renogram and an indirect cystogram is helpful at follow-up, usually 6-9 months after the procedure to demonstrate the resolution of VUR and

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to show possible complications (most commonly obstruction at the VUJ).

Ureteric Reimplantation. Surgical treatment of VUR in the form of open or laparoscopic- or robot-assisted ureteric reimplantation is considered whenever endoscopic treatment has been unsuccessful or is inappropriate. It is an alternative in children older than 1 year, in patients with persistent VUR after 2-3 years of follow-up, in patients in whom decreasing renal function is observed, or in patients presenting with recurrent UTI despite adequate antibiotic therapy.

Imaging VUR. Imaging is the basis of diagnosis and management of VUR. The aim in detecting VUR and initiating a prophylactic treatment is to prevent long-term complications.[98-101]

Micturating Cystogram. MCUG is the most widely used radiological examination for the study of the lower urinary tract and especially of VUR. It is the only method that allows precise grading of VUR and the detection of intrarenal reflux.[102-106] MCUG should always be performed in infant boys to exclude posterior urethral valves but less so in girls. The main disadvantages of the technique are the risk of infection, the need for retrograde filling of the bladder, and the possible deleterious effect of radiation on children. In recent years, tailored low-dose fluoroscopic MCUG has been used for the evaluation of VUR in girls to minimize radiological exposure.

Direct Radionuclide Cystogram. DRC is a sensitive technique to diagnose VUR. The advantages of DRC are the extremely low radiation dose and the ability to continually screen for VUR during both the bladder filling and emptying. This unique ability of the DRC is the reason for its high sensitivity in picking up reflux, with higher sensitivity and higher temporal resolution than MCUG.[107] The disadvantages include the insertion of a bladder catheter and poor anatomical detail. As mentioned previously, this technique is used in the follow-up of non–toilet-trained boys who have already had a MCUG to exclude posterior urethral valves and in non–toilet-trained girls when detailed anatomy of the bladder and ureters is not required.

Indirect Radionuclide Cystogram. IRC represents an attractive alternative to conventional cystography, as previously noted, especially when following patients with reflux because of its lower dose of radiation and lack of catheterization. Disadvantages are poor image resolution and difficulty in detecting lower urinary tract abnormalities.[108]

Imaging Strategies in Children With UTI and VUR

The use of diagnostic imaging tests in a child with UTI is still a matter of controversy. In much of the literature, considerable attention has been placed on the diagnosis of VUR with the conclusion that the only useful examination after a first febrile UTI is a MCUG.[66] Most researchers would agree that detecting VUR with associated dilatation is important, given the increased risk of scarring and the ability to intervene medically and surgically in this condition.[94,95] Because the presence and the severity of VUR can be reliably determined only by MCUG, these groups advocate performing MCUG in all children after a first febrile UTI.[66]

Alternatively, the so-called "top down" approach is adopted in many countries. This imaging strategy aims to reduce the number of MCUGs. A DMSA scan is performed during the acute phase of the UTI. If this is positive, the chance of dilating VUR is high and a MCUG will be performed. If the acute DMSA is negative, a MCUG is not performed. Some studies have shown a strong correlation between clinically relevant VUR with dilatation and abnormal scintigraphic scans[24,109-113]; however, other studies have disputed this approach.[28,114]

Other groups feel reluctant to adopt the "top down" approach, because the result of an acute DMSA would not change the duration and the form of delivery of antibiotic therapy. Previous studies have shown that longer courses (7-14 days) of intravenous antibiotic therapy, compared to shorter courses (3-4 days) followed by oral treatment,[115-117] resulted in no difference in rates of subsequent renal damage, irrespective of the duration of therapy. Oral antibiotics have been compared to a regimen including 3 days of intravenous cefotaxime followed by 11 days of oral cefixime alone with no difference in outcome.[118]

In 2007, the National Institute for Health and Clinical Excellence (NICE) in the UK published a set of guidelines on UTIs.[69] The main philosophy of these guidelines is to concentrate imaging studies in the child clinically at risk of developing renal damage following an episode of infection. Children with a nonfebrile UTI do not need any initial imaging of their urinary tract. Children with recurrent attacks of lower UTI might need imaging that focuses on bladder function. Children with febrile UTI can be divided into two groups—children at high risk and at low risk of developing renal damage. If the UTI is atypical or they have recurrent UTI, the children fall in the high-risk category and need an US 6 weeks after the UTI and a DMSA scan at 4-6 months. High-risk children younger than 6 months require a renal tract ultrasound during the acute infection followed by a DMSA 4-6 months after infection and a MCUG. Children between 6 months and 3 years of age do not require any imaging if they respond to antibiotic treatment within 48 hours and are classified as low risk. Low-risk children need no imaging if they do not develop a second infection (which brings them into the high-risk group). A MCUG is not routinely performed unless there is evidence of dilatation on US, poor urine flow, non-*Escherichia coli* UTI, or family history of VUR. In children older than 3 years, a DMSA scan is performed at 4-6 months only if the child has had recurrent UTI.[69]

The NICE guidelines have been criticized by studies that show that a significant number of abnormalities, especially high-grade VUR, may be missed if the guidelines are followed[119-121]; the authors of these studies state that the NICE guidelines should be used with full awareness of their limitations.

The Italian Renal Infection Study Group has proposed an alternative imaging approach in young children with a first febrile UTI.[71] Their results in a group of 300 children aged <2 years with a first febrile UTI suggest that the benefit of performing US at diagnosis and acute DMSA is minimal. They recommend a specific role for US, namely for children in whom it was not performed antenatally, in those with poor

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response to antibiotics, and in those with complicated or recurrent infections. A good-quality US during the prenatal screening will detect the small proportion of congenital abnormalities. In their study, the MCUG yielded positive results for VUR in only 22% of children, with only 4 children showing grade IV or V VUR. They concluded that the use of MCUG in 300 children to detect four cases of severe VUR, which could be diagnosed after a second UTI, is not justified. The acute DMSA was positive in 54% of cases and showed changes compatible with acute pyelonephritis. However, this did not change management as no significant difference has been demonstrated between administering antibiotics intravenously or orally.[122] Therefore, the authors question the value of routinely performing acute DMSA scans in children with a first febrile UTI. This study emphasizes the importance of renal scarring, rather than VUR, as the main prognostic factor for a patient's outcome after a UTI. The detection of VUR was poorly correlated with subsequent renal scarring in children with a first febrile UTI, with no evidence that its diagnosis improved outcomes or warranted alteration in management. Those patients with scarring on late DMSA (done at 12 months after the UTI) and those with recurrent febrile UTI should be considered for further investigation. The effect of such renal scars on the development of long-term complications has yet to be determined.

Conclusion

Controversy still exists in imaging and management of UTI. Long-term cohort studies with sufficient statistical power that establish the prognostic significance of renal scarring are needed. Ultrasound of the kidneys and bladder is always the first-line investigation to assess dilatation and secondary signs of reflux such as intermittent collecting system dilatation, uroepithelial thickening in the collecting system and ureters, and evidence of scarring.

Antenatally Diagnosed Hydronephrosis

Antenatally diagnosed hydronephrosis may have several causes, of which the most common is the PUJ anomaly (PUJA).[123]

PUJ Anomaly

Dilatation of the upper urinary tract still presents a significant clinical challenge in determining which patient may gain benefit from therapy. Owing to the widespread use of US during pregnancy, antenatal hydronephrosis is often found. The challenge in the management of dilated upper urinary tracts is to decide which child can be observed, which one should be managed medically and which one requires surgical intervention.

Diagnostic Imaging: Definition of Obstruction. An antenatally diagnosed hydronephrosis is normally monitored with ultrasound after birth. On ultrasound, the anteroposterior diameter of the renal pelvis, calyceal dilatation, kidney size, thickness of the parenchyma, cortical echogenicity, ureters, bladder wall, and residual urine are assessed. The sonographic diagnosis of a PUJA depends on the demonstration of a dilated renal pelvis in the absence of any dilation of ureter or bladder. It should particularly be suspected when moderate (10-15 mm) or severe (>15 mm) dilation is seen.[124] Hydronephrosis has been classified in different grades (Fig. 2).

The pathologic basis of the PUJA is an abnormal muscle arrangement with an anomalous collagen collar at the level of the PUJ. In vast majority of cases an antenatally diagnosed hydronephrosis resolves spontaneously as a manifestation of physiological change during development.[125,126]

Not all children with antenatally diagnosed hydronephrosis require assessment with dynamic renography. This is reserved for children with a moderately to very dilated renal pelvis (>12 mm in anteroposterior diameter) and with calyceal dilatation. For an infant, 6 weeks of age is generally accepted as a reasonable time to undergo first renal scintigraphy. As mentioned earlier, Tc-99m-MAG3 provides superior diagnostic images and is the agent of choice for renal scintigraphy in children.[127]

It has been noted that the vast majority of cases of antenatally diagnosed hydronephrosis resolve spontaneously.[125,128] In approximately 25%-30% of cases, the PUJA in an asymptomatic patient causes a significant resistance to urinary outflow with backward pressure on the renal tubules. This causes stretching of the parenchyma and, in the long run, loss of kidney function if the condition is left untreated.[128] These are the kidneys that get obstructed.

