Pediatric Obstructive Uropathy

55

Bärbel Lange-Sperandio

Contents

B. Lange-Sperandio (✉)
Dr. v. Hauner Children's Hospital, Department of Pediatric Nephrology, LMU, Munich, Germany
e-mail: baerbel.lange-sperandio@med.uni-muenchen.de

E.D. Avner et al. (eds.), *Pediatric Nephrology*,
DOI 10.1007/978-3-662-43596-0_51

Introduction

Congenital obstructive uropathy is a heterogeneous group of pathologies with a varying natural history. Obstruction of the urinary tract can be at the level of the ureteropelvic or the ureterovesical junction or at the level of the bladder outlet or urethra. It can be either unilateral or bilateral and it may involve some or all of the urinary tract. Congenital obstructive uropathy represents a major cause of renal failure in infants and children. Together with renal hypoplasia and dysplasia, it accounts for almost half of all cases of chronic kidney diseases in children.

Epidemiology

Urinary tract abnormalities identified by ultrasound are one of the most common anomalies with a rate of 1 in 250–1 in 1,000 pregnancies [1, 2]. Congenital obstructive uropathies account for most of these cases: approximately 1 in 2,000 pregnancies [2]. The mean prevalence of all types of renal malformation is 1.6 per 1,000 births. The most frequent diagnosis is hydronephrosis with more than 80 % being detected prenatally [3–5]. Unilateral hydronephrosis is more common than bilateral, and most cases can be described as mild and will resolve spontaneously. The differential diagnosis of hydronephrosis includes ureteropelvic junction obstruction, vesicoureteral reflux, ureterovesical junction obstruction, posterior urethral valves, Eagle-Barrett / prune belly syndrome, urethral atresia, and duplicated collecting system with ureterocele. Ureteropelvic junction obstruction is the most frequent cause of hydronephrosis (reported incidences of 39–64 %), followed by vesicoureteral reflux (33 %) and ureterovesical junction obstruction (9–14 %) [2]. The incidence of lower urinary tract obstruction is 2.2 per 10,000 newborns with posterior urethral valves being the most common malformation at 64 % (1.4/10,000 births), followed by urethral atresia at 39 % (0.7/10,000 births) and Eagle-Barrett syndrome (4 %) [6].

Definition of Obstruction

Whitaker et al. described urinary tract obstruction as any condition "that impairs urinary drainage from the pelvicalyceal system and leads to increased pressure and reduced urine flow rate" [7]. This was the first approach to define obstructive uropathy with a more functional understanding. Koff et al. included potentially endangered renal function and not just urinary drainage in the definition of obstruction, which thus would be "any restriction to urine flow that will cause progressive renal deterioration" [8, 9]. Peters et al. created the most recent and generally accepted definition describing obstruction as "any condition that, left untreated, endangers renal function and growth potential" [10]. Clinically, obstruction is usually presumed when urinary tract dilatation (i.e., hydronephrosis) is detected by ultrasound. But not every patient with hydronephrosis has an obstruction, and most cases of antenatal hydronephrosis will improve without surgical intervention or renal damage. It is important to state that hydronephrosis per se does not correlate with the affected kidney's function. Hydronephrosis becomes a problem when it endangers renal function. At the time of diagnosis, some patients will have irreversible renal damage, whereas others will have progressive renal injury if left untreated. It is still a challenge for physicians to identify and categorize this heterogeneous group of obstructive pathologies.

Pathophysiology

The urinary tract consists of conduits and reservoirs transporting the urine produced by the kidneys. To better understand the pathophysiology of obstructive uropathy, the properties of this system have to be considered, including structural compliance, flow impairment, renal function, and urine production. It is important to understand that the onset and the duration of obstruction correlate with abnormal kidney development and loss of kidney function. In fetal development, urinary tract obstruction impairs renal growth

and development. It is therefore fundamentally distinct from obstruction acquired later in life. The development of congenital obstructive uropathy is regulated by a complex interplay of genetic and nongenetic factors, only some of which have been identified [11–13].

Animal Models

Congenital obstructive uropathy initiates a complex sequence of events resulting in impaired renal function. Its pathophysiology has been studied intensively, leading to the development of multiple animal models, including complete and partial ureteral obstruction, unilateral and bilateral obstruction, and acute and chronic obstruction [11–13]. Experimental obstructive uropathy is usually created by unilateral ligation of the ureter. Advantages of this surgical model include experimental manipulation of the severity, duration and timing of obstruction, as well as the study of recovery following release. The unilateral ligation of the ureter induces progressive tubular cell injury in the kidney, including apoptosis, reduced proliferation, loss of differentiation, and tubular atrophy. Ureteral obstruction also leads to interstitial inflammation, interstitial fibrosis, and extracellular matrix deposition. Experimental obstructive uropathy induces glomerular and vascular hemodynamic changes and is different in neonatal mice and rats when compared to adult rodents where nephrogenesis is complete.

Tubular Injury After Ureteral Obstruction

Early changes observed after ureteral obstruction consist in tubular dilatation, which is mostly pronounced in the collecting ducts [14, 15]. The mechanical stretch of tubular cells induces progressive tubular apoptosis accounting for the huge loss of renal tissue [14, 15]. A large variety of molecules mediate these tubular changes, including those related to apoptosis and cell cycle regulation (caspases, intrinsic and extrinsic death pathway molecules, reactive oxygen species, catalase, and inhibitors of cyclin-dependent kinases p27 and p21) [11, 13]. Upon injury, some tubular segments of the nephron change their epithelial expression pattern. They lose epithelial markers (E-cadherin) and gain de novo expression of mesenchymal cell markers (α-smooth muscle actin, vimentin), which likely suggests the transformation of tubular epithelial cells into mesenchymal fibroblasts, a process termed epithelial-mesenchymal transformation [11, 16, 17]. Ureteral obstruction also leads to glomerulotubular disconnection, resulting in atubular glomeruli and aglomerular nephron segments [18]. The functional tubular changes observed after ureteral obstruction include impaired reabsorption of solutes and water and reduced capacity to concentrate and acidify the urine [19–21].

Interstitial Inflammation After Ureteral Obstruction

Unilateral ureteral obstruction induces immediate recruitment and infiltration of inflammatory cells into the kidney. This inflammatory infiltrate consists predominantly of macrophages and activated T-lymphocytes, which together with injured tubular cells release chemokines, proinflammatory and profibrotic cytokines, and reactive oxygen species. Neutrophils in the obstructed kidney are absent or very scanty. Apart from being the source of cytokines, infiltrating leukocytes also release chemokines (f.e. CCL2) and express chemokine receptors (f.e. CCR1, CCR5) as well as other receptors (Toll-like receptor-2), activating both paracrine and autocrine loops for macrophage and T-cell recruitment. Multiple chemokines, chemoattractants, and adhesion molecules mediate these interstitial changes (CCL2, osteopontin, IL-1, VCAM-1, ICAM-1, angiotensin II, selectins, β2-integrins, receptor for advanced glycation end products (RAGE)) [22–32]. Different macrophage subpopulations, either harmful or protective, have been found in the kidney after unilateral ureteral ligation and may become an important target for future therapies [33–36].

Interstitial Fibrosis After Ureteral Obstruction

Experimental ureteral obstruction eventually leads to interstitial fibrosis, characterized by the activation of interstitial fibroblasts, the production and deposition of extracellular matrix, and the loss

of peritubular capillaries in the obstructed kidney. Increased fibroblast density in the kidney was traditionally explained by the local proliferation of resident fibroblasts. Recently, it has been shown that this mitogenic process accounts for only about half of interstitial fibroblasts. Other mechanisms like recruitment of bone marrow-derived fibrocytes from the circulation and epithelial to mesenchymal transformation of tubular cells may contribute to the increased number of interstitial renal fibroblasts [11, 16, 17, 37, 38]. Pericytes and endothelial cells have been identified as additional sources of interstitial fibroblasts [39, 40]. Various molecules mediate these interstitial changes like the regulators of epithelial to mesenchymal transformation (hepatocyte growth factor, bone morphogenic protein-7, TGF-β1, nestin, and HIF1-α) [41–44], hypoxic injury responses, cytokines, and growth factors (TGF-β1, EGF, VEGF, IGF-1, PDGF-C, connective tissue growth factor, and TNF-α) [11–13]. These changes collectively induce progressive scarring and the loss of renal tissue and kidney function. Extracellular matrix proteins found in the obstructed kidney include collagen types I, II, III, IV, V, VII, and XV, fibronectin, laminin, and heparin sulfate proteoglycans [45].

Glomerular, Vascular, and Hemodynamic Changes After Ureteral Obstruction

In adult animals with ureteral obstruction, glomerular and vascular changes are present in advanced stages. Nonspecific glomerular changes like capillary wall thickening or collapse, global sclerosis, and vascular intimal thickening reflect chronic ischemia of the obstructed kidney. In contrast to the adult situation, glomerular changes are much more pronounced in neonatal animals. Renal blood flow, glomerular filtration rate, and tubular function change immediately after ureteral obstruction. After a brief period of hyperemia and transient increase in renal blood flow, a progressive and permanent vasoconstriction leads to a decline of renal perfusion and glomerular filtration rate. Vasoconstrictive agents angiotensin II, thromboxane A2, and prostacyclins in combination with a reduced production of vasodilating substances including nitric oxide, prostaglandins, and platelet-activating factor mediate these functional changes [11–13].

Renal Injury in Neonatal Ureteral Obstruction

Most experiments to investigate the pathophysiology of ureteral obstruction have been performed in adult animals. Only a few studies have been conducted in fetal sheep and monkeys or in neonatal rodents (mice, rats). In humans, nephrogenesis is complete at 34–36 weeks of gestation [46, 47] and thereafter only functional maturation occurs. In contrast, in rats and mice only 10 % of glomeruli are generated at birth, with the remaining nephrons being formed postnatally. Based on the duration of nephrogenesis, the rat or mouse at birth parallels the midtrimester human fetus [13]. This is the time point where the onset of renal obstruction usually occurs in the human system. Thus, ureteral obstruction experimentally conducted in the newborn mouse offers a suitable animal model to investigate obstructive uropathy.

Following this idea, pioneering work by Chevalier and his coworkers established the model of neonatal obstructive nephropathy in newborn mice and rats at the second day of life. His technique of unilateral ureteral obstruction allows for the study of obstructive uropathy during kidney development [48, 49]. Complete unilateral ureteral obstruction in neonatal rodents results in arrested renal development, renal dysplasia, fewer glomeruli, and reduced glomerular surface area; it impairs growth and maturation and reduces the number of nephrons. The severity of renal injury depends on the severity and the duration of obstruction. Neonatal ureteral obstruction for 4 days (and release thereafter) reduces renal growth by 60 % and the number of glomeruli by 50 % [50, 51]. Neonatal ureteral ligation leads to hemodynamic changes, tubular atrophy, interstitial fibrosis, and abnormal development of the renal vasculature. Similar histologic lesions were found in kidney biopsies of children obtained during pyeloplasty [52]. Some of the underlying pathways driving interstitial inflammation, tubular apoptosis, and interstitial fibrosis in neonatal ureteral obstruction have been identified (Table 1, modified from [53]).

Table 1 Pathogenesis of obstructive uropathies. There are three major pathways for obstructive renal injury: apoptosis (and other forms of cell death), interstitial inflammation, and eventual interstitial fibrosis. Epidermal growth factor (EGF), tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β), receptor for advanced glycation end products (RAGE), nuclear factor-κB, (NF-κB), epithelial-mesenchymal transition (EMT), endothelial-mesenchymal transition (EndMT), extracellular matrix (ECM), α-smooth muscle actin (α-SMA)

Apoptosis	Inflammation	Fibrosis
Hypoxia, ischemia	Angiotensin II	TGF-β
Reactive oxygen species	TGF-β	Angiotensin II
Caspases	Chemokines (CCL2, CCL5)	EMT/EndMT
Cellular stretch	Adhesion molecules (selectins, β2-integrins), RAGE	Activated myofibroblasts
EGF	Macrophage infiltration	ECM, α-SMA
TNF-α	NF-κB	Smad 2, Smad3

For lower urinary tract obstruction, the fetal sheep has been the most used model, with the majority of work done by Harrison and colleagues. Using this model, the effect of ureteric and urethral obstruction, both partial and complete, and its effects on pulmonary and renal development have been demonstrated [54, 55]. Complete urethral obstruction produced severe hydronephrosis, megaureter, megacystis, and pulmonary hypoplasia. However, Harrison et al. could not demonstrate cystic and dysplastic changes in the kidney. In contrast, complete unilateral ureteral obstruction in the fetal lamb induced dysplastic kidneys. These histologic lesions were similar to those seen in the human fetus [56]. In addition, in utero decompression either prevented or greatly improved renal dysplasia [57]. Other animal models have reproduced the finding of dysplastic kidneys with ureteral obstruction [57].