Unfortunately this definition of obstruction is retrospective and unhelpful. Contrary to the adult practice where an obstructed kidney declares itself with symptoms, the vast majority of children with antenatally diagnosed hydronephrosis are asymptomatic, including the majority of those who will develop obstruction to urinary outflow. Therefore, it is difficult to clinically identify the kidney at risk.

Slow drainage and urinary stasis at the level of the PUJ does not necessarily mean obstruction.[129] It may signify a condition of equilibrium, thereby there is a degree of resistance to urinary outflow, but not sufficient to cause a fall of renal function; with time and with maturation and growth of the excretory system, the PUJ stenosis may resolve. Therefore, it is important to consider that the previously widely accepted classification of the diuretic renogram curve patterns as no obstruction,

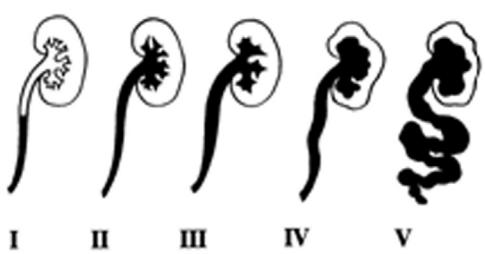

Figure 2 Classification of upper tract dilatation by the Society for Foetal Urology, based on the post-natal appearance of the renal pelvis, calyces and renal parenchyma. This classification system incorporates collecting system dilation with renal parenchymal findings. The grading system is a spectrum, with grade 1 demonstrating normal parenchymal thickness and only renal pelvis splitting, and grade 5 revealing distension of the renal pelvis and calyces.

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indeterminate, or obstruction[49,130] has been superseded by a better understanding of the urodynamics. A large renal pelvis may cause very slow drainage, with no significant deterioration in renal function and eventually spontaneous improvement.

In a young child with hydronephrosis, one should not arrive at the diagnosis of obstruction based on a single examination. A single study provides only a "snapshot" of a changing situation. Serial studies over time provide a better indication of the natural progression of renal dilatation and help determine the presence of an obstruction. Future deterioration of renal function cannot be predicted solely based on the findings of increasing dilatation on ultrasound, or a rising curve or a low differential function on diuretic scan.

The function of the hydronephrotic kidney will be affected by the severity of the PUJ stenosis. High pressure in the pelvicalyceal system can result in reduced renal blood flow and decreased cortical function. In the young, this can be reversed after relief of the urinary obstruction. Renal blood flow decreases rapidly with increased pressure in the pelvicalyceal system. This can be reversible for a period, but if increased pressure is long-standing, reduction in blood flow and function can become permanent.

It is usually possible to identify a single site of obstruction at the VUJ or the PUJ, but obstruction at both the PUJ and VUJ may be difficult to detect. Detection of the level of urinary stasis depends on adequate renal function and the presence or absence of dilatation of the pelvicalyceal system and ureter.[124]

In studies of hydronephrosis due to a severe PUJ stenosis, the affected kidney paradoxically may take up more tracer than the contralateral side (supranormal kidney). It is thought that the kidney with a tight PUJ stenosis develops transiently increased blood flow. Over time, renal function in an obstructed kidney will reduce.

Symptomatic obstruction (recurrent flank pain and UTI) and decreased split renal function at initial assessment are often used as absolute indications for surgery.

The recommendation is to perform an open, laparoscopic- or robotic-assisted pyeloplasty according to the standardized technique of Anderson and Hynes.[131] Open surgery remains the management of choice in neonate and young infants compared with a minimally invasive approach. In older children, the choice is more controversial but the laparoscopic approach continues to gain increasing acceptance.

Renal scintigraphy may help physicians in the follow-up of patients after surgery. Scintigraphy is usually performed 6-9 months after pyeloplasty. Young patients with moderately impaired DRF and patients diagnosed because of symptoms may have the greatest likelihood of a functional improvement.[132]

The Hydronephrotic Kidney at Risk. The identification of the hydronephrotic kidney at risk of losing function is still controversial, with different approaches to the management of the child.[133]

The degree of hydronephrosis in the postnatal period is important. Spontaneous resolution takes place in approximately 50% of the cases with mild hydronephrosis, whereas it is much less frequent in cases with more pronounced dilatation.[134] No intervention is required in most cases. It is more likely that the child will need surgery if the renal pelvis diameter is greater; however, a convincing demonstration that pyeloplasty is mandatory is missing. Some urologists have shown that a dilated renal pelvis may have a protective role on the kidney.[135]

Decreased split function at initial assessment is often used as an absolute indication for surgery, but this has been questioned in a prospective study with conservative follow-up.[136,137] Moreover, the overall impression is that improvement does not occur when surgery is performed because of initial decreased function. Very different is the sudden increase of hydronephrosis during follow-up, which indicates imbalance of a urodynamic equilibrium and the risk of renal deterioration.

A parameter thought to be diagnostically helpful is the renal cortical transit of the tracer, in other words the passage of tracer from the outer cortex to the medulla and collecting system. In a normal kidney, a rapid cortical transit is expected in the first minutes of the acquisition. It has been suggested that impaired cortical transit of tracer, with absence of activity in the subcortical structures of the kidney within 3 minutes of tracer injection, might be predictive of a significant improvement of function after pyeloplasty, or might represent a high risk of deterioration if surgery is delayed [138-140] (Fig. 3).

Conclusion. The identification of the antenatally diagnosed asymptomatic hydronephrotic kidney at risk of losing function is still the main clinical challenge. Slow cortical transit of tracer may be a helpful sign but larger studies are necessary to confirm this finding.

Megaureters and VUJ Anomaly

Fetal US has identified a greater prevalence of megaureter (ureteric diameter 47 mm) in the general pediatric population than previously thought. Megaureters are reported to occur in approximately 23% of neonates noted to have antenatal hydroureteronephrosis. They occur more often in men and more likely on the left side.[141]

Dynamic renography with Tc-99m-MAG3 is indicated to assess the cortical renal function and confirm the level of urinary hold up with a full and an empty bladder. It is worth noticing that in the case of VUJ anomalies with a dilated renal pelvis, the MAG3 renogram may show predominant or exclusive urinary stasis within the renal pelvis, with little or no significant urinary stasis within the dilated ureter. In this case, if the ultrasound shows a dilated ureter down to the level of the VUJ (and possibly more dilated at the distal end), the diagnosis of a megaureter is still likely, even if the dynamic renography has not demonstrated this. This is a well-recognized pitfall of renography in this condition (Fig. 4A-D).

Only 10%-20% of megaureters require surgical treatment, whereas the remainder may be monitored conservatively. The characteristic adynamic segment of the distal ureter just before its insertion into the bladder can either be cut using balloons at cystoscopy, or excised with subsequent reimplantation of the ureter.

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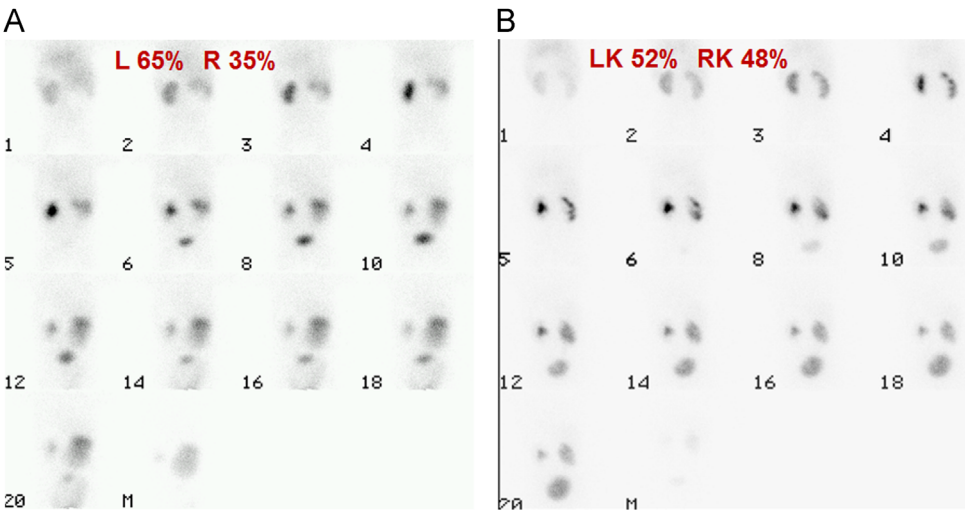

Figure 3 Three months' old boy, with an ante-natally diagnosed right hydronephrosis. A post-natal ultrasound showed a right renal pelvic diameter measuring 3.7 cm. The MAG3 renogram at diagnosis (**a**) shows a tilted right kidney with reduced function (35% contribution to total renal function) and slow drainage with hold up at the level of the PUJ. There is slow cortical transit of tracer, with activity demonstrated within the right renal pelvis only by 6-8 minutes (the normal left kidney shows activity in the renal pelvis by 3 minutes). The child had a right pyeloplasty. The follow up MAG3 renogram one year after surgery (**b**) shows significant improvement in the drainage of the right kidney. The right renal function has also significantly improved from 35% to 48%. The delayed cortical transit of tracer on the right suggested that the right kidney was at risk of losing function if left untreated, and correctly predicted functional improvement after surgery.