Unfortunately, interstitial fibrosis and irreversible renal damage, which are present in patients with poor kidney function, rarely improve after surgical correction. Therefore, the focus of most studies shifted to the identification of novel biomarkers to characterize and identify obstructive uropathies [58].

Genetics

Experimental studies to identify genetic defects in patients with obstructive uropathy have provided an enormous wealth of data regarding affected genes and signaling pathways. The mouse has been instrumental in further characterizing putative genes involved in obstructive uropathy. The strong similarities between the human and the mouse genome together with genetic engineering technologies provided excellent research tools to study the effects of human mutations in vivo [58, 59]. Although only a few causative genes associated with obstructive uropathy in humans have been discovered so far, basic research in this area gave important insights on early urinary tract development (Table 2). Most cases of kidney and urinary tract anomalies are sporadic and restricted to the urinary tract [47]. Only some forms of "congenital anomalies of the kidney and urinary tract" (CAKUT) are part of a syndrome or are associated with a positive family history [1, 47].

Genes and Signaling Pathways in Human and Mice

Many genes and signaling pathways have been identified to play important roles in early ureteric budding and ureter development [60, 61]. These include the renin-angiotensin system (e.g., *Agt*, *Ren*, *Agtr1*, *Agtr2*), the receptor tyrosine kinase (RTK) signaling pathway (e.g., *Gdnf*, *Ret*), the Wnt signaling pathway (e.g., *Ctnnb1*, *Wnt7b*, *Wnt9b*, *Fzd1*), the Hedgehog signaling pathway (e.g., *Shh*, *Gli3*, *Smo*, *Tshz3*), the TGF-β signaling pathway (e.g., *Bmp4*, *Smad4*), and the retinoic acid mediated nuclear receptor signaling pathway (e.g., *Rara*, *Rarb*). Urinary tract diseases can modify the expression and activity of these genes and pathways. Global profiling studies have shown that urinary tract infections influence the activity of these pathways [62, 63].

Genetic studies in both human and mice have identified many genes associated with

Table 2 Genes associated with hydronephrosis and/or hydroureter (no VUR) in human. Abbreviations: Chr, chromosomal location; Signaling, signaling pathway; Ref, references; RAS, renin-angiotensin system (Table modified from Ref. [64])

Gene	Chr	Type of protein	Signaling	Human disease (OMIM)
Agtr2	Xq22-q23	G-protein-coupled angiotensin II receptor	RAS	X-linked mental retardation-88 (OMIM 300852)
Wfs1	4p16.1	Transmembrane protein		Wolfram syndrome (OMIM 222300): hydronephrosis, dilated ureters, distended bladder without VUR
Foxc1	6p25	Forkhead transcription factor	Foxc	Axenfeld-Rieger syndrome type 3 (OMIM 602482): UPJO
Gli3	7p13	Zinc finger	Hedgehog	Pallister-Hall syndrome (OMIM 146510)
Ret	10q11.21	Receptor	RTK	Hydronephrosis, megaureters, renal dysplasia
Stra6	15q24.1	A receptor for retinol/retinol-binding protein complexes	Retinoic acid signaling	Hydronephrosis

hydronephrosis due to lower urinary tract abnormalities [64]. Antenatal hydronephrosis can originate from kidney defects (e.g., mutations in *AQP2* that encodes the aquaporin-2 water channel in the collecting tubule) [65] or from defects in the ureter such as vesicoureteral reflux or from urinary tract obstruction [66, 67]. Mutations in many genes controlling the developmental process of the ureter have been shown to cause hydronephrosis in mice [64]. In addition, mutations in several murine genes have been shown to cause ureteropelvic junction obstruction and ureter-bladder connections defects [68–71]. Loss of both retinoic acid receptor alpha (*Rara*) and beta (*Rarb*) in mice leads to megaureter and hydronephrosis due to abnormal apoptosis mediated by vitamin A signaling at the ureter-bladder insertion site [68, 69]. Deletions of uroplakins (*Upk3a* and *Upk2*) in the urothelium in mice cause loss of the superficial cell layer, overgrowth of the urothelium, urothelial leakage, and vesicoureteral reflux [72, 73]. Stromal cells are also important for ureteral development and function [74, 75]. Loss of disc-large homolog 1 (*Dlg1*) causes absence of the stromal cell layer in the ureter, which leads to abnormal ureteral smooth muscle cell orientation, impaired ureteral peristalsis, and severe antenatal hydronephrosis [74, 75]. *Dlg1* is the only gene identified so far that is required for ureteral stromal cell formation. Many genes associated with hydronephrosis in mice are genes controlling ureteral typical smooth muscle cell development [76]. These include genes in the sonic hedgehog pathway (e.g., *Shh*, *Gli3*, *Smo*, *Tshz3*) [77–79], the TGF-β pathway (e.g., *Bmp4*, *Smad4*) [80–82], and the Wnt pathway (e.g., *Ctnnb1*) [83]. Canonical Wnt signaling is required for the ureteral adventitial fibroblast differentiation [83]. In mice, loss of the T-box transcription factor *Tbx18* induces failure of the ureteral mesenchymal cells to differentiate into ureteral smooth muscle cells as well as an abnormal differentiation of the urothelium, leading to ureterovesical junction obstruction, short hydroureter, and antenatal hydronephrosis [84]. The abnormal smooth muscle phenotype in *Tbx18* mutant mice may be caused by the downregulation of the sonic hedgehog signaling (e.g., *Ptch1*) in the ureteral mesenchyme and lower *Bmp4* expression in the ureter [84, 85]. These results underline the importance of typical smooth muscle cells in the ureter, which produce contractile forces to transport urine from the kidney to the bladder [86]. Different genes control the development of ureteral pacemaker cells and the peristalsis machinery [76, 79, 87–89]. In the urinary tract, the proto-oncogene Kit is a marker for interstitial cells of Cajal (ICC)-like cells (ICC-LCs) [87]. *Hcn3* (hyperpolarization-activated cation channel 3) plays a fundamental role coordinating proximal-to-distal ureter peristalsis [89]. Inactivation of *Smo* (smoothened) and upregulation of the *Gli3* repressor, two members of the sonic hedgehog signaling pathway, lead to

abnormal ureteral peristalsis, nonobstructive hydronephrosis, and hydroureter in mice [79]. Although the urothelium and smooth muscle cells develop normally in these mutant mice, the number of ureteral pacemaker cells (marked by *Kit* and *Hcn3* expression) is significantly reduced. Sonic hedgehog signaling controls ureteral pacemaker cell development. Mice with defective pacemaker cell differentiation show abnormal ureteral peristalsis and hydronephrosis [79, 90]. Consistent with these findings, mutations in *Gli3* gene have been identified in patients with the Pallister-Hall syndrome, which includes urinary tract phenotypes like hydronephrosis and hydroureter (Table 2) [91–93]. In the mouse urinary tract, mesenchymal expression of one of the calcineurin subunit B isoform genes called *Cnb1* (also named *Ppp3r1*) is required for the development of the pyeloureteral peristalsis [88]. Tissue-specific knockout of *Cnb1* in mice causes an abnormal formation of the renal pelvis and ureter as well as defective peristaltic waves, which lead to progressive renal tract obstruction and hydronephrosis after birth [88].

The angiotensin type 1 receptor (*Agtr1*) plays an important role in ureteral peristalsis. *Agtr1* knockout mice have abnormal renal pelvis and lack ureteral peristaltic waves and subsequently develop hydronephrosis phenotype [94]. However, no causative mutations in either *CNB1* or *AGTR1* have been reported in patients with urinary tract anomalies although mutations in *AGTR1* are associated with autosomal recessive renal tubular dysgenesis (RTD) [95, 96]. Molecular mechanisms leading to hydronephrosis and hydroureter in the absence of anatomic obstruction include T-box transcription factor 18 (*Tbx18*) or six 1-dependent delay in differentiation of ureteral smooth muscle cells [84, 97]. The rearranged in transfection (RET) tyrosine kinase signaling system is a major pathway guiding the normal development of the kidneys, ureters, peripheral, and enteric nervous system. In the kidneys, RET is activated by interaction with the ligand glial cell line-derived neurotrophic factor (GDNF) and its coreceptor GFRα1. This activated complex regulates a number of downstream signaling cascades that control proliferation, migration, and apoptosis. RET mutations are found in 5–30 % of CAKUT patients [98], and a number of Ret mouse mutants show a spectrum of kidney and urinary tract defects reminiscent of CAKUT in humans [99]. Both loss and overexpression of Ret can cause urinary tract anomalies. Recently, it has been shown that in mice with a mutation in the Ret-PLCγ docking site (Y1015), the common nephric ducts (CNDs) do not undergo timely degeneration and fail to separate from the Wolffian duct (WD), resulting in obstructive uropathy [100]. The ureter defect in RetY1015F mice is different than that in Ret-null mice, as it manifests during the ureter maturation stage after the Wolffian duct has reached the cloaca. A phenotype similar to Y1015F ureter defects (ureterovesical junction obstruction) was shown in mice deficient for leukocyte antigen-related (Lar) family protein tyrosine phosphatase, receptor type S and F (*Ptprs* and *Ptprf*) [71]. These ureter-bladder connection defects cause urinary obstruction, hydroureter, and hydronephrosis in *Ptprs/Ptprf* double-deficient embryos [71]. Increased activation of Ret-docking tyrosines in these mice implies an interaction between Lar and Ret signaling pathways. Sprouty protein (*Spry1*) inhibits Ret tyrosine signaling by suppressing RAS-MAPK activity [101]. Therefore, a *Spry1*-null mutation causes hyperactivation of the RAS-MAPK cascade [102]. *Spry1*-null mice show multiplexed dysplastic kidneys with megaureters and an increased number of ureteric buds [102]. Double knockout mice lacking Ret-PI3K-MAPK signaling and *Spry1* show morphological correction of the renal anomalies in contrast to the individual null mice [103]. The mechanism for normalization of the renal defects was explained by an increase in RAS-MAPK signaling via a pathway other than Ret. A possible candidate for this was FGFR signaling as in the absence of Gdnf/Ret signaling, FGF7 can induce ureteric buds [104]. Support for alternative tyrosine kinase activity came from compound homozygous mice lacking Gdnf or Ret and Spry1. Removing Fgf10 from *Ret-Spry1* double nulls resulted in no ureteric buds, suggesting that Fgf10 was the alternative RTK signal for ureteric bud induction [105].

Kidney and urinary tract development is sensitive to precise timing and to the level of MAPK

activity. This activity can be altered by the dosage of the Ret signaling complex or through activation of key docking tyrosine of Ret or by interactions with negative regulators such as *Spry1* [99]. The Gata-Raldh2-Ret molecular network plays a fundamental role in guiding the correct insertion of the nephric duct into the mouse bladder [70]. Absence of *Ret*, *Gata3*, or *Raldh2* causes similar defects of ureter insertion with urinary tract obstruction and hydronephrosis in mice [70].

Gene expression may also be regulated at the posttranscriptional level by noncoding microRNAs (miRNAs). A critical role for miRNAs in kidney development is evident from the observation that targeted genetic inactivation of Dicer, the miRNA-processing enzyme, in ureteric bud in mice results in hydronephrosis [106].

The broad phenotypic spectrum of obstructive uropathy and the variability in genotype-phenotype correlation indicate that its pathogenesis is a complex process depending on many factors. Derangements in cellular, molecular, and morphogenetic mechanism that direct normal renal system development are important causes of congenital genitourinary disorders.

Genetics and the Renin-Angiotensin System

The renin-angiotensin system (RAS) plays a major role in controlling blood pressure, fluid, and electrolyte homeostasis. The developing mammalian kidney expresses all components of the RAS as early as the fifth week of gestation, when metanephric organogenesis is initiated [107–109]. Mutations in the genes encoding components of the RAS in mice cause diverse forms of congenital kidney and urinary tract malformation (CAKUT), which include hydronephrosis, hypoplastic medulla and papilla, thickening of renal arterial walls, duplex ureters, and vesicoureteral reflux [110–112]. The mechanistic basis of CAKUT due to RAS mutations involves hypoplastic ureteral smooth muscle layer with impaired ureteral peristalsis [94]. Association of a single polymorphism in the human AT_2R gene (1332A > G transition) with CAKUT has been reported in several, but not all, studies. This alteration in the AT_2R is described in American and German Caucasian males with ureteropelvic junction obstruction, megaureter, and multicystic dysplastic kidneys [112, 113]. The same polymorphism was detected in Korean children with unilateral multicystic dysplastic kidney, renal agenesis, and hydronephrosis [114]; in Italian children with vesicoureteral reflux, hypoplastic kidneys, ureteropelvic junction obstruction, nonobstructive megaureter, and posterior urethral valves [115]; and in Serbian children with ureteropelvic junction obstruction, vesicoureteral reflux, or megaureter [116]. In contrast, a large European study published by Cordell et al. found no association of primary vesicoureteral reflux with mutations in AT_2R [117]. This difference may be explained by limitations in study design, low penetrance of the mutation, or contribution of modifier genes. ACE polymorphism is also associated with kidney hypodysplasia caused by posterior urethral valves [118]. Collectively, these observations indicate that the pathogenesis of obstructive uropathy is a complex process that depends on the interplay of many factors. A concerted effort to provide new insights into pathologic processes is in progress within the Genitourinary Development Molecular Atlas Project (GUDMAP). Genetic counseling is recommended for all patients with familial cases of urinary tract malformations or newly diagnosed forms of CAKUT that suggest presence of genetic anomalies.