Nonobstructed Megaureters. Children with asymptomatic megaureters associated with a DRF in excess of 40% may be managed conservatively. If a functional study reveals adequate ureteral drainage, low-dose prophylactic antibiotics within the first year of life are recommended for prevention of UTIs, although there are no prospective randomized trials to evaluate this regimen.[142] Close follow-up every 3-4 months with ultrasound and antibiotic prophylaxis are warranted, especially in cases with significant dilatation (>1 cm ureteral diameter).[143,144] Megaureters with grades 0-2 hydronephrosis at diagnosis are likely to resolve between 12 and 36 months of age. Grades 3-4 hydronephrosis may take longer to resolve, up to 72 months.[144,145]

Obstructed Megaureters. In some clinical scenarios, surgical management is necessary: increasing hydroureteronephrosis, deteriorating renal function on scintigraphy, recurrent UTIs despite antibiotics, or presence of pain, pyonephrosis, or stones.

Traditionally, the surgical management of an obstructing megaureter has been via ureteric reimplantation with or without ureteral remodeling. Ureteral reimplantation has good results, with a success rate of 90%-96%.[146,147]

In general, follow-up investigations using US and radionuclide imaging are performed between 6 and 9 months after surgery. After the first follow-up, prophylactic antibiotics are usually stopped if the child is toilet-trained.

Renovascular Hypertension

Renal disease associated with hypertension can be caused by conditions that involve the renal arteries or the renal parenchyma. Renovascular disease (RVD) is an important but uncommon cause of hypertension in children, accounting for approximately 10% of cases.[148-150] Renal pathology is the cause of hypertension in more than 90% of children after 1 year of age. Less frequently, secondary hypertension may be caused by disorders of the endocrine, cardiovascular, or nervous systems. Radionuclide renal studies play an important role in the evaluation of hypertension in infants and children.

Fibromuscular dysplasia is the commonest cause of RVD in childhood, but other associations include neurofibromatosis type 1, Williams syndrome, and vasculitis, especially Takayasu disease. Middle aortic syndrome is a morphologic 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.[149,151]

Imaging

Noninvasive imaging alone cannot reliably exclude RVD as the cause of pediatric hypertension,[152,153] but may confirm or exclude an alternative pathology. Ultrasound is a simple first imaging test in a child found to have high blood pressure. It may detect small 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 normal ultrasound study does not exclude a single renal scar, renovascular pathology (especially within smaller intrarenal branches), or a small pheochromocytoma (especially if it is extraadrenal). If ultrasound has demonstrated Doppler abnormalities clearly suggesting RVD, it

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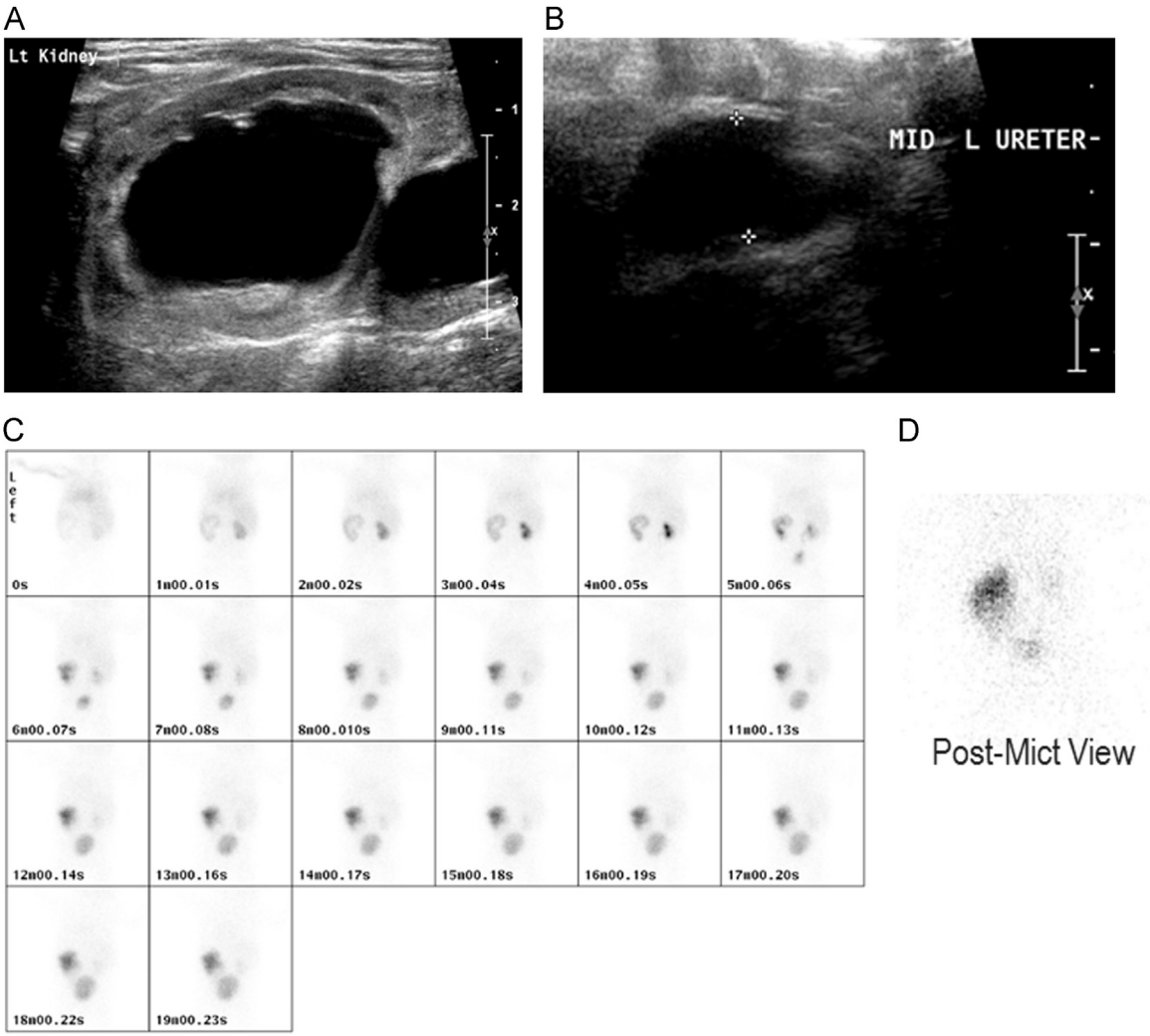

Figure 4 Two months' old boy, with left hydronephrosis. The ultrasound scan shows severe dilatation of the left renal pelvis and left ureter (A,B). A MAG3 renogram (C) shows a stretched left renal parenchyma with good tracer uptake and urinary stasis within the left renal collecting system at the level of the PUJ. The post-micturition view (D) shows persisting activity mainly in the collecting system, with no significant tracer seen in the left ureter. From the MAG3 renogram findings taken in isolation, a PUJ problem would have been suspected. However, taking the ultrasound findings into account, it is likely that this child has a problem at the level of the left VUJ. A retrograde contrast study confirmed a VUJ anomaly and the child had a left incisor balloon dilatation during cystoscopy with a JJ stent put in place. The MAG3 renogram has to be reported in conjunction with the ultrasound findings to avoid serious errors of interpretation.

is most appropriate to proceed directly to angiography. If this is not the case then further investigations are focused on confirming or excluding an alternative renal cause for the hypertension.

Some of the renal causes of hypertension, such as infarction, scarring, and posttraumatic lesions, are readily diagnosed by DMSA scintigraphy. 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 still be considered and a diagnostic angiogram may still be indicated.