Classification

Table 3 shows the differential diagnosis of prenatally detected urinary tract dilatation, which includes ureteropelvic junction obstruction, ureterovesical junction obstruction, ectopic ureteral insertion with and without duplex system, posterior urethral valves, Eagle-Barrett syndrome, urethral atresia, and duplicating collecting system with and without ureterocele. Many of these prenatal dilatations will improve without surgical intervention or evidence of impaired kidney function. Nonobstructive causes of urinary tract dilation like vesicoureteral reflux must also be

Table 3 Causes of antenatally detected urinary tract dilatation

Ureteropelvic junction obstruction
Ureterovesical junction obstruction
Posterior and anterior urethral valves
Ectopic ureteral insertion w/o duplex system
Ureteral stricture
Retrocaval and retroiliac ureter
Ureterocele w/o duplex system
Vesicoureteral reflux
Prune belly / Eagle Barrett syndrome
Extrinsic compression of the urinary tract
Neurogenic dysfunction, megacystis microcolon intestinal hypoperistalsis syndrome
Complex anatomical abnormalities (cloaca, cloacal exstrophy)

considered. The causes of obstruction can be classified on the anatomical level of obstruction (renal, ureter, bladder, or urethra) or on the underlying pathology (neoplastic, traumatic, inflammatory). Obstructive uropathies can be clinically classified as symptomatic or asymptomatic. Infants and children may present with febrile urinary tract infection, hematuria, a palpable flank mass, vomiting, or unexplained abdominal pain. However, with the use of antenatal ultrasound, symptomatic presentation has become less frequent. Occasionally, patients may show dual abnormalities, for example, ureteropelvic junction obstruction and vesicoureteral reflux, which can be difficult to isolate. It is important to identify patients with involvement of both kidneys (bilateral ureteropelvic junction obstruction or ureterovesical junction obstruction), patients with a solitary kidney, or patients with poor function in the contralateral kidney [119]. These children do not have the advantage of reserve functional kidney tissue; they very often profit from a low threshold-oriented surgical intervention. If the diagnosis of obstruction is based on the loss of kidney function on a nuclear scan, it can be difficult to identify those kidneys with obstruction. Under these circumstances, serial ultrasound examinations or magnetic resonance imaging (MRI) may be the best available indicator for surgical intervention.

Table 4 Society of Fetal Urology Grading System of Antenatal Hydronephrosis

Grade	Renal pelvic complex	Renal parenchymal thickness
0	Intact	Normal
I	Mild splitting	Normal
II	Moderate splitting (confined to renal border)	Normal
III	Marked splitting (outside renal border, calyceal dilatation)	Normal
IV	Pelvicalyceal dilatation	Thin

Diagnosis

In the clinical setting, obstructive uropathy is assumed when dilatation, defined as an increased diameter of one or more components of the renal collecting system, is detected. Unfortunately, this dilatation does not necessarily correlate with the presence or degree of urinary flow impairment. Nonobstructive conditions can show similar findings (e.g., vesicoureteral reflux), and hydronephrosis per se does not correlate with kidney function. It is important to state that urinary tract dilatation also depends on the level of hydration. The fetal kidneys produce four to six times more urine before delivery than after; this increased volume may cause dilatation of the renal pelvis, at least transiently [120]. All imaging techniques (ultrasound, nuclear scan, magnetic resonance urography) pre- and postnatally require sufficient hydration to depict and categorize urinary tract obstruction.

Prenatal Diagnosis

The majority of congenital abnormalities of the urinary tract are diagnosed during the second trimester ultrasound scan, which is usually performed at 18–20 weeks of gestation. However, with the increasing use of first trimester ultrasound screening, more severe renal abnormalities are being noted between 11 and 14 weeks [2, 121]. The findings of prenatal ultrasound depend on the level and severity of the obstruction (Table 4). Unfortunately no prenatal diagnostic test is

available, which differentiates between obstructive and nonobstructive causes of hydronephrosis. Ultrasonography can detect increased echogenicity and cysts in the fetal kidney, which are suggestive of renal dysplasia; it can determine amniotic fluid volume, associated anomalies, and fetal sex. Predictors of outcome in lower urinary tract obstruction that can be identified by ultrasound include the gestational age at diagnosis, oligohydramnios, and kidney appearance. Detection of lower urinary tract obstruction (e.g., posterior urethral valves) before or at 24 weeks of gestation, oligohydramnios, and evidence of renal cortical cysts has been shown to predict poor outcome [2]. Ultrasonography directs diagnostic procedures (amniocentesis) and therapeutic interventions (vesicoamniotic shunts). When ultrasound has proved unsatisfactory (e.g., in cases of maternal obesity or anhydramnios), magnetic resonance imaging is superior to provide sufficient anatomical detail.

Whereas in upper urinary tract obstruction the prognosis of the fetus is relatively good, in lower urinary tract obstruction the situation is very different, because of associated cystic renal dysplasia, oligohydramnios, pulmonary hypoplasia, dysmorphia, and limb contractures. Prenatal diagnosis allows for the planning of appropriate prenatal and postnatal care, consideration of prenatal intervention, and psychological adjustment of the parents. However, for some fetal abnormalities of the lower urinary tract, there is still uncertainty regarding best management [122, 123]. The use of fetal urine samples, fetal serum, amniotic fluid, and finally, fetal renal biopsies is still limited. The prognostic value of markers to assess fetal renal function is uncertain and the effectiveness of therapy remains to be established [122–124]. However, some factors have been shown to be predictive of poor outcome in terms of renal function at birth and infancy. The main goal of imaging studies today is to distinguish as early as possible those kidneys that do not require surgery from those that will deteriorate and lose function or growth potential and thus benefit from surgery.

Fetal Urine Analysis

In the presence of severe fetal obstructive uropathy (e.g., posterior urethral valves), the analysis of fetal urine is most commonly used before performing in utero therapy. The first urine sample may not reflect kidney function, as this urine may have been in the bladder for some time. Sequential sampling of fetal urine seems to improve the accuracy. Measured values that remain stable or even increase over time are more suggestive of renal dysplasia. Different electrolytes (sodium, calcium, and chloride), α_1-microglobulin, β_2-microglobulin, total protein, microalbumin, *N*-acetyl-β-glucosaminidase, osmolality, and various urinary analytes (IGF-1, IGF-BP3, creatinine, cystatin C) have been used as markers for fetal kidney function. Recently, fetal urinary peptides have been shown to predict postnatal renal function in fetuses with posterior urethral valves [124]. Among more than 4,000 fetal urinary peptides, 26 peptides were identified that were specifically associated with early end-stage renal disease before the age of 2 years [124]. Fetal tubular dysfunction can be indicated by raised urinary sodium concentration. At around 20–30 weeks of gestation, sodium concentrations in the fetal urine fall below 90 mmol/l. Fetal urinary sodium or chloride concentrations above 100 mmol/l have been shown to be predictive of fetal or perinatal death from renal or pulmonary failure [125, 126]. Increased values of fetal urinary β_2-microglobulin >13 mg/l, which is normally filtered by the glomerulus and >99.9 % reabsorbed in the proximal tubule, were associated with a fatal outcome [127]. The two most accurate tests to select suitable candidates for in utero therapy were the detection of urinary calcium and sodium >95th percentile for gestation. But a systematic review to evaluate the usefulness of fetal urine analysis in congenital urinary tract obstruction concluded that the evidence is insufficient [128].

Postnatal Diagnosis

In upper urinary tract obstruction (e.g., ureteropelvic junction obstruction), patients who elude antenatal diagnosis may develop abdominal pain or discomfort, hematuria, or urinary tract infection. It can be difficult to realize that

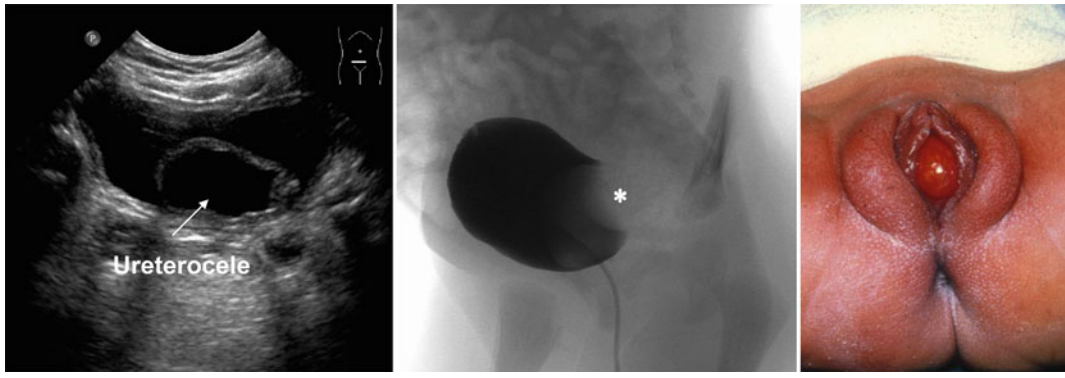

Fig. 1 Prolapsed ureterocele in a newborn shown by ultrasound and VCUG with filling defect (*) (Courtesy Dr. B. Kammer, Dept. Radiology, Dr. H.G. Dietz, Dept. Surgery, Dr. v. Hauner Children's Hospital, LMU, Munich)

recurrent episodes of vomiting are related to obstructive uropathy. Patients with congenital anomalies (VATER/VACTER-L association, congenital heart disease, CNS malformations) may be diagnosed with urinary tract obstruction during the workup for related malformations.

In lower urinary tract obstruction, the presence of abdominal masses (bladder, kidney), delayed voiding (e.g., urethral valves), deficient abdominal wall musculature, or undescended testes (e.g., Eagle-Barrett syndrome) indicates the need for further evaluation. Unfortunately, a normal voiding pattern does not exclude obstruction. In infants with a palpable bladder and in female newborns with an interlabial cystic mass (prolapsed ureterocele), bladder outlet obstruction should be considered (Fig. 1). Delayed diagnosis of lower urinary tract obstruction can be found in children with chronic renal failure, hypertension, recurrent urinary tract infections, sepsis, growth failure, and urinary incontinence.

Imaging and Nuclear Medicine Studies

The evaluation of congenital obstructive uropathy includes the assessment of morphologic and structural changes (e.g., dilatation of the urinary tract, bladder wall thickness, kidney parenchyma) as well as the assessment of functional changes (e.g., impaired ^{99m}Tc-MAG-3 excretion or differential renal uptake). A combination of repeated imaging and nuclear scan examinations provides complementary information and helps to establish the diagnosis.