Dynamic renal scintigraphy has been used in the diagnostic workup of renovascular hypertension,[154] especially before and after administration of an angiotensin-converting enzyme inhibitor such as captopril.[155-157] Although pre- and post-captopril scintigraphy has been suggested in the investigation of secondary causes of hypertension,[158] this technique is weak in bilateral or segmental disease, and its use in the diagnostic algorithm of renovascular hypertension is not routinely advocated.[159] The sensitivity and specificity of captopril renal scintigraphy for RVD are reported to be 59%-73% and 68%-88%, respectively.[160,161] Although detection of segmental abnormalities is sometimes possible with this technique,[162] the high prevalence of bilateral or branch artery RVD limit its usage in children.

For the time being, digital subtraction angiography is the cardinal investigation in the assessment of pediatric RVD due to its superior spatial resolution. In addition, digital subtraction angiography is the basis of endovascular intervention.[163] Renal DMSA scanning has a role in monitoring the cortical function of a kidney supplied by a functionally significant artery stenosis before and after revascularization procedures such as angioplasty.[158] A kidney supplied by a very stenotic renal artery can

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gain significant function after arterial dilatation with possible stenting at angiography.

Renal Vein Thrombosis

In neonates, renal vein thrombosis (RVT) is usually related to venous stasis secondary to shock, septicemia, or dehydration. The diagnosis may be suggested by the presence of oliguria, macroscopic hematuria, and proteinuria, with a clinically enlarged and hard kidney. RVT is also seen in infants of diabetic mothers and children with congenital heart disease. Nephrotic syndrome is a very frequent cause of large-vessel thrombosis because of urinary losses of antithrombin III, protein C, protein S, and other factors. The venous obstruction then leads to infarction and hemorrhage.

Although RVT is associated with low mortality, the outcome of renal function is not always good, so these patients require close clinical follow-up with serial sonography and a baseline DMSA scan at between 6 months and 1 year of age.[164] In severe cases, there may be apparent function of the involved side. A follow-up study may be useful to demonstrate the residual renal function after recovery. Radionuclide studies may reveal information of prognostic significance, with a normal study predicting a rapid and complete recovery. Dynamic renography is not indicated unless there are issues of impaired drainage.[127]

Renal Infarction

Renal infarction can occur in patients with cyanotic congenital heart disease, polycythaemia, atrial fibrillation, dehydration, or trauma. Aortic thrombosis and renal infarction are also well-recognized complications of prolonged umbilical artery catheterization. Treatment with thrombolytic agents may allow resolution of the clot and recovery of renal function in some cases. DMSA scintigraphy demonstrates focal perfusion defect (s) in the affected kidney(s).

Urolithiasis and Nephrocalcinosis

Urolithiasis and nephrocalcinosis (NC) are two patterns of calcification associated with the urinary tract. Urolithiasis is macroscopic calcification in the urinary tract causing renal calculi. Urinary calculi are composed of crystal aggregates, sometimes mixed with proteins. NC represents increased calcium content in the kidney, in the form of microscopic calcification in the tubules, tubular epithelium, or interstitial tissue of the kidney. NC is not a uniform entity, but rather a complication of various renal disorders, metabolic disturbances, or pharmacotherapy. Hypercalciuria appears to be the most common abnormality associated with NC.[165]

Urolithiasis in children is an increasingly common cause of morbidity and hospital admissions. Recent studies have shown that the incidence of urolithiasis in children has increased 6%-10% annually during the past 25 years.[166,167] No one factor accounts for this dramatic increase; this is likely due to a combination of genetic predisposition, socioeconomic conditions, and dietary intake. Metabolic risk factors in pediatric urolithiasis can be identified in 75%-84% of evaluated children.[168,169]

Urolithiasis may be related to hypercalciuria, hyperoxaluria, hypocitraturia, cystinuria, or hyperuricosuria. Additional risk factors for lithiasis include prematurity, UTI, urinary tract abnormalities, immobilization, chronic bowel disease, and neurologic disorders. Medications may be associated with an increased risk of nephrolithiasis, such as furosemide, vitamin D excess, vitamin C excess, topiramate, and zonisamide.

The most common symptoms of calculi are abdominal pain, sometimes clearly identifiable as colicky pain, vomiting, UTI, gross or microscopic nonglomerular hematuria and, more rarely, flank or loin tenderness or urinary retention. However, one in six children do not complain of any of these symptoms and their stones are detected unexpectedly on imaging.[170]

Renal calculi in children are treated by extracorporal shock wave lithotripsy (ESWL), percutaneous nephrolithotomy (PCNL), ureterorenoscopic retrograde intrarenal surgery and, less frequently, by open surgery or laparoscopy.

With PCNL, stones are removed directly from the renal collecting system using keyhole access into the pelvicalyceal system. PCNL is favoured in cases of renal stones of high density (Hounsfield Unit [HU] >1000 on CT kidneys ureters bladder—KUB), stones situated in a dilated renal pelvis or a calyx from which fragments are unlikely to clear after ESWL, or when the calculus is stuck in a calyceal infundibulum causing obstruction to urinary outflow.

ESWL is the preferred surgical technique in cases of less dense (HU $<$ 500), renal stones up to 2 cm in size, or in the presence of other comorbidities that preclude PCNL. This technique uses high-energy sound waves to break a stone into small pieces that can more easily travel through the urinary tract and pass urethrally.

Imaging

Urinary tract calcification and stones are usually easily diagnosed by US, abdominal radiographs, and low-dose CT KUB, although small stones may not be detectable even when their presence is strongly suggested. Urolithiasis and NC can coexist in the same patient and NC may be permanent even after eliminating the cause.

Most urinary tract calculi are visible on abdominal radiograph because of their calcium content, although fecal loading within the large bowel may obscure detail of the urinary tract and thus miss small calculi. A good-quality ultrasound and an abdominal radiograph are, therefore, complementary techniques.[171] CT is still commonly used to investigate suspected urolithiasis in children, as most institutions involved in acute pediatric care are adult-centered and thus influenced by adult-centered practices.[172] CT should be reserved for problem-solving or treatment planning, as it is more accurate in determining stone size and it also helps with the identification of ureteric stones.

Functional imaging plays a role in selected patients. DMSA scan or MAG3 renogram contributes little to the management of a patient with a subcentimeter parenchymal renal stone, with normal surrounding parenchyma visible on ultrasound.

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However, a DMSA scan is important in a child with renal stones complicated by UTI, particularly if recurrent, as it will show possible renal scarring of the surrounding renal parenchyma. A MAG3 with diuretic will demonstrate function and drainage of a kidney with a stone obstructing the infundibulum of a calyx or partially obstructing the renal pelvis.

A DMSA scan with planar and tomographic images, with SPECT images coregistered to a contemporaneous CT scan (acquired either on a SPECT/CT scanner or on a stand-alone CT scanner, with the images subsequently coregistered to the SPECT images) can be a helpful imaging technique to define the anatomy, determine the number and density of the stones, precisely localize the calculus in the renal collecting system, and to provide information on the function of the renal parenchyma adjacent to the stone, thereby guiding surgical decision-making (Fig. 5). It will also help differentiate NC from calculi and identify any possible ureteric stones with their associated risk of obstruction.

The latest CT scanners with pediatric-friendly protocols, minimize radiation levels to a fraction of that of a plain abdominal radiograph (0.056 vs 0.7 mSv) as well as allowing a very short acquisition time (only approximately 1.5 seconds), thereby avoiding the need for sedation or general anesthesia.

Congenital Renal Anomalies

Duplex

A duplex collecting system refers to a kidney with two pelvicalyceal systems, generally defined as the upper and lower moieties. If the kidney has two ureters that connect separately into the bladder (double ureters), it is considered a complete duplication. In contrast, in a partial or incomplete duplication (Y duplication), a common single ureter enters the bladder. A bifid system is a form of duplication with two pelvicalyceal systems joining before or at the PUJ (bifid pelvis).[173] The upper moiety ureter tends to insert more caudally and medially into the bladder than the normally inserting lower moiety ureter. The lower moiety ureter is often affected by VUR, whereas the upper moiety ureter is associated with a ureterocele and, therefore, may obstruct.

Ureteroceles are cystic dilatation of the distal segments of the ureters. This obstruction may lead to partial or complete loss of function of the upper moiety. The upper moiety ureter may also insert ectopically, such as in the vagina in a girl or below the bladder neck. If it is obstructed and thus atrophic and almost invisible on ultrasound, a girl may present with constant wetting. A careful high-quality ultrasound may find the cryptic upper moiety, or an MRI urogram may show the ureter and its ectopic insertion.

Functional imaging is very important. A MAG3 renogram may confirm the diagnosis of a duplex kidney, clarifying the ultrasound findings. The diagnosis of a duplex on MAG3 may be suspected by differential tracer uptake in the upper and in the lower moiety; the tracer distribution in the collecting system during the drainage phase of the renogram can also suggest the presence of a duplex if tracer is seen in two complete separate collecting systems not merging into a common pelvis.

If the upper moiety of a duplex is obstructed by a ureterocele, it may show very poor or no function on DMSA or MAG3. It may not be visible on functional imaging and, therefore, the ultrasound should be scrutinized for the presence of a duplex (Fig. 6).

VUR is the most common anomaly associated with renal duplex systems. VUR may occur in both moieties, but it is much more frequent into the lower moiety. The ureter draining the lower moiety of a duplex kidney opens more laterally in the bladder. This type of VUR may be associated with renal damage of the corresponding lower pole. A MAG3 renogram with an indirect cystogram can provide accurate information on the cortical function of each moiety of the duplex kidney, as well as show the presence of VUR. VUR into a lower pole still has a potential of spontaneous resolution just as VUR into a single collecting system can spontaneously resolve.[174-176] If the child is not toilet-trained, reflux may be seen during the dynamic renography itself, if the child voids in

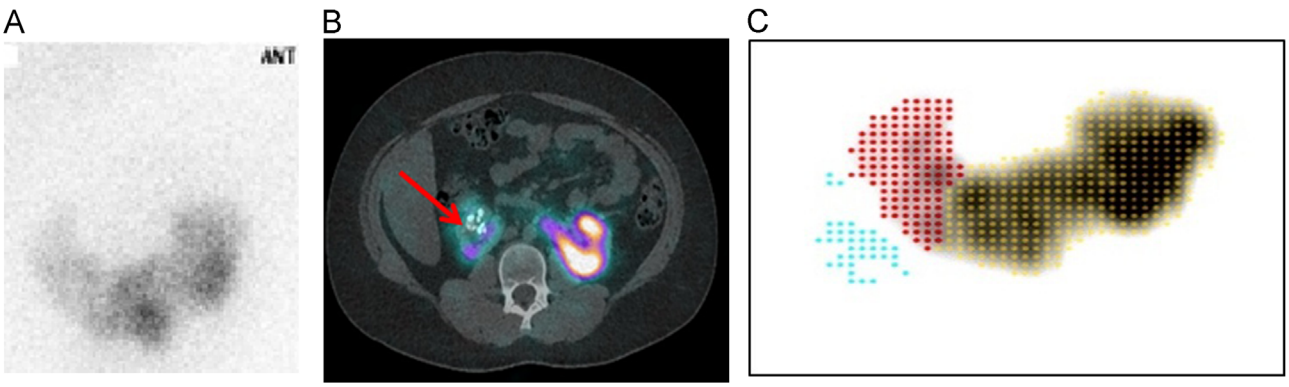

Figure 5 DMSA planar images with SPECT CT acquisition in an 11 year old boy with a horseshoe kidney and renal calculi in the right moiety. The referring clinical team had planned PCNL on the right moiety to extract the stones. The planar images (anterior view, A) show reduced tracer uptake in the right moiety of the horseshoe kidney. The SPECT CT study (B) shows multiple stones within the right moiety, with very poor function of the renal parenchyma adjacent to the calculi. Using a volumetrix algorithm (C), the contribution of the right moiety to total renal function was calculated as 13%. As a result, the urologists decided to surgically remove the right moiety of the horseshoe kidney, rather than performing a PCNL.

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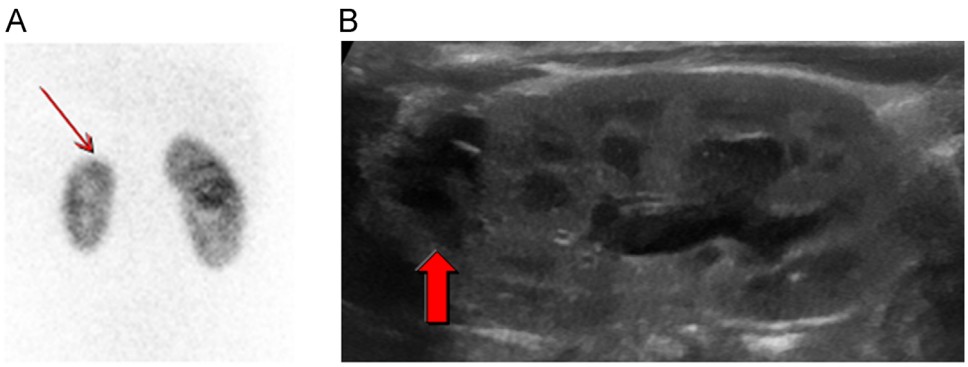

Figure 6 Three months' old boy with febrile UTI. The DMSA scan (A) shows a smaller functioning renal parenchyma on the left in comparison to the right and contributing 36% to total renal function (right kidney 64%) with no renal scarring. However, the ultrasound scan (B) shows a left duplex kidney with a smaller upper moiety, with very thin renal cortex, and a dilated collecting system. With the ultrasound findings in mind, it is important to report the DMSA scan as showing a left duplex kidney with a non-functional upper moiety and a normally functioning lower moiety.

the nappy (Fig. 7). In this case, a catheter cystogram may be avoided. Reflux in an obstructed upper moiety, draining via a dilated and tortuous ureter due to the presence of a ureterocele is very uncommon; however, it is demonstrated in approximately 30% of duplex kidneys following puncture of the ureterocele.

The treatment depends on the function of the affected moiety and the presence of symptoms, and it varies from conservative management with or without prophylactic antibiotics, to surgery. 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

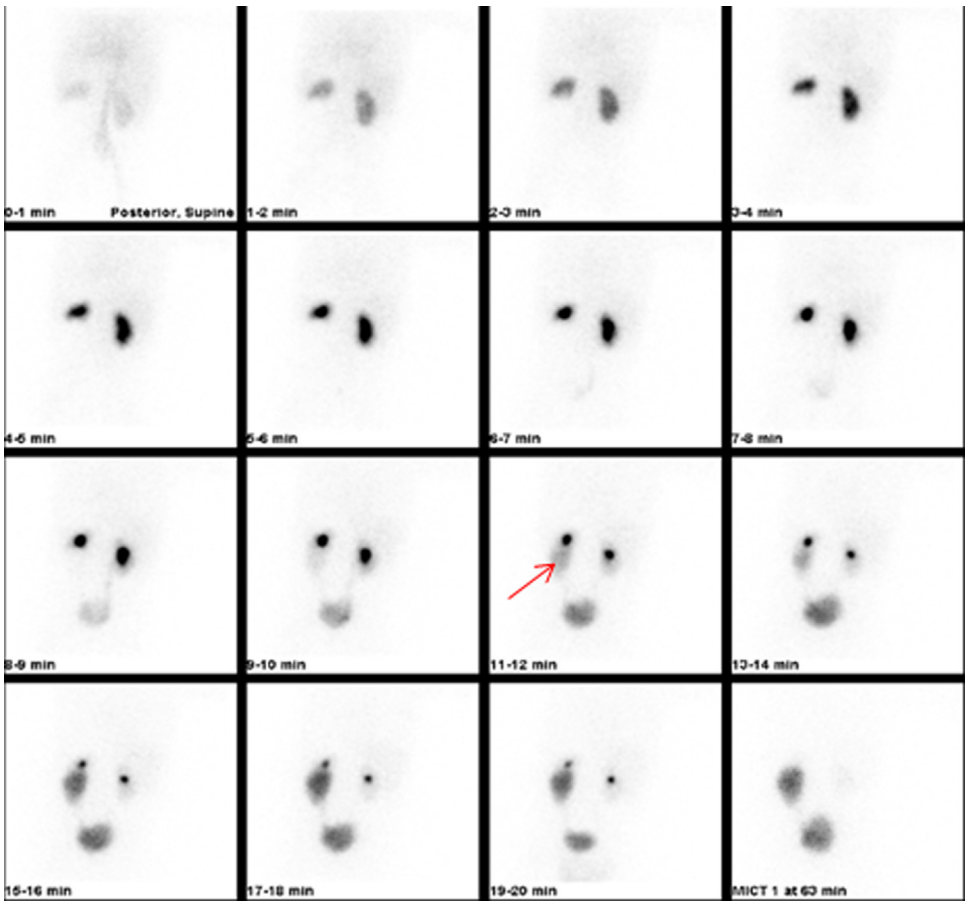

Figure 7 MAG3 renogram in an eight months' old boy with an ante-natally diagnosed left hydronephrosis. The ultrasound clearly demonstrated a left duplex kidney with a very dilated lower moiety collecting system. The MAG3 renogram clearly shows evidence of VUR into the left lower moiety during the dynamic sequence. It would not have been possible to perform an IRC on this child due to the very young age.