Ultrasonography

Ultrasonography is the first noninvasive diagnostic test in urinary tract obstruction pre- and postnatally. It is widely available and relatively inexpensive and allows for the morphological assessment of both the lower and upper urinary tract. However, it can be difficult to perform in patients who are not cooperative. Assessment of the fetal urinary tract is part of all routine prenatal ultrasound examinations. Dilatation of the renal pelvis and fluid filled areas as small as 1–2 mm may be visualized in utero using high-resolution real-time ultrasound [129]. Most relevant urinary tract obstructions are currently detected in the second trimester. A fetal pelvic dilatation of more than 3 mm during the second trimester and of more than 6 mm after 32 weeks of gestation may be considered abnormal. Postnatal evaluation is recommended in all cases of prenatal hydronephrosis. In congenital obstructive uropathy, a renal ultrasound should be performed within the first week of life and repeated 4–6 weeks later. The first postnatal ultrasound should not be performed within the first few days of life, when the kidneys produce little urine. This can mask hydronephrosis and give rise to false-negative results. After the first week post-delivery, a renal ultrasound should be performed in term

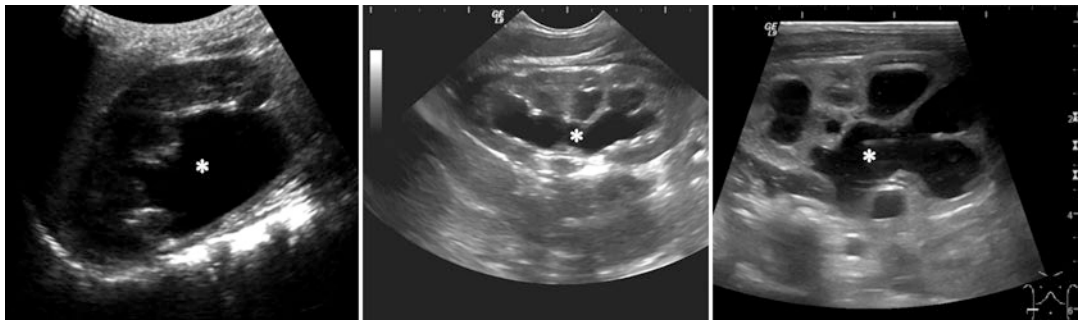

Fig. 2 Ultrasound images of hydronephrosis with pelvicalyceal dilatation (*) (Courtesy Dr. B. Kammer, Dept. Radiology, Dr. v. Hauner Children's Hospital, LMU, Munich)

infants with both a full and an empty bladder; it should assess renal pelvic dilatation, calyceal dilatation, pelvic or ureteral wall thickening, and signs of renal dysplasia. In the absence of calyceal dilatation, the degree of obstruction is limited. In these patients, functional imaging such as nuclear renal scan is not recommended. In contrast, dilatation of all renal calyces indicates a greater degree of obstruction, even with less renal pelvis dilatation (Fig. 2). The renal pelvis diameter should be measured in the transverse plane and at the anteroposterior diameter. An anteroposterior diameter of more than 7 mm in a newborn is considered abnormal (in an older child >1 cm). All measurements should be adjusted to age and size and compared with normal values. Pelvic dilatation is often measured as an indicator of severity, yet may be overestimated with an extrarenal pelvis, which is insignificant. It is important to examine the contralateral normal kidney for hypertrophy, which is an important indicator for decreased function in the obstructed kidney. When abnormalities are found, significant pathology is seen in 70 % and further investigation is mandatory. However, if the postnatal ultrasound shows normal kidneys and urinary tract, only 3 % will have pathology, usually low-grade vesicoureteral reflux [130]. Further investigations include a voiding cystourethrogram, nuclear scans, and, in rare cases, magnetic resonance imaging to detect and determine degree of reflux and obstruction.

Voiding Cystourethrogram

The voiding cystourethrogram (VCUG) is an essential part of most basic evaluations of patients with hydronephrosis. The VCUG provides anatomical information in terms of bladder morphology, bladder capacity, patency of the urethra, bladder emptying, and, in case of reflux, an anatomical description of the upper urinary tract. It still serves as the gold standard for detecting posterior urethral valves, vesicoureteral reflux, ureteroceles, and bladder diverticulae (Fig. 3). Vesicoureteral reflux can both cause and coexist with hydronephrosis; it can contribute to additional obstruction due to ureteral dilatation and should be assessed early. It is important to state that grading of reflux can be difficult if obstruction is present. Because of the relatively high incidence of reflux in children with congenital urinary tract obstruction, most physicians keep patients on antibiotic prophylaxis until the VCUG is obtained.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a noninvasive, radiation-free imaging modality, which is considered ideal for assessment of detailed anatomy, particularly of ectopic ureteral insertion, complicated duplex systems, or when other complex pathologies are suspected [131]. The administration of a specific nonnephrotoxic intravenous contrast medium allows for the functional evaluation of parenchymal perfusion, glomerular

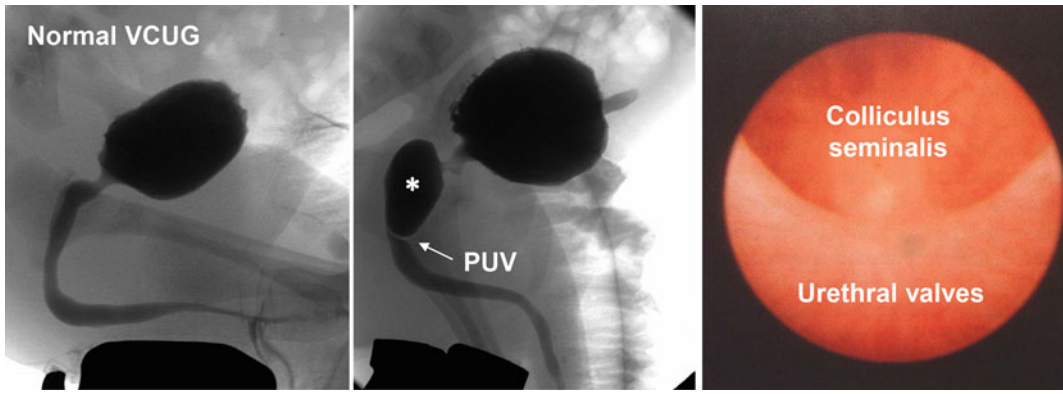

Fig. 3 Posterior urethral valves (PUV) on a voiding cystourethrogram with dilated posterior urethra (*). Endoscopic image of PUV (Courtesy Dr. B. Kammer, Dept. Radiology and Dr. H.G. Dietz, Dept. Surgery, Dr. v. Hauner Children's Hospital, LMU, Munich)

filtration, and renal excretory function. Indications for MRI include preoperative anatomic imaging and the assessment of vascular anatomy. With its fine resolution, the presence of a crossing blood vessel causing obstruction may be detected. The MRI may also differentiate between hydronephrosis and parapelvic cysts. It provides excellent anatomic and functional details of the collecting system [132]. Thus, ureteral strictures in children can be diagnosed more accurately [133]. Its use is restricted in younger children by the need for sedation, its high costs, and limited availability. The correlation with functional outcomes in obstructive uropathy has yet to be established.

Radionuclide Renal Scintigraphy

Nuclear medicine studies play an important role in the functional assessment of the kidneys. Radionuclide scintigraphy can evaluate relative renal function, estimate absolute renal function, indicate functional renal parenchyma and renal scars, estimate renal blood flow, and measure excretory function [134, 135]. Several radiopharmaceuticals are available to image the kidney and monitor function. ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA), ^{99m}Tc-dimercaptosuccinic acid (DMSA), and ^{99m}Tc-mercaptoacetyltriglycine (MAG-3) are the most commonly used substances. In children with obstructive uropathies, ^{99m}Tc-MAG-3 is the main radiopharmaceutical for renal imaging. Following intravenous administration, ^{99m}Tc-MAG-3 is highly protein-bound and removed from the plasma primarily by the organic anion transporter 1 located on the basolateral membrane of the proximal renal tubules in the kidney. ^{99m}Tc-MAG-3 accumulates in the proximal tubular cell and is secreted into the tubular lumen via organic anion transporters on the apical membrane. If the apical transporter is impaired to a greater extent than the basolateral transporter, ^{99m}Tc-MAG-3 activity is retained in the kidneys. The ^{99m}Tc-MAG-3 scintigraphy sometimes described as tubular extraction rate can be used as a measure of relative renal function. Relative renal function is indicated as the percentage of the right and the left kidney, with both adding up to 100 % global function. Each kidney normally contributes 50 %. With regard to the standard deviation, a relative renal function of less than 40 % is mostly considered abnormal. Decreased renal function either reflects unilateral renal impairment or congenital anomalies (e.g., dysplasia). Normal relative function results may be also obtained with bilaterally damaged kidneys. Because of its more efficient extraction (more than twice that of ^{99m}Tc-DTPA), ^{99m}Tc-MAG-3 is preferred in patients with suspected obstruction and impaired kidney function. Multiple protocols have been used for ^{99m}Tc-MAG-3 nuclear scans with different time points of furosemide administration and variable acquisitions [134–137]. The "F = 0 protocol" is the most convenient protocol, in which

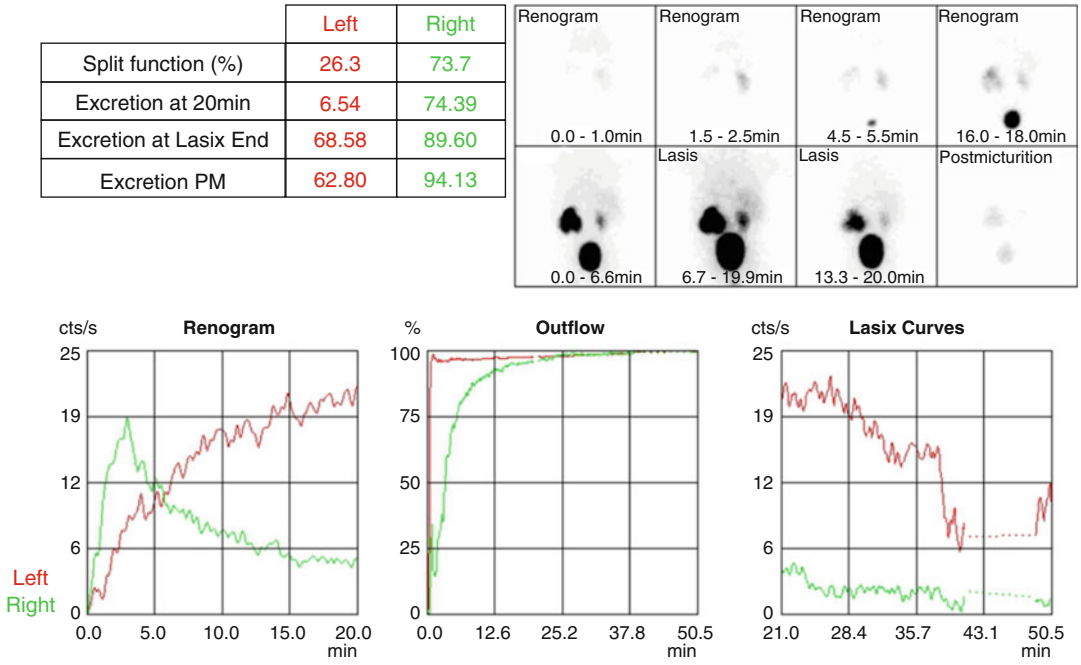

Fig. 4 MAG-3 diuretic renogram in ureteropelvic junction obstruction (UPJO), demonstrating reduced split function and delayed washout of the tracer on the left side, suspicious for obstruction (Courtesy Dr. T. Pfluger, Dept. Nuclear Medicine, LMU, Munich)

furosemide (1 mg/kg with a maximum dose of 20 mg in a child) is administered simultaneously with the tracer. The "F + 20 protocol" gives furosemide 20 min after the beginning of the investigation and allows for the direct evaluation of the tracer washout. The washout phase is used to examine the severity of obstruction; it is conventionally assessed by measuring the half-time (T1/2) after furosemide administration. The nuclear scan report describes a ^{99m}Tc-MAG-3-time-activity curve for each individual kidney. The normal curve shows a steep rising, followed by an early peak and a rapidly declining phase. In contrast, urinary tract obstruction with dilatation results in a continuously rising curve. The application of furosemide is used to differentiate between obstruction and "reservoir effect." The time required to clear one-half of ^{99m}Tc-MAG-3 is monitored in minutes (T1/2). If the half-time is less than 10 min, then drainage is normal, while 10–20 min is uncertain, and a T1/2 over 20 min may indicate obstruction (Fig. 4). It is important to state that a prolonged T1/2 should never be the sole criterion for the obstruction. Clinical correlation with ultrasound is mandatory and sequential nuclear scans are often needed to obtain reasonable results. The Santa Fe consensus report recommends a 35 min acquisition with furosemide administered after 20 min. This diuretic MAG3 renography with the "F + 20 protocol" is the method of choice in young children with obstructive uropathy [131, 138]. In the meantime, criteria have also been developed for children that allow the furosemide application to be omitted when the baseline drainage is normal [139]. ^{99m}Tc-MAG-3 scintigraphy can be used as early as at the end of the first week of life to assess differential renal function. Because immature nephrons of the newborn kidney are less sensitive to furosemide, a diuretic ^{99m}Tc-MAG-3 study should be postponed for at least 4–6 weeks to allow for nephron maturation. In the typical patient with unilateral hydronephrosis and dilated calyces, the ^{99m}Tc-MAG-3 scintigraphy would be performed at

2–3 months of age and repeated 3–12 months later depending on the results obtained. Patterns of change over time are probably the most useful markers to indicate the status of the affected kidney. Nuclear scans remain the "gold standard" for the functional assessment of the kidney with obstruction, but better diagnostic tools are clearly needed.

^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA) is the only renal radiopharmaceutical available for routine imaging that is purely filtered by the glomerulus. Consequently, it can be used to measure glomerular filtration rate.

^{99m}Tc-dimercaptosuccinic acid (DMSA) is an excellent cortical imaging agent that is used primarily to evaluate relative function, pyelonephritis, and renal scarring [140, 141]. Approximately 40 % of the injected dose is retained by the renal tubules within 1 h after injection. ^{99m}Tc-DMSA initially binds to α_1-microglobulin; the complex is then filtered by the glomerulus and accumulates in the kidney via megalin-/tubulin-mediated endocytosis [142]. Thus, the renal uptake of ^{99m}Tc-DMSA depends on renal blood flow, glomerular filtration, and proximal tubule receptor-mediated endocytosis.