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child grows. Higher grades of reflux may benefit from reimplantation of the ureter, if the refluxing lower moiety shows maintained parenchymal function, or lower pole heminephrectomy if the lower moiety functions poorly. A poorly functioning upper moiety of a duplex is usually treated with upper pole heminephrectomy.

Ectopic Kidney

Single renal ectopia refers to a kidney that remains in the ipsilateral retroperitoneal space, the most common position being the pelvis. US can make the diagnosis in most cases. One or both kidneys may be ectopic in association with, or independent of, other renal malformations. Scintigraphy with DMSA is very useful to estimate the contribution of the ectopic kidney to total renal function: an anterior view is required in all cases, with the split renal function calculated using the geometric mean, in view of the asymmetric position compared to the contralateral kidney and the attenuation artefact from the renal pelvic bones in the posterior view. A MAG3 can be helpful to evaluate drainage, as this can be slow due to the possible high insertion of the ureter in the renal pelvis.

Horseshoe Kidney and Crossed Renal Ectopia

Horseshoe kidneys are characterized by fusion of the lower poles across the midline by an isthmus lying anteriorly to the aorta and inferior vena cava. Radionuclide studies are useful to confirm the diagnosis (which may be unsuspected on ultrasound in view of the overlying bowel gas) and to look for possible functional abnormalities such as infection, hypertension, and hematuria. DMSA imaging (including anterior views or SPECT imaging) shows the function of the renal parenchyma and whether the kidneys are joined by functioning renal tissue or by a fibrous band.

PUJ obstruction in one of the moieties of a horseshoe kidney is common, due to high insertion of the ureter or to an anomalous crossing renal vessel. A MAG3 renogram will confirm the diagnosis and assess the drainage, confirming the level of possible urinary stasis. Renal calculi develop in 20% of patients with horseshoe kidneys.[177]

Crossed renal ectopia is the second most common fusion anomaly after the horseshoe kidney. Crossed renal ectopia with fusion is much more common than without fusion. There are many possible combinations of crossed renal ectopia. The crossed ectopic side lies on the opposite side to the ureteral insertion in the bladder. It may be difficult to differentiate a crossed fused kidney from a crossed kidney without fusion on ultrasound. A functional assessment with DMSA (better if supplemented with SPECT imaging) is often required to evaluate renal parenchymal integrity and confirm the diagnosis. If further anatomical details are required, especially with regard to vascular supply, ultrasound and MRI urography are the imaging methods of choice in children.

Renal Hypoplasia

This condition originates from disturbed differentiation of metanephrogenic tissue or problems with the induction of tissue differentiation. Histologically, it is defined by reduction in the number and size of nephrons, mostly in combination with dysplastic elements. Many children are otherwise healthy, and renal hypoplasia is detected by chance; others with more severe and bilateral disease may suffer from renal failure, UTI, and hypertension.

Imaging usually starts with US. Volume calculations show a small kidney with otherwise often normal sonographic appearance. Additional workup is performed with MCUG to rule out VUR as a possible cause for a radiologically small kidney. A DMSA scan is very useful to confirm the diagnosis: this shows homogenously reduced tracer uptake, with no evidence of focal cortical defects.

Multicystic Dysplastic Kidney

Multicystic dysplasia of the kidney (MCDK) is the most common cystic disorder of infants and children with an incidence of approximately 1 in 4000 births and is more common in men (2.4:1). By definition, the affected kidney is nonfunctioning and is usually associated with an atretic ureter.

The aim of imaging in MCDK is to establish the diagnosis, confirm a normal contralateral renal unit, and to rule out associated anomalies. Imaging is initially performed with US.[178] Associated urinary tract anomalies are present in one-third of patients (PUJ urinary stasis in 12% and VUR in 20%).Scintigraphy with DMSA shows no tracer uptake in the MCDK, confirming absence of cortical function, and dynamic renography will confirm normality of the contralateral kidney. MCDK may involve a portion of a duplex (usually the upper moiety) or of a horseshoe kidney.

Most MCDKs involute during the first decade of life. Previously, MCDK was managed with nephrectomy to prevent potential development of proteinuria, hypertension, and degeneration into Wilms tumor (WT). Several large studies have since shown these risks to be extremely low if present at all.[179,180]

Conservative management with serial ultrasounds is now standard practice for MCDK.[181] Although exact imaging protocols vary, renal US is often performed every 3-6 months in the first 2 years and annually thereafter. Cystograms are unnecessary in isolated MCDK with a normal contralateral kidney.

Nephrectomy is only reserved for cases where the large size of the kidney is causing abdominal distension, discomfort, pain, difficult feeding, or respiratory compromise in the first few months of life, where the cysts continue to increase in size and in case of hypertension. Failure to regress is considered by some as a relative indication for surgery.

Cystic Renal Disease

Cystic renal disease includes a variety of entities. Inherited diseases as well as a disturbed renal embryogenesis and renal development create a wide spectrum of manifestations that spans diffuse, severe, bilateral congenital disease to simple, single renal cysts occurring in the adult.

Imaging in cystic kidneys always starts with ultrasound. Functional imaging is occasionally requested to evaluate the amount of cortical function present, especially if the condition is unilateral. Occasionally, it may be difficult to distinguish a single cyst from a dilated calyx. A MAG3 renogram with

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delayed images can be helpful: a cyst will remain photopenic on delayed images, whereas a dilated calyx will fill with tracer.

Lower Urinary Tract Dysfunction

Voiding Dysfunction

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 UTIs, VUR, and daytime and nighttime urinary incontinence.

The following two main entities have been identified: overactive bladder (or unstable bladder and urge syndrome) and dysfunctional voiding. The common denominator of LUTD is bladder sphincter discoordination leading to chronic high intravesical pressure, with resulting negative consequences for the urinary tract.

Nuclear Medicine may have a potential role in the screening for LUTD, through the use of the indirect cystogram supplemented by a noninvasive urodynamic bladder assessment with a flow meter.

Overactive Bladder (Unstable Bladder)

The primary abnormality is the failure to suppress involuntary detrusor contractions because of the inability to exert complete voluntary control over the micturition reflex. 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 nonphysiological contraction of both the bladder and external urethral sphincter and also leads to symptoms such as urgency, frequency, and urge incontinence (overactive bladder syndrome).[182] The IRC study may show episodes of VUR with no micturition, in keeping with ineffective bladder contractions.

Detrusor-Sphincter Dysfunction During Micturition (Dysfunctional Voiding)

The primary abnormality of this dysfunction is overactivity of the sphincter mechanism during 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.
- *Interrupted voiding* is caused by hypoactivity of the detrusor muscle, with voiding consisting 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 long-standing dysfunctional voiding. It results from detrusor decompensation. Abdominal pressure is mostly responsible for voiding. Large volumes of urine can be observed.[183]

High intravesical pressure is the main mediator that leads to morphologic changes of the urinary bladder in trabeculation and formation of diverticula, and this may lead to VUR.

There is a clear coprevalence between LUTD and VUR. LUTD refers to the presence of lower urinary tract symptoms, including urgency, urge incontinence, weak stream, hesitancy, frequency, and UTIs, which reflect the filling and emptying dysfunction. The development of VUR may be caused by the anatomical distortion of the VUJ as a consequence of chronic high pressure; high pressure itself does not cause VUR. In cases of borderline-competent ureteric orifices, chronic high pressure itself may directly induce and perpetuate VUR.

A modified IRC with the addition of a flow meter may be a possible screening test for bladder function, while at the same time looking for VUR and assessing the function and drainage of the upper tracts (Fig. 8). The child sits on the commode and voids in a jug placed on the flow meter platform, with wireless connection to a computer. The platform is sensitive to the pressure of the jet of urine. This noninvasive urodynamic assessment informs on voiding time, time to maximum urine flow, maximum urine flow in milliliters per second, and average flow. The shape of the bladder contraction curve gives some insight into bladder function. A normal bladder contraction curve typically has a bell shape, reflecting a harmonious synchronous and efficient contraction. Fractionated voiding is reflected by a bladder contraction curve with multiple spikes. Lazy bladder syndrome will show as incomplete bladder emptying over a prolonged period, with an elongated bladder contraction curve and multiple small spikes on the flow meter study. It is important to take note of the voided volume of urine: a large voided volume, in excess of that expected for a child of that particular age (see previous formula to calculate the expected voided volume for age), raises the possibility of a decompensated bladder. Conversely, if the child passes very little urine, this may mean it was not well hydrated and, therefore, the IRC may be suboptimal.

The IRC supplemented with a flow meter study may potentially be a screening tool for bladder dysfunction and direct patients to a comprehensive urodynamic bladder assessment. This approach needs proper evaluation. If VUR is detected, the initial goal of management is the normalization (or improvement) of bladder function.