Excretory Urography and Pressure Perfusion Studies

The intravenous pyelogram (IVP) has practically vanished, except for rare circumstances and conditions such as urolithiasis or pre- and postoperative evaluation in complex conditions, particularly when other imaging tools are not available or applicable. In selected cases, in which the anatomy is not satisfactorily defined, the IVP can provide structural and functional information of the urinary tract. The "Whitaker test," which was developed in the late 1960s and early 1970s, combines a urodynamic study with antegrade pyelography to assess potential upper urinary tract obstruction. They are invasive by instilling contrast directly into the affected kidney and require general anesthesia. The "Whitaker test" may differentiate between patients with residual or recurrent obstruction and those with dilatation secondary to permanent ureteral changes. In selected cases, it can be used to determine when percutaneous nephrostomy tubes can be safely removed in postoperative patients [143].

Ureteropelvic Junction Obstruction

Ureteropelvic junction obstruction (UPJO) is the most common cause of prenatal hydronephrosis and has an incidence of 1 in 1,000–1,500 newborns. UPJO is more common on the left side (2:1 – left to right) and more common in boys (2:1 – male to female). Bilateral obstruction is rare. UPJO is characterized by an obstruction at the proximal portion of the ureter where the pelvis narrows into the ureter. The obstruction can be classified as intramural, mural, or extramural. Intramural causes are exceptionally rare in children and include abnormal mucosal valves or fibroepithelial polyps. Mural obstructions, which are most common, result from a dysfunctional or adynamic ureteral segment that shows abnormal distribution of smooth muscle cells and collagen fibers. In mural UPJO, the lumen is almost always patent, albeit narrow and irregular. Extramural or extrinsic causes, which are less common, include aberrant or crossing renal vessels, artery and/or vein, bands, or adhesions (Fig. 5). Usually a lower pole renal vessel fixes the ureter in position; but not all so-called crossing vessels are obstructive. They may cause intermittent reductions in urine flow with intermittent dilatation of the pelvis. In the majority of UPJO, the underlying cause is thought to be functional.

Development of the Ureter and the Ureteral Peristaltic Machinery

The kidney starts to produce urine at ~10 weeks of gestation. At the same time, the trunk of the ureteric bud starts elongating without branching to form the ureter, a muscular tube structure transporting urine [144]. Similar to the kidney, the morphogenesis of the ureter requires a close interaction between the inner ureteral epithelial cells and the surrounding ureteral mesenchymal cells. In response to the molecular signals from the

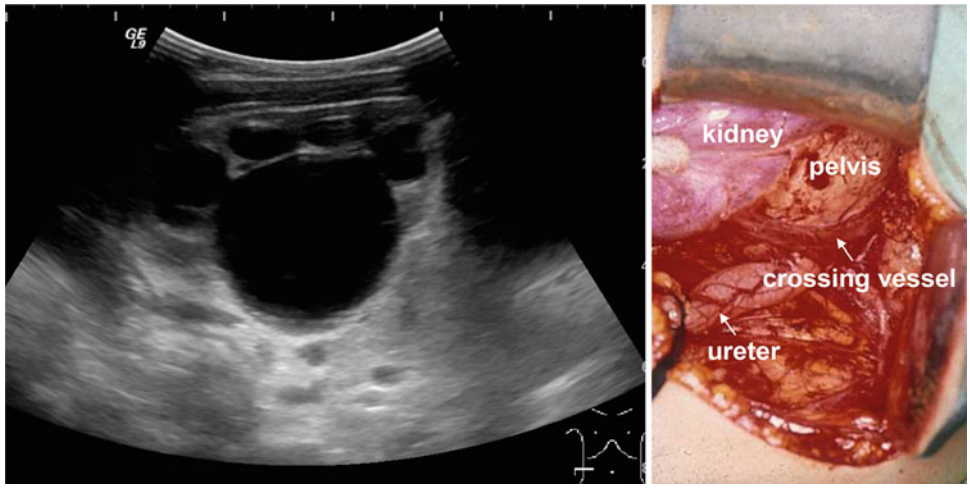

Fig. 5 Ureteropelvic junction obstruction with pelvicalyceal dilatation and crossing vessel (Courtesy Dr. B. Kammer, Dept. Radiology and Dr. H.G. Dietz, Dept. Surgery, Dr. v. Hauner Children's Hospital, LMU, Munich)

epithelial and mesenchymal cells, the early simple cuboidal ureteral epithelial cells differentiate into the multilayered urothelium (also called transitional epithelium). The urothelium is covered by urothelial plaques expressing uroplakin proteins and is impermeable to urine [72, 73, 145]. This process occurs at around 10 weeks in humans, which coincides with the beginning of urine production by the fetal kidney. Meanwhile, the mesenchymal cells differentiate into stromal cells, smooth muscle cells, and adventitial fibroblasts (serosa after maturation). Differentiated smooth muscle cells are further organized into layers with inner circular and outer longitudinal orientation and express α-smooth muscle actin [77, 78, 84, 146]. Interestingly, the ureter smooth muscle differentiation occurs in an ascending fashion from the distal ureter close to the bladder to the proximal ureter that is next to the pelvis [146]. This process is in the opposite direction to the propagation of ureteral peristalsis that transports urine from the kidney to the bladder. Peristaltic waves are initiated in the renal pelvis and are propagated through the ureter wall to the bladder. This contractile activity is triggered by special pacemaker cells located in the most proximal calyceal region of the pelvic-kidney junction, which produces regular pulsatile electrical signals transmitted along the electrically active "typical" smooth muscle cells (SMC) in the ureter [147]. Two types of special pacemaker cells have been identified in the renal pelvis and the ureter. The primary pacemaker cells are also called "atypical" smooth muscle cells (SMC) because they contain fewer contractile filaments with a weak α-smooth muscle actin expression compared to the regular "typical" smooth muscle cells. Atypical SMCs are mainly located within the most proximal region of the renal pelvis and display many morphological features similar to those of the cardiac sinoatrial pacemaker cells [148]. The other type of the pacemaker cells in the renal pelvis and ureter is the interstitial cell of Cajal (ICC)-like cells (ICC-LCs), which are characterized by the expression of the proto-oncogene Kit and have thin and long cytoplasmic processes that are similar to those of the intestinal ICCs [87]. These ICC-LCs are located sparsely throughout the ureter (including renal pelvis, UPJ, UVJ) [149, 150]. However, the distribution of ICC-LCs is not even, with most ICC-LCs located in the proximal renal pelvis and reduced cell density in the distal segments of the ureter [149, 150]. The ICC-LCs can produce electrical slow-wave potentials that control the propagation of the peristaltic activity [150]. The molecular mechanism and physiological functions of the ureteral peristaltic machinery are still unclear.

It has been suggested that atypical SMCs in the tip of the renal pelvis act as the primary pacemaker to initiate spontaneous potentials that are propagated and modulated by ICC-LCs to the adjacent typical SMCs in order to trigger intermediate action potentials and ureteral smooth muscle contraction. The ICC-LCs may also produce additional autorhythmicity and can take over pacemaking in the renal pelvis and ureter in the absence of the primary pacemaker activity [150, 151]. The development of this ureteral peristaltic machinery is also not well understood. A recent study shows that mouse Kit-expressing ICC-LCs are first detected at E15.5 in a subset of renal epithelial cells and cells of the ureteropelvic adventitia [87]. This developmental time point is followed by the beginning of urine production by the mouse embryonic kidney around E16.5 and is well before the initial ureteral peristaltic waves which are first observed around E18.5 in mice [87]. It is still unclear when the ICC-LCs appear in the human fetal ureter and at what embryonic stage human fetuses start to have rhythmic ureteral peristalsis.

Genetics in Ureteropelvic Junction Obstruction (UPJO)

Weisschuh et al. have described a ureteropelvic junction obstruction phenotype in patients with Axenfeld-Rieger syndrome (Table 2) [152]. The Axenfeld-Rieger syndrome is caused by mutations in FOXC1, a transcription factor of the forkhead family that is highly expressed in the metanephric mesenchyme. In addition, mutations in the transcription factor *FOXF1*, another member of the forkhead box genes, cause the "alveolar capillary dysplasia with misalignment of pulmonary veins" (ACDMPV) syndrome. ACDMPV is associated with ureteral valve-like constriction at the ureteropelvic junction, tortuous ureters, and hydronephrosis [152, 153]. *FOXF1* is located at the same chromosomal locus as *FOXC2* and is a part of the sonic hedgehog and TGF-β signaling pathway (Table 2) [154]. Other genes in the sonic hedgehog and TGF-β signaling pathways play critical roles in lower urinary tract development and congenital anomalies. *FOXC1* is the only gene so far that has been associated with UPJ obstruction in humans [152, 153].

Clinical Presentation in UPJO

Most UPJO is detected prenatally, but some may still present later in life with acute flank pain, nausea, vomiting, and abdominal discomfort. Many of these patients are thought to have gastrointestinal symptoms. Pain usually results from intermittent obstruction of the urinary tract when the urine flow overwhelms the capacity to drain. The pattern of abrupt onset with severe abdominal pain, nausea, and vomiting, often in the late evening, is typical for older children with UPJO. Late-onset hypertension can occur in patients with obstruction [155, 156]. Urinary tract infection (UTI) is an uncommon presentation in UPJO, but may be quite severe requiring urgent intervention and drainage. Vesicoureteral reflux (VUR) should be evaluated in patients with UPJO and UTI, since the incidence of VUR in infants and young children who present with pyelonephritis is higher than any other anomaly of the urinary tract including obstruction. Nevertheless, most children with UPJO are asymptomatic and rarely require intervention.

Management of UPJO

The majority of patients with UPJO can be managed conservatively by a "watchful waiting" policy, i.e., close observation and regular imaging monitoring. This is usually accomplished by regular serial ultrasound investigations in well-hydrated infants and children using standardized ultrasound grading and pelvicalyceal system measurements, complemented by intermittent ^{99m}Tc-MAG-3 diuretic scans, particularly if the ultrasound demonstrates suspicion of deterioration. The postnatal evaluation of a child with prenatally detected hydronephrosis should begin with an ultrasound. Spontaneous resolution of hydronephrosis within the first weeks of life has been shown for 17 % of cases [157]. Of the

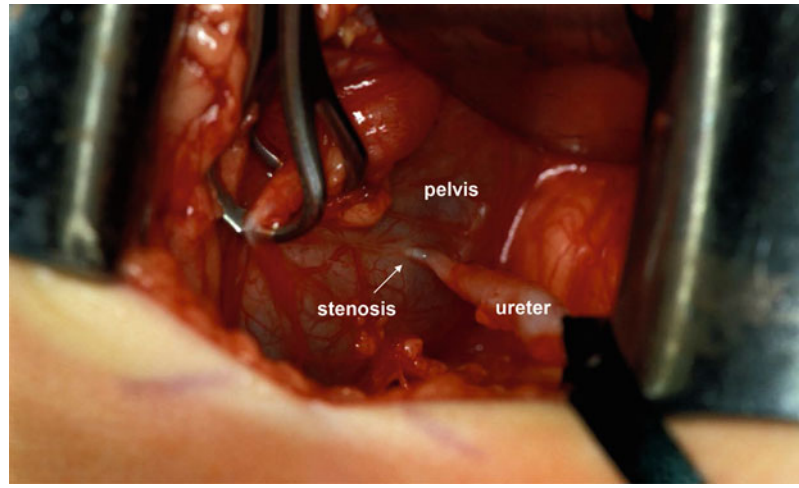

Fig. 6 Ureteropelvic junction obstruction (Courtesy Dr. H.G. Dietz, Dept. Surgery, Dr. v. Hauner Children's Hospital, LMU, Munich)

remaining infants, 72 %, 19 %, and 2 % demonstrate mild (5–9 mm), moderate (10–15 mm), and severe (>15 mm) dilatation, respectively [157]. Whereas almost 90 % of cases with mild or moderate hydronephrosis resolve or stabilize within the first 2 years of life, the remaining 10 % show persistent moderate to severe dilatation. Infants with severe postnatal dilatation on initial ultrasound will stabilize or resolve to normal or mild dilation in 25 %, while 50 % stabilize at moderate dilatation within the first 2 years. 25 % of initially severely dilated cases will show persistent severe dilatation [157, 158].

In summary, it can be stated that infants with moderately severe to severe hydronephrosis with caliectasis will need ongoing monitoring and functional assessment. This will be with a ^{99m}Tc-MAG-3 diuretic renogram to evaluate differential function and washout times (Fig. 4). If the initial function is lower than 45 %, follow-up ^{99m}Tc-MAG-3 may be exercised in 3–9 months. Ultrasound evaluation should be repeated every 3–6 months. Progressive hydronephrosis, decreasing differential renal function, and recurrent urinary tract infections may be all indicative of surgical intervention. It appears as if the first year is the most dynamic in UPJO. Most surgical interventions are performed within the first 2 years of life [159]. For children with less severe hydronephrosis, functional imaging is not usually useful unless regular ultrasound detects progressive hydronephrosis and deterioration. Ultrasound intervals are usually increased over time; most children with UPJO are followed until normal. Closer monitoring should be exercised in patients with a higher risk for adverse outcome (bilateral hydronephrosis, solitary kidney with UPJO) [131].