Neuropathic Bladder

Children with neuropathic bladder sphincter dysfunction may be unable to retain urine normally, to evacuate normally, or both. Most neurologic conditions in children leading to a neuropathic bladder dysfunction include myelomeningocele, lipomeningocele, sacral agenesis, and occult lesions such as congenital neurospinal dysraphisms.[184] Children after sacrococcygeal teratoma resection may also develop a neuropathic bladder.[185] The neurourological changes may arise from the tumor itself due to spinal compression and from the surgery. Therapeutic goals in children with neuropathic bladder are the

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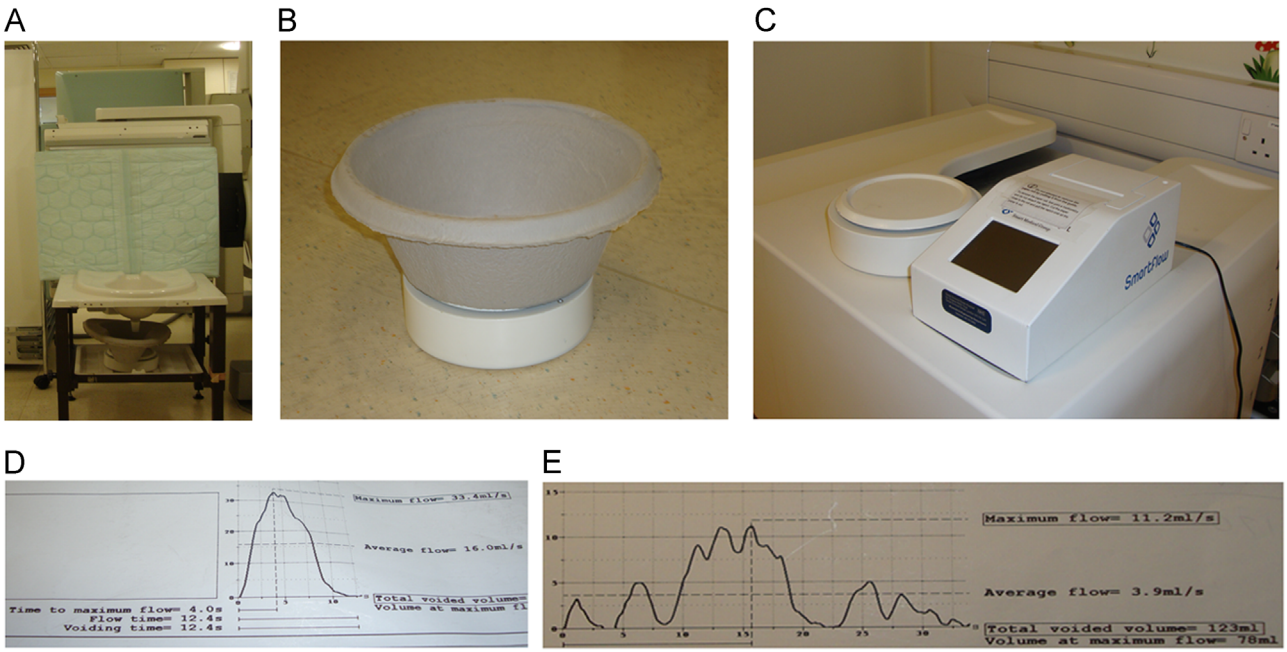

Figure 8 Modified indirect radionuclide cystography supplemented with a non-invasive urodynamic bladder assessment with a flow meter. The gamma camera has been prepared for the acquisition (A). The bowl that collects the patient's urine has been placed on the flow meter platform (B), which is connected wirelessly to a computer (C). During micturition, the pressure of the urine jet is translated into the bladder contraction curves (D,E). A normally contracting bladder (D) shows a typical bell-shaped curve. A dysfunctional bladder (E) shows multiple spikes and reduced urine flow, in keeping with multiple ineffective contractions. This system allows an initial non-invasive evaluation of bladder function.

preservation of renal function, avoidance of UTI, and achievement of appliance-free and social continence.

Neuropathic bladder occurs also in 80%-90% of patients who suffer from myelodysplasia. Myelomeningocele is the most common defect. Neonatal assessment consists of an ultrasound of the bladder and kidneys and, in most centers, a MCUG as well.

Although continence is readily appreciable by history, there is an insidious risk of renal damage. Therefore, regular assessment of the upper tracts with ultrasound is required to detect changes before irreversible damage has occurred. In these patients, renal scintigraphy with DMSA is used to monitor renal cortical function and to identify scars secondary to recurrent infections as well as congenital renal displasia.[186]

Renal Trauma

Radionuclide imaging is used infrequently in these patients. In the case of minor injuries, such as renal contusion, intrarenal and subrenal hematoma, minor laceration without extension to the renal collecting system, or small subcortical infarcts, nuclear medicine investigations are usually not necessary, as management is conservative. CT is the imaging modality of choice in the initial trauma staging.

In the case of major injuries, for example, major renal laceration extending through the cortex to the medulla and collecting system, patient's management can vary. If the patient is haemodynamically stable, management can still be conservative. If the patient is unstable, surgical exploration is required. In this case, DMSA scintigraphy (if feasible, in view of the patient's clinical conditions) may be helpful before surgery to assess viability of renal parenchyma. Renal scintigraphy with DMSA can be also used to assess recovery or residual damage several months after trauma. Studies using Tc-99m-MAG3 or Tc-99m-DTPA can effectively detect urinary leaks following trauma.

Recipients of Renal Transplants

It is possible to assess perfusion of the transplant with scintigraphic methods during the early and late postoperative periods, and assist in the differential diagnosis of diminished graft function, which includes rejection, obstruction, and urinary leak.[187] In practice, Doppler ultrasound is commonly used to assess renal perfusion; the ultrasound examination can also raise the suspicion of obstruction to outflow by showing increasing renal pelvic or ureteric dilatation in comparison with the baseline ultrasound. When rejection is suspected, a renal biopsy is usually performed, making scintigraphy assessment almost always unnecessary.

Renal transplant recipients have a high incidence of UTIs. A DMSA scan is useful to assess the degree of renal damage after a UTI. A DMSA in renal transplant recipients a few weeks after transplantation may be a helpful baseline, particularly in those young renal transplant recipients with a previously unused of "hostile" bladder (such as in posterior urethral valves or augmented bladders). The acquisition of six views (anterior, posterior, right and left posterior obliques, and right and left

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anterior obliques) is highly recommended for better visualization of the transplanted kidney. A SPECT data set is helpful where the transplant may be unusually positioned.

Obstruction

Urinary obstruction is a possible complication following renal transplantation. Obstruction soon after surgery may be due to edema or inflammation in the region of the VUJ, which may be temporary. Later, obstruction may be due to external compression, which may be caused by a lymphocele or surgical scars or by stenosis at the ureteral anastomosis site. Because the transplant ureter obtains its blood supply only from the graft, the distal ureter may be poorly perfused, which may result in distal ureteral scarring and obstruction. Partial or even total obstruction of a transplant kidney may be relatively asymptomatic, as the graft is not innervated. Diagnosis of partial obstruction is sometimes difficult, and radionuclide dynamic renography with furosemide may be helpful.

Urinary Leak

Urinary leak usually occurs in the first few months following transplantation. It can occur at the site of anastomosis of the transplant ureter or through necrosis of the distal transplant ureter related to diminished perfusion. In cases of suspected urinary leak following transplantation, multiple serial images, usually as part of a MAG3 renogram can effectively detect the presence of urinary leak and urinoma.[188] Renal scintigraphy with Tc-99m-MAG3 can also be used to differentiate urinoma from lymphocele or seroma. On the series of scintigrams, the leakage appears as a focal or diffuse area of increasing tracer accumulation outside the confines of the transplant, the ureter, or the bladder. Urinoma usually appears as a photo-deficient area on early images (5-10 minutes), because of the presence of nonradioactive urine, with subsequent accumulation of tracer on later images. If the initially photopenic area does not concentrate radiotracer on later images, this region may represent an hematoma or a lymphocele.

Nuclear Medicine in Some Pediatric Nephro-Urological Tumors

Wilms' Tumors

Wilms' tumors (WT) is the most common renal tumor in children. It accounts for 6% of all pediatric malignancies; the overall survival at 5 years exceeds 90%.[189] Most WTs contain a mixture of blastemal, stromal, and epithelial cell components in varying proportions. Up to 10% will demonstrate anaplasia, which is associated with a poorer prognosis.[190] Prognosis depends mostly on stage at diagnosis and histologic components of the lesion (intermediate vs anaplastic histology).

Treatment of WT is based on histopathology and the stage of the disease. Staging is based on surgical and imaging findings. The primary goals of surgery are tumor resection, resection of involved lymph nodes, and avoidance of tumor spillage. Adjuvant chemotherapy and radiation therapy depend on the extent of the disease.[191,192]

Local tumor staging requires information on tumor location, size, local extension, vascular compression or invasion, and local lymph node metastases. Initial staging requires ultrasound, CT, and MRI. Bone scan is used if there is suspicion of skeletal metastases; however, skeletal metastases in WT are rare. The most common site for metastases is the lungs, which are typically evaluated with chest CT.

The use of FDG-PET/CT in WTs has not been fully tested. The studies available are preliminary and include few patients. Possible applications for FDG-PET/CT in WTs are evaluation of response to neoadjuvant chemotherapy and recurrent or metastatic disease.

Wilms' tumors show intense FDG uptake,[193,194] in particular anaplastic tumors. Misch et al[194] found PET advantageous in ruling out residual disease after completion of first-line treatment and in pretherapeutic staging of relapsed patients. There was also a good correlation of standardized uptake value and histologic differentiation. Begent et al[193] showed that PET/CT findings following initial chemotherapy correlated with histologically confirmed viable tumor, presence of lung metastases, and areas of anaplasia. Another study showed no significant correlation between FDG uptake and histopathology.[192] FDG-PET/CT may have the potential of predicting WT response to chemotherapy, with a significant correlation between pathologic response and reduction of standardized uptake value before and after induction chemotherapy[195]; however, in view of conflicting reports, further evaluation is needed.

No systematic studies exist on the use of FDG-PET/CT in nephroblastomatosis, clear cell sarcoma, genitourinary rhabdoid tumor, and renal cell carcinoma. A study to compare FDG uptake in WT and nephroblastomatosis would be particularly useful.

DMSA-SPECT/CT studies are becoming increasingly useful in specialized centers where stage V bilateral WTs are managed. The bilateral disease most often occurs in children with a genetic mutation leading to a WT1 gene alteration (for example in Denys-Drash syndrome) or in other syndromes associated with the development of WT such as Beckwith-Wiedemann syndrome. Nephron-sparing surgery is being performed for bilateral disease in these high-risk children, who may develop metachronous tumors. DMSA-SPECT/CT, with or without fusion of three-dimensional contemporaneous MRI data sets, aids in attempting innovative preservation of renal tissue in those children who were previously rendered anephric (Fig. 9).

Rhabdomyosarcoma

Most studies that evaluate FDG-PET/CT in soft tissue sarcomas of childhood include small numbers and heterogeneous series of patients. Within this group of tumors, rhabdomyosarcomas of the genitourinary tract constitute a small portion of pediatric rhabdomyosarcomas (10% in some series, Casey et al[196]).

For most of these tumors, MRI or CT are used to define the primary tumor, and CT of the lungs is used to exclude pulmonary metastases. Reports of using ^{18}F-FDG-PET are becoming more common in staging, in assessing response to treatment, and in detecting residual, recurrent, or metastatic disease. Several studies on heterogeneous groups of patients with soft tissue sarcomas showed that the sensitivity and

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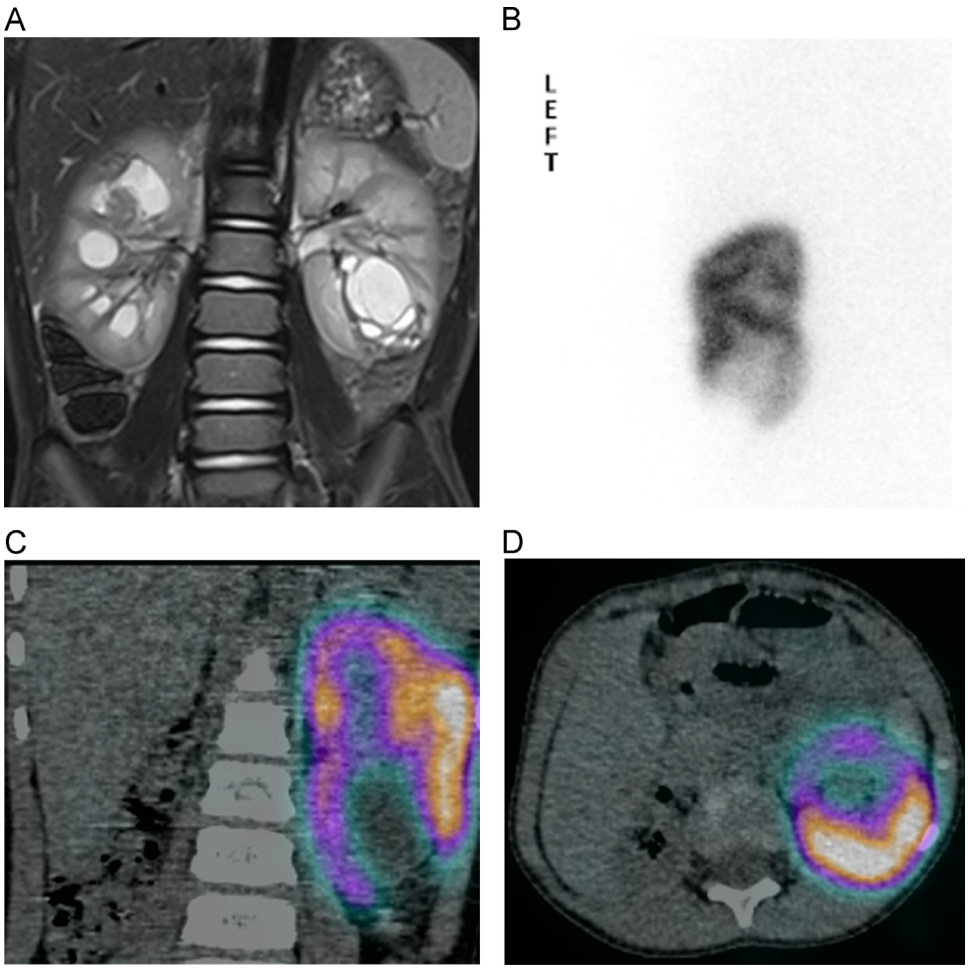

Figure 9 Three years old boy with bilateral Wilms' tumour. The MRI scan at diagnosis (A) shows the right Wilms' tumour that invades most of the right kidney. Following induction chemotherapy the child underwent right nephrectomy. The left Wilms' tumour is mainly cystic with a small solid component and could be amenable to nephron sparing surgery. The planar DMSA images after chemotherapy and right nephrectomy (B) show an overall well-maintained function in the left kidney, with a focal defect at the lower pole. The SPECT CT study (C,D) shows the deep mainly cystic lesion with normal renal cortex posteriorly. The lesion does not invade the renal hilum. The child underwent successfully nephron sparing surgery.

accuracy of FDG-PET in the detection of bony lesions was higher than Tc-99m-methylene-diphosphonate bone scans[197,198] and cross-sectional imaging with CT and MRI.[199]

The presence of regional lymph node metastases is a strong prognostic factor in patients with rhabdomyosarcoma.[200] FDG-PET/CT has been shown to be more accurate than conventional imaging for detection of lymph node metastases.[201,202] FDG-PET/CT can also predict survival in pediatric patients with sarcoma based on the metabolic activity of the primary tumor at diagnosis.[203,204]

Conclusion

Much ground has been covered since the introduction of nuclear medicine examinations in pediatric nephro-urology; however, scintigraphy still has a significant role to play. High-quality examinations that address a specific clinical question, complemented by a fully informative report that takes into account all the previous imaging and clinical details, are essential. Detailed guidelines on the acquisition and interpretation of the different radionuclide techniques have been published and are widely available online, leaving no room for unapproved and untested protocols.

It is important to be aware of the already available applications of radionuclide imaging in congenital renal anomalies, renal calculi, and renovascular disorders with hypertension. The availability of SPECT supplemented by low-dose child-friendly CT acquisition parameters has significantly improved the diagnostic yield of DMSA scanning in urolithiasis.

Research that can answer some important clinical questions is needed. Long-term appropriately powered cohort studies need to fully inform on the clinical significance of different degrees of renal scarring in children with UTIs and the associated risk of hypertension, chronic kidney disease and, in women, complications in pregnancy. In the context of an antenatally diagnosed hydronephrosis, only a fraction of patients are at risk of losing renal function if left untreated; in the others the renal pelvic dilatation undergoes spontaneous resolution with time. Currently, we still struggle to reliably

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identify the hydronephrotic kidney at risk. It is essential to further evaluate in large pediatric studies promising parameters, such as the cortical tracer transit time, for the identification of the kidney at risk.

Finally, in recent years new promising possible applications of FDG-PET/CT in sarcomas of the genitourinary tract have been proposed; these need proper testing. The advent of PET/MRI imaging will likely benefit the management of paediatric patients with urogenital tumors, opening up new exciting developments.

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