At present, indications for surgical correction of UPJO vary between institutions, countries, and continents. In a retrospective study of 343 children with prenatally diagnosed UPJO initially conservatively managed, over 50 % eventually required surgical treatment [159]. Advanced skill and experience as well as new surgical techniques have improved surgical results even in very early infancy (e.g., neonatal pyeloplasty, endoscopic and/or endoluminal pyeloplasty). Laparoscopic pyeloplasty has been used for over a decade, but still remains of limited availability. Success rates are good and morbidity seems to be decreased. With the advent of robotic surgical technology, the learning curve for this type of laparoscopic surgery is markedly shortened [160–162].

Open surgery is still the gold standard for relief of UPJO through the dismembered pyeloplasty. This can be performed in the flank position or through a dorsal lumbar incision, which both are cosmetically reasonable. The procedure includes the resection of the stenotic segment, some size reduction of the dilated pelvis, and reanastomosis of the ureter to the renal pelvis (Fig. 6). Success rates are in the 95–97 % range [163]. Following UPJO surgery, recovery is quick in infants but

slower in older children. Percutaneous nephrostomy (PCN) was more regularly performed one or two decades ago, for example, in neonates with "gross dilatation" as "bridging" until surgery. Today this is only considered for untreatable pyonephrosis, severe bilateral obstruction with renal insufficiency, or in a severely obstructed single kidney with elevated serum creatinine.

Biomarkers in UPJO

The lack of precise and reliable markers of urinary tract obstruction is a critical issue [164]. Numerous urinary biomarkers (TGF-β, TNF-α, *N*-acetyl-β-D-glucosaminidase, epidermal growth factor (EGF), CCL2, angiotensinogen) have been evaluated in patients with UPJO [165–169]. The detection of urinary polypeptides by capillary electrophoresis and mass spectrometry (CE-MS) was shown to predict the outcome of infants with UPJO [170, 171]. A recent meta-analysis included 14 studies with reported data on 380 UPJO patients who underwent surgery, 174 who were treated conservatively, and 213 controls. The authors conclude that some biomarkers offer promising results. However, more multicenter, prospective studies are needed to evaluate their diagnostic and prognostic value [172, 173].

Long-Term Follow-Up in UPJO

The long-term outcome seems to be remarkably positive for most patients with UPJO. Nevertheless, long-term studies are missing. Many children undergoing successful pyeloplasty are lost for follow-up after several years. In light of the experimental evidence, as well as the limited clinical data, it is very likely that some of these patients will develop proteinuria, hypertension, or chronic renal insufficiency. In a long-term follow-up study of children after pyeloplasty for ureteropelvic junction obstruction, renal function measured by nuclide scan improved in all but one patient. Persistent abnormal renal function was present in 14 of 33 patients [174]. Renal function improved significantly in children undergoing surgery at <1 year of age, but normalized in only one of six patients >1 year of age [174]. Children undergoing pyeloplasty for grade IV hydronephrosis showed a broad range of renal interstitial fibrosis [167]. Delay of pyeloplasty in these children was associated with greater macrophage infiltration and a lower glomerular filtration rate [167]. In addition, renal interstitial fibrosis can be found in kidney biopsies of UPJO patients and correlates significantly with the differential function of the affected kidney [52, 175]. Differences in the urinary peptidome excretion at a five-year follow-up may indicate permanent changes in the kidney or urinary tract in the nonoperated patients with UPJO, while based on clinical parameters, these children are considered normal [176]. These data strongly support the need for long-term follow-ups in less severe cases of UPJO. For the long-term prognosis, it will be important to determine whether these changes are deleterious or the result of an ongoing and possibly beneficial remodeling process.

Ureterovesical Junction Obstruction

Ureterovesical junction obstruction (UVJO) is characterized by an obstruction at the distal end of the ureter and results in a megaureter (Fig. 7). The term obstructive megaureter or primary obstructive megaureter (POM) is often used for this entity and should be distinguished from a refluxing megaureter. UVJO is usually caused by an adynamic segment of the distal ureter. Similar to UPJO, histological studies show changes of disordered smooth muscle cells and abnormal collagen deposition. UVJO is less common than UPJO; it is a rare cause of hydronephrosis (reported incidences 9–14 %) [2]. UJVO is seen more often in boys and left-sided involvement is more frequent. Bilateral involvement occurs.

Pathogenesis of UVJO

The "bud theory" developed by Mackie and Stevens explains that the ureteral orifice derives from

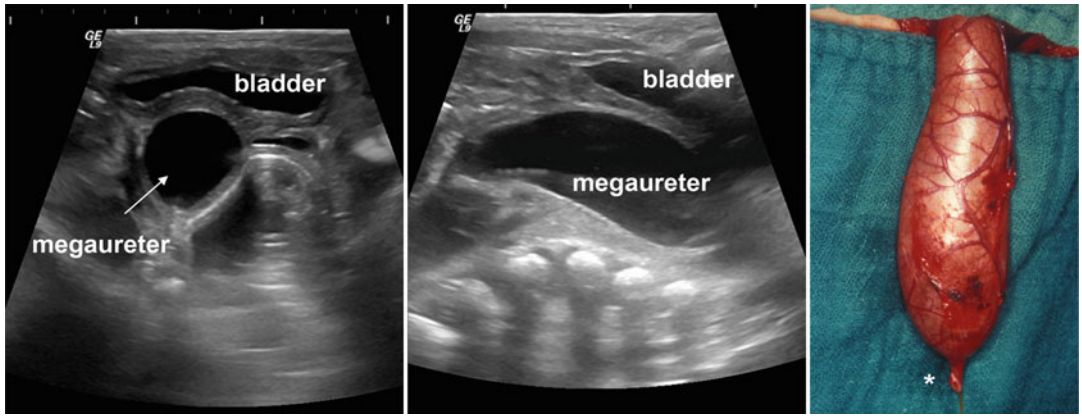

Fig. 7 Ureterovesical junction obstruction with dilated megaureter (*stenosis) (Courtesy Dr. B. Kammer, Dept. Radiology, Dr. H.G. Dietz, Dept. Surgery, Dr. v. Hauner Children's Hospital, LMU, Munich)

the original ureteric budding site on the Wolffian duct during embryologic development [177]. When the ureteric buds arise at abnormal sites of the Wolffian duct, the final sites of the ureteric orifices may be also abnormal, resulting in disturbed ureterovesical junctions, vesicoureteral reflux, or UJVO. In addition, multiple ureteric buds may also lead to short duplex ureters, duplex kidneys, ectopic, and dysplastic kidneys [47, 68, 69, 80, 102, 177–180]. Therefore, mutations of genes controlling early ureteric bud formation and positioning can cause ureteral phenotypes like urinary obstruction, vesicoureteral reflux, and hydronephrosis [144, 180–183]. Additionally, maldevelopment of the ureter and its peristaltic machinery may cause UVJO as well (see section "Development of the Ureter and the Ureteral Peristaltic Machinery").

Clinical Presentation in UVJO

Most UVJO is detected prenatally. Urinary tract infection is a frequent clinical presentation of UVJO and should prompt evaluation for additional vesicoureteral reflux in infants and young children. Most physicians keep patients with UVJO on antibiotic prophylaxis during the first 6–12 months. During acute infection, the megaureter may appear far more dilated than before, which is presumably due to the effect of bacterial toxins on the ureteral muscle tone. Abdominal or flank pain, nausea, and vomiting are less common in UVJO.

Diagnosis and Management of UVJO

Diagnosis of UVJO is usually achieved by ultrasound. Only rare cases of ureteral valves can pose a problem, as they can easily be missed. As with UPJO, most cases of UVJO resolve spontaneously. The pattern of resolution is cranial to caudal and often the distal dilatation is the last to disappear, which can take years. Isolated distal dilatation as a residue of UVJO may be found in older children and adults. While UJVO was initially often operated early, there is now general agreement that a conservative approach is usually feasible without endangering the kidney. With the conservative approach, repeated follow-up studies using ultrasound are essential. Monitoring for urinary tract infection, often with uncommon bacteria or fungus, is mandatory. Peristalsis of the obstructive megaureter can be assessed sonographically when using cine loop clips or M-mode tracks and the ureteral inflow jet [131]. For quantification of drainage, a diuretic ^{99m}Tc-MAG-3 scintigraphy with a "F + 20 protocol" should be performed with good hydration as well as bladder emptying and upright positioning for assuring maximum drainage. Approximately

10 % of UVJO patients will need surgical correction. It is important to differentiate those children who do well with primary reimplantation from those who benefit from temporary diversion by ureterocutaneostomy to enable maturation and retonisation of the ureter.

Megacystis Microcolon Intestinal Hypoperistalsis Syndrome

Megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS) is an extremely rare cause of antenatally detected urinary tract dilatation. MMIHS is a cloacal plate anomaly that is more often seen in females. It is a rare genetic disease with autosomal recessive inheritance. MMIHS is characterized by a dilated bladder and hydronephrosis in the presence of normal or increased amniotic fluid. Smooth muscle cells in the bladder and distal bowel are dysfunctional. Tissue analysis of patients with MMIHS demonstrates a lack of the alpha$_3$-nicotinic acetylcholine receptor subunit giving a possible explanation for the underlying pathogenesis in some cases.

Prune Belly Syndrome (Eagle-Barrett Syndrome)

Prune belly syndrome (PBS) is a rare lower urinary tract malformation affecting about 1 in 30,000 newborns [184]. PBS consists of a triad of typical features, which include a partial or complete lack of abdominal wall musculature with a dry prune-like wrinkly skin appearance of the abdomen (so-called prune belly), the dilation of the proximal and distal urinary tract with hydronephrosis, hydroureters, a distended thin-walled bladder, and bilateral cryptorchidism. All these signs are present in the neonatal period [185]. The majority of PBS patients are males. Coexisting morbidities include pulmonary hypoplasia, vesicoureteral reflux, abnormalities of the urethra, and dysplastic kidneys, which commonly lead to chronic renal failure and kidney transplantation. Mutations in *HNF-1B* and *CHRM3* gene have been described in patients with PBS [186–188]. The prenatal presentation is similar to posterior urethral valves (PUV). In contrast to PUV, both sexes can be affected in PBS, and the so-called keyhole sign, which is typical for PUV, is missing on ultrasound.

Posterior Urethral Valves (PUV)

Posterior urethral valves (PUV) are the most common cause of lower urinary tract obstruction in male infants. They are characterized by the formation of sail-like membrane folds from the verumontanum to the prostatic urethra, which causes severe bladder outlet obstruction exclusively in boys. PUV occur in 1:5,000 live births and are observed in 0.003 % of fetal ultrasound screenings [189]. PUV are the most common cause of obstructive uropathy leading to end-stage renal failure [5, 122]. PUV is a condition with high mortality and morbidity [129].

Development of the Bladder and Urethra

Unlike the mesodermal ontogenetic origin of the kidney and ureter, the bladder and urethra arise from the endodermal urogenital sinus after the urorectal septum (i.e., Tourneux's fold) separates the embryonic cloaca into the ventral urogenital sinus and the dorsal rectum [190]. At around 5 weeks of human gestation, the urogenital sinus is further separated into the anterior vesicourethral canal and the posterior urogenital sinus. The anterior portion of the urogenital sinus becomes the bladder, which has an open outflow tract at its apex that is connected to the allantois during early fetal development. This outflow tract is only functional at the early embryonic stage to drain the developing bladder to the allantois through the umbilical cord. By ~15 weeks of human gestation, the bladder separates from the umbilicus and becomes a remnant called the urachus, which is further stretched to become the median umbilical ligament. In the meantime, the posterior vesicourethral canal becomes the pelvic portion of urethra in the male (which can be

further divided into three segments: preprostatic, prostatic, and membranous urethra) and the entire urethra in the female [190, 191]. The fetal origin of PUV formation is still unclear. It is thought to develop due to an abnormal insertion of the Wolffian duct into the cloaca resulting in the formation of abnormal ridges or folds in the posterior urethra [192].

Pathophysiology of PUV

The classic form of PUV is found in the prostatic urethra, below or proximal to the verumontanum. Although the precise mechanism of PUV formation is unknown [193], four theories have been proposed to explain their development. They include hypertrophy of the urethral mucosal folds, persistence and continuation of the urogenital membrane [194], abnormal development of the Wolffian or Mullerian duct [195], and fusion of the verumontanum or the posterior urethral roof epithelium [122]. The upstream effects of PUV may be profound, leading to abnormal renal development in the most severe cases. PUV may result in massive hydronephrosis and ureteral dilatation; the bladder can be markedly thickened with muscle hypertrophy and matrix deposition. Severe obstructions are associated with oligohydramnios and pulmonary hypoplasia, which causes high mortality and morbidity.

Genetics in PUV

There is no single gene mutation or biologic model that reproduces the phenotype of posterior urethral valves or congenital bladder outlet obstruction. So far, no causative genes have been identified for PUV although familial inheritance has been reported [196].

Clinical Presentation and Diagnosis

Most patients with PUV are detected prenatally. The typical findings at second trimester ultrasound are bilateral hydronephrosis, distended bladder, dilated posterior urethra (keyhole sign), and thickened bladder wall in a male fetus. Increased echogenicity (bright kidneys) and cysts in the fetal kidney are suggestive of renal dysplasia. Amniotic fluid volume, associated anomalies, and fetal sex need to be assessed by ultrasound (for prenatal diagnosis, see section "Prenatal Diagnosis"). Unless there is consideration for antenatal intervention, there is little change in obstetric management. Early delivery is not beneficial and exposes the child to the risks of prematurity. There are no contraindications to vaginal delivery in PUV. Postnatally, the definitive diagnosis of PUV can be made by VCUG. Older children with PUV may present with urinary tract infections, urosepsis, renal failure, or urinary incontinence. In most cases, there will be evidence of an abnormality on ultrasound, which can be then confirmed by VCUG.

Management in PUV

The clinical management of PUV continues to challenge pediatric nephrologists and urologists due to the wide spectrum of severity, the variable clinical progression, the inability to predict long-term consequences, and the inability to alter established renal damage. PUV is a lifelong condition.

Prenatal Management of PUV

Early intrauterine shunting (vesicoamniotic or vesicoperitoneal shunt) cannot improve outcome, but carries the risk of severe complications. Vesicoamniotic shunting was first reported in 1982. Since then, a few case series have suggested that survival could be improved in fetuses that undergo this procedure [197, 198]. Recently, in a randomized trial in the UK, Ireland, and the Netherlands, women whose pregnancies with a male fetus were complicated by PUV were randomly assigned to receive either the intervention (placement of vesicoamniotic shunt) or conservative management [123]. The primary outcome was survival of the patient to 28 days postnatally. Survival seemed to be higher in the fetuses receiving vesicoamniotic shunting, but the size and

direction of the effect remained uncertain, such that benefit could not be conclusively proven. The results show that the chance of newborn babies surviving with normal renal function is very low irrespective of whether or not vesicoamniotic shunting is done [123]. Unfortunately, the trial was stopped because of poor recruitment. At present, these prenatal procedures are recommended only in fetuses with relatively unimpaired fetal urine samples (see section "Fetal Urine Analysis"). If untreated, fetal lower urinary tract obstruction carries a mortality rate of 45 %, which is mainly due to the association with severe oligohydramnios in the midtrimester with pulmonary hypoplasia [199]. The initial management of fetuses with lower urinary tract obstruction may therefore require respiratory support and intensive care.

Postnatal Management of PUV

In suspected posterior urethral valves, early postnatal ultrasound is performed. Perineal ultrasound may demonstrate the valve, but VCUG is still mandatory. Usually early intervention is necessary to ensure sufficient urinary drainage by catheterization, cystostomy, or percutaneous nephrostomy before transurethral valve resection can be performed. The postnatal management focuses on preventing further renal damage that could arise by urinary tract infections. The commonly observed renal damage in these neonates is usually an irreversible renal dysplasia. Adverse prognostic factors in children with PUV include the gestational age at diagnosis, the presence of VUR or bright kidneys at the time of diagnosis, the serum creatinine at one year of age (>1 mg/dl), the presence of urinary tract infections, and later in life, proteinuria and hypertension. Long-term urethral obstruction is potentially associated with cystic renal dysplasia and abnormal renal function (glomerular and tubular). Of those who survive the neonatal period, 25–30 % develop end-stage renal disease necessitating dialysis and/or transplantation. Optimal management of the lower urinary tract is essential for preserving renal function. Bladder dysfunction requires close monitoring and regular urodynamic investigations [200]. In some patients, decreased renal concentrating ability will expose the bladder to high urine volumes, which will further aggravate a small capacity, stiff, and poorly compliant bladder. Recognition and interruption of this cycle of voiding dysfunction is important. Urinary tract infections in children with PUV carry the risk of further deterioration of kidney function and should be treated promptly.

References

1. Rodriguez MM. Congenital anomalies of the kidney and the urinary tract (CAKUT). Fetal Pediatr Pathol. 2014;33:293–320.
2. Morris RK, Kilby MD. Congenital urinary tract obstruction. Best Pract Res Clin Obstet Gynaecol. 2008;22:97–122.
3. Lee RS, Cendron M, Kinnamon DD, Nguyen HT. Antenatal hydronephrosis as a predictor of postnatal outcome: a meta-analysis. Pediatrics. 2006;118:586–93.
4. Ek S, Lidefeldt KJ, Varricio L. Fetal hydronephrosis; prevalence, natural history and postnatal consequences in an unselected population. Acta Obstet Gynecol Scand. 2007;86:1463–6.
5. Wiesel A, Queisser-Luft A, Clementi M, Bianca S, Stoll C. Prenatal detection of congenital renal malformations by fetal ultrasonographic examination: an analysis of 709,030 births in 12 European countries. Eur J Med Genet. 2005;48:131–44.
6. Anumba DO, Scott JE, Plant ND, Robson SC. Diagnosis and outcome of fetal lower urinary tract obstruction in the northern region of England. Prenat Diagn. 2005;25:7–13.
7. Bullock KN, Whitaker RH. Does good upper tract compliance preserve renal function. J Urol. 1984;131:914–16.
8. Koff SA, Peller PA. Diagnostic criteria for assessing obstruction in the newborn with unilateral hydronephrosis using the renal growth-renal function chart. J Urol. 1995;154:662–6.
9. Koff SA, McDowell GC, Byard M. Diuretic radionuclide assessment of obstruction in the infant: guidelines for successful interpretation. J Urol. 1988;140:1167–8.
10. Peters CA. Urinary tract obstruction in children. J Urol. 1995;154:1874–83.
11. Truong LD, Gaber L, Eknoyan G. Obstructive uropathy. Contrib Nephrol. 2011;169:311–26.
12. Klein J, Gonzalez J, Miravete M, et al. Congenital ureteropelvic junction obstruction: human disease and animal models. Int J Exp Pathol. 2011;92:168–92.
13. Chevalier RL, Thornhill BA, Forbes MS, Kiley SC. Mechanisms of renal injury and progression of

renal disease in congenital obstructive nephropathy. Pediatr Nephrol. 2010;25:687–97.
14. Truong LD, Petrusevska G, Yang G, et al. Cell apoptosis and proliferation in experimental chronic obstructive uropathy. Kidney Int. 1996;50:200–7.
15. Gobe GC, Axelsen RA. Genesis of renal tubular atrophy in experimental hydronephrosis in the rat. Role of apoptosis. Lab Invest. 1987;56:273–81.
16. Iwano M, Plieth D, Danoff TM, et al. Evidence that fibroblasts derive from epithelium during tissue fibrosis. J Clin Invest. 2002;110:341–50.
17. Lange-Sperandio B, Trautmann A, Eickelberg O, et al. Leukocytes induce epithelial to mesenchymal transition after unilateral ureteral obstruction in neonatal mice. Am J Pathol. 2007;171:861–71.
18. Thornhill BA, Forbes MS, Marcinko ES, Chevalier RL. Glomerulotubular disconnection in neonatal mice after relief of partial ureteral obstruction. Kidney Int. 2007;72:1103–12.
19. Pedersen TS, Hvistendahl JJ, Djurhuus JC, Frokiaer J. Renal water and sodium handling during gradated unilateral ureter obstruction. Scand J Urol Nephrol. 2002;36:163–72.
20. Li C, Wang W, Kwon TH, et al. Altered expression of major renal Na transporters in rats with bilateral ureteral obstruction and release of obstruction. Am J Physiol Renal Physiol. 2003;285:F889–901.
21. Wang G, Ring T, Li C, et al. Unilateral ureteral obstruction alters expression of acid–base transporters in rat kidney. J Urol. 2009;182:2964–73.
22. Giachelli CM, Lombardi D, Johnson RJ, Murry CE, Almeida M. Evidence for a role of osteopontin in macrophage infiltration in response to pathological stimuli in vivo. Am J Pathol. 1998;152:353–8.
23. Wada T, Furuichi K, Sakai N, et al. Gene therapy via blockade of monocyte chemoattractant protein-1 for renal fibrosis. J Am Soc Nephrol. 2004;15:940–8.
24. Lange-Sperandio B, Cachat F, Thornhill BA, Chevalier RL. Selectins mediate macrophage infiltration in obstructive nephropathy in newborn mice. Kidney Int. 2002;61:516–24.
25. Shappell SB, Mendoza LH, Gurpinar T, et al. Expression of adhesion molecules in kidney with experimental chronic obstructive uropathy: the pathogenic role of ICAM-1 and VCAM-1. Nephron. 2000;85:156–66.
26. Yoo KH, Thornhill BA, Forbes MS, et al. Osteopontin regulates renal apoptosis and interstitial fibrosis in neonatal chronic unilateral ureteral obstruction. Kidney Int. 2006;70:1735–41.
27. Rouschop KM, Sewnath ME, Claessen N, et al. CD44 deficiency increases tubular damage but reduces renal fibrosis in obstructive nephropathy. J Am Soc Nephrol. 2004;15:674–86.
28. Fan YY, Nishiyama A, Fujisawa Y, et al. Contribution of chymase-dependent angiotensin II formation to the progression of tubulointerstitial fibrosis in obstructed kidneys in hamsters. J Pharmacol Sci. 2009;111:82–90.
29. Satoh M, Kashihara N, Yamasaki Y, et al. Renal interstitial fibrosis is reduced in angiotensin II type 1a receptor-deficient mice. J Am Soc Nephrol. 2001;12:317–25.
30. Esteban V, Lorenzo O, Ruperez M, et al. Angiotensin II, via AT1 and AT2 receptors and NF-kappaB pathway, regulates the inflammatory response in unilateral ureteral obstruction. J Am Soc Nephrol. 2004;15:1514–29.
31. Lange-Sperandio B, Schimpgen K, Rodenbeck B, et al. Distinct roles of Mac-1 and its counter-receptors in neonatal obstructive nephropathy. Kidney Int. 2006;69:81–8.
32. Gasparitsch M, Arndt AK, Pawlitschek F, et al. RAGE-mediated interstitial fibrosis in neonatal obstructive nephropathy is independent of NF-kappaB activation. Kidney Int. 2013;84:911–19.
33. Nishida M, Hamaoka K. Macrophage phenotype and renal fibrosis in obstructive nephropathy. Nephron Exp Nephrol. 2008;110:e31–6.
34. Wang Y, Harris DC. Macrophages in renal disease. J Am Soc Nephrol. 2011;22:21–7.
35. Lin SL, Castano AP, Nowlin BT, Lupher Jr ML, Duffield JS. Bone marrow Ly6Chigh monocytes are selectively recruited to injured kidney and differentiate into functionally distinct populations. J Immunol. 2009;183:6733–43.
36. Anders HJ, Ryu M. Renal microenvironments and macrophage phenotypes determine progression or resolution of renal inflammation and fibrosis. Kidney Int. 2011;80:915–25.
37. Grande MT, Lopez-Novoa JM. Fibroblast activation and myofibroblast generation in obstructive nephropathy. Nat Rev Nephrol. 2009;5:319–28.
38. Wada T, Sakai N, Matsushima K, Kaneko S. Fibrocytes: a new insight into kidney fibrosis. Kidney Int. 2007;72:269–73.
39. Zeisberg EM, Potenta SE, Sugimoto H, Zeisberg M, Kalluri R. Fibroblasts in kidney fibrosis emerge via endothelial-to-mesenchymal transition. J Am Soc Nephrol. 2008;19:2282–7.
40. Lin SL, Kisseleva T, Brenner DA, Duffield JS. Pericytes and perivascular fibroblasts are the primary source of collagen-producing cells in obstructive fibrosis of the kidney. Am J Pathol. 2008;173:1617–27.
41. Gao X, Mae H, Ayabe N, et al. Hepatocyte growth factor gene therapy retards the progression of chronic obstructive nephropathy. Kidney Int. 2002;62:1238–48.
42. Yang J, Liu Y. Delayed administration of hepatocyte growth factor reduces renal fibrosis in obstructive nephropathy. Am J Physiol Renal Physiol. 2003;284:F349–57.
43. Klahr S, Morrissey J. Obstructive nephropathy and renal fibrosis: the role of bone morphogenic protein-7 and hepatocyte growth factor. Kidney Int. 2003;64 suppl 87:S105–12.
44. Sakairi T, Hiromura K, Yamashita S, et al. Nestin expression in the kidney with an obstructed ureter. Kidney Int. 2007;72:307–18.

45. Sharma AK, Mauer SM, Kim Y, Michael AF. Interstitial fibrosis in obstructive nephropathy. Kidney Int. 1993;44:774–88.
46. Macdonald MS, Emery JL. The late intrauterine and postnatal development of human renal glomeruli. J Anat. 1959;93:331–40.
47. Song R, Yosypiv IV. Genetics of congenital anomalies of the kidney and urinary tract. Pediatr Nephrol. 2011;26:353–64.
48. Chevalier RL, Forbes MS, Galarreta CI, Thornhill BA. Responses of proximal tubular cells to injury in congenital renal disease: fight or flight. Pediatr Nephrol. 2014;29:537–41.
49. Forbes MS, Thornhill BA, Galarreta CI, et al. Chronic unilateral ureteral obstruction in the neonatal mouse delays maturation of both kidneys and leads to late formation of atubular glomeruli. Am J Physiol Renal Physiol. 2013;305:F1736–46.
50. Ito K, Chen J, El CM, et al. Renal damage progresses despite improvement of renal function after relief of unilateral ureteral obstruction in adult rats. Am J Physiol Renal Physiol. 2004;287:F1283–93.
51. Chevalier RL, Thornhill BA, Chang AY, Cachat F, Lackey A. Recovery from release of ureteral obstruction in the rat: relationship to nephrogenesis. Kidney Int. 2002;61:2033–43.
52. Huang WY, Peters CA, Zurakowski D, et al. Renal biopsy in congenital ureteropelvic junction obstruction: evidence for parenchymal maldevelopment. Kidney Int. 2006;69:137–43.
53. Chevalier RL. Pathogenesis of renal injury in obstructive uropathy. Curr Opin Pediatr. 2006;18:153–60.
54. Harrison MR, Ross N, Noall R, de Lorimier AA. Correction of congenital hydronephrosis in utero I. The model: fetal urethral obstruction produces hydronephrosis and pulmonary hypoplasia in fetal lambs. J Pediatr Surg. 1983;18:247–56.
55. Harrison MR, Nakayama DK, Noall R, de Lorimier AA. Correction of congenital hydronephrosis in utero II. Decompression reverses the effects of obstruction on the fetal lung and urinary tract. J Pediatr Surg. 1982;17:965–74.
56. Glick PL, Harrison MR, Halks-Miller M, et al. Correction of congenital hydrocephalus in utero II: efficacy of in utero shunting. J Pediatr Surg. 1984;19:870–81.
57. Glick PL, Harrison MR, Adzick NS, Noall RA, Villa RL. Correction of congenital hydronephrosis in utero IV: in utero decompression prevents renal dysplasia. J Pediatr Surg. 1984;19:649–57.
58. Bascands JL, Schanstra JP. Obstructive nephropathy: insights from genetically engineered animals. Kidney Int. 2005;68:925–37.
59. Skarnes WC, Rosen B, West AP, et al. A conditional knockout resource for the genome-wide study of mouse gene function. Nature. 2011;474:337–42.
60. Stuart RO, Bush KT, Nigam SK. Changes in global gene expression patterns during development and maturation of the rat kidney. Proc Natl Acad Sci U S A. 2001;98:5649–54.
61. Rumballe B, Georgas K, Wilkinson L, Little M. Molecular anatomy of the kidney: what have we learned from gene expression and functional genomics? Pediatr Nephrol. 2010;25:1005–16.
62. Duell BL, Carey AJ, Tan CK, et al. Innate transcriptional networks activated in bladder in response to uropathogenic Escherichia coli drive diverse biological pathways and rapid synthesis of IL-10 for defense against bacterial urinary tract infection. J Immunol. 2012;188:781–92.
63. Tan CK, Carey AJ, Cui X, et al. Genome-wide mapping of cystitis due to Streptococcus agalactiae and Escherichia coli in mice identifies a unique bladder transcriptome that signifies pathogen-specific antimicrobial defense against urinary tract infection. Infect Immun. 2012;80:3145–60.
64. Rasouly HM, Lu W. Lower urinary tract development and disease. Wiley Interdiscip Rev Syst Biol Med. 2013;5:307–42.
65. McDill BW, Li SZ, Kovach PA, Ding L, Chen F. Congenital progressive hydronephrosis (cph) is caused by an S256L mutation in aquaporin-2 that affects its phosphorylation and apical membrane accumulation. Proc Natl Acad Sci U S A. 2006;103:6952–7.
66. Nguyen HT, Herndon CD, Cooper C, et al. The Society for Fetal Urology consensus statement on the evaluation and management of antenatal hydronephrosis. J Pediatr Urol. 2010;6:212–31.
67. Mendelsohn C. Functional obstruction: the renal pelvis rules. J Clin Invest. 2004;113:957–9.
68. Batourina E, Choi C, Paragas N, et al. Distal ureter morphogenesis depends on epithelial cell remodeling mediated by vitamin A and Ret. Nat Genet. 2002;32:109–15.
69. Batourina E, Tsai S, Lambert S, et al. Apoptosis induced by vitamin A signaling is crucial for connecting the ureters to the bladder. Nat Genet. 2005;37:1082–9.
70. Chia I, Grote D, Marcotte M, et al. Nephric duct insertion is a crucial step in urinary tract maturation that is regulated by a Gata3-Raldh2-Ret molecular network in mice. Development. 2011;138:2089–97.
71. Uetani N, Bertozzi K, Chagnon MJ, et al. Maturation of ureter-bladder connection in mice is controlled by LAR family receptor protein tyrosine phosphatases. J Clin Invest. 2009;119:924–35.
72. Hu P, Deng FM, Liang FX, et al. Ablation of uroplakin III gene results in small urothelial plaques, urothelial leakage, and vesicoureteral reflux. J Cell Biol. 2000;151:961–72.
73. Kong XT, Deng FM, Hu P, et al. Roles of uroplakins in plaque formation, umbrella cell enlargement, and urinary tract diseases. J Cell Biol. 2004;167:1195–204.
74. Iizuka-Kogo A, Ishidao T, Akiyama T, Senda T. Abnormal development of urogenital organs in

Dlgh1-deficient mice. Development. 2007; 134:1799–807.
75. Mahoney ZX, Sammut B, Xavier RJ, et al. Discs-large homolog 1 regulates smooth muscle orientation in the mouse ureter. Proc Natl Acad Sci U S A. 2006;103:19872–7.
76. Martin E, Caubit X, Airik R, et al. TSHZ3 and SOX9 regulate the timing of smooth muscle cell differentiation in the ureter by reducing myocardin activity. PLoS One. 2013;8:e63721.
77. Caubit X, Lye CM, Martin E, et al. Teashirt 3 is necessary for ureteral smooth muscle differentiation downstream of SHH and BMP4. Development. 2008;135:3301–10.
78. Yu J, Carroll TJ, McMahon AP. Sonic hedgehog regulates proliferation and differentiation of mesenchymal cells in the mouse metanephric kidney. Development. 2002;129:5301–12.
79. Cain JE, Islam E, Haxho F, Blake J, Rosenblum ND. GLI3 repressor controls functional development of the mouse ureter. J Clin Invest. 2011;121:1199–206.
80. Miyazaki Y, Oshima K, Fogo A, Hogan BL, Ichikawa I. Bone morphogenetic protein 4 regulates the budding site and elongation of the mouse ureter. J Clin Invest. 2000;105:863–73.
81. Brenner-Anantharam A, Cebrian C, Guillaume R, et al. Tailbud-derived mesenchyme promotes urinary tract segmentation via BMP4 signaling. Development. 2007;134:1967–75.
82. Tripathi P, Wang Y, Casey AM, Chen F. Absence of canonical Smad signaling in ureteral and bladder mesenchyme causes ureteropelvic junction obstruction. J Am Soc Nephrol. 2012;23:618–28.
83. Trowe MO, Airik R, Weiss AC, et al. Canonical Wnt signaling regulates smooth muscle precursor development in the mouse ureter. Development. 2012;139:3099–108.
84. Airik R, Bussen M, Singh MK, Petry M, Kispert A. Tbx18 regulates the development of the ureteral mesenchyme. J Clin Invest. 2006;116:663–74.
85. Mendelsohn C. Going in circles: conserved mechanisms control radial patterning in the urinary and digestive tracts. J Clin Invest. 2006;116:635–7.
86. Lye CM, Fasano L, Woolf AS. Ureter myogenesis: putting Teashirt into context. J Am Soc Nephrol. 2010;21:24–30.
87. David SG, Cebrian C, Vaughan Jr ED, Herzlinger D. c-kit and ureteral peristalsis. J Urol. 2005;173:292–5.
88. Chang CP, McDill BW, Neilson JR, et al. Calcineurin is required in urinary tract mesenchyme for the development of the pyeloureteral peristaltic machinery. J Clin Invest. 2004;113:1051–8.
89. Hurtado R, Bub G, Herzlinger D. The pelvis-kidney junction contains HCN3, a hyperpolarization-activated cation channel that triggers ureter peristalsis. Kidney Int. 2010;77:500–8.
90. Herzlinger D. Upper urinary tract pacemaker cells join the GLI club. J Clin Invest. 2011;121:836–8.
91. Johnston JJ, Olivos-Glander I, Killoran C, et al. Molecular and clinical analyses of Greig cephalopolysyndactyly and Pallister-Hall syndromes: robust phenotype prediction from the type and position of GLI3 mutations. Am J Hum Genet. 2005;76:609–22.
92. Kang S, Graham Jr JM, Olney AH, Biesecker LG. GLI3 frameshift mutations cause autosomal dominant Pallister-Hall syndrome. Nat Genet. 1997;15:266–8.
93. Pallister PD, Hecht F, Herrman J. Three additional cases of the congenital hypothalamic "hamartoblastoma" (Pallister-Hall) syndrome. Am J Med Genet. 1989;33:500–1.
94. Miyazaki Y, Tsuchida S, Nishimura H, et al. Angiotensin induces the urinary peristaltic machinery during the perinatal period. J Clin Invest. 1998;102:1489–97.
95. Gribouval O, Gonzales M, Neuhaus T, et al. Mutations in genes in the renin-angiotensin system are associated with autosomal recessive renal tubular dysgenesis. Nat Genet. 2005;37:964–8.
96. Gubler MC, Antignac C. Renin-angiotensin system in kidney development: renal tubular dysgenesis. Kidney Int. 2010;77:400–6.
97. Nie X, Sun J, Gordon RE, Cai CL, Xu PX. SIX1 acts synergistically with TBX18 in mediating ureteral smooth muscle formation. Development. 2010;137:755–65.
98. Chatterjee R, Ramos E, Hoffman M, et al. Traditional and targeted exome sequencing reveals common, rare and novel functional deleterious variants in RET-signaling complex in a cohort of living US patients with urinary tract malformations. Hum Genet. 2012;131:1725–38.
99. Davis TK, Hoshi M, Jain S. To bud or not to bud: the RET perspective in CAKUT. Pediatr Nephrol. 2014;29:597–608.
100. Hoshi M, Batourina E, Mendelsohn C, Jain S. Novel mechanisms of early upper and lower urinary tract patterning regulated by RetY1015 docking tyrosine in mice. Development. 2012;139:2405–15.
101. Hanafusa H, Torii S, Yasunaga T, Nishida E. Sprouty1 and Sprouty2 provide a control mechanism for the Ras/MAPK signalling pathway. Nat Cell Biol. 2002;4:850–8.
102. Basson MA, Akbulut S, Watson-Johnson J, et al. Sprouty1 is a critical regulator of GDNF/RET-mediated kidney induction. Dev Cell. 2005;8:229–39.
103. Rozen EJ, Schmidt H, Dolcet X, et al. Loss of Sprouty1 rescues renal agenesis caused by Ret mutation. J Am Soc Nephrol. 2009;20:255–9.
104. Maeshima A, Sakurai H, Choi Y, et al. Glial cell-derived neurotrophic factor independent ureteric bud outgrowth from the Wolffian duct. J Am Soc Nephrol. 2007;18:3147–55.

105. Michos O, Cebrian C, Hyink D, et al. Kidney development in the absence of Gdnf and Spry1 requires Fgf10. PLoS Genet. 2006;6:e1000809.
106. Pastorelli LM, Wells S, Fray M, et al. Genetic analyses reveal a requirement for Dicer1 in the mouse urogenital tract. Mamm Genome. 2009;20:140–51.
107. Reidy KJ, Rosenblum ND. Cell and molecular biology of kidney development. Semin Nephrol. 2009;29:321–37.
108. Schutz S, Le Moullec JM, Corvol P, Gasc JM. Early expression of all the components of the renin-angiotensin-system in human development. Am J Pathol. 1996;149:2067–79.
109. Yosypiv IV. Renin-angiotensin system in ureteric bud branching morphogenesis: implications for kidney disease. Pediatr Nephrol. 2014;29:609–20.
110. Yosypiv IV. Renin-angiotensin system-growth factor cross-talk: a novel mechanism for ureteric bud morphogenesis. Pediatr Nephrol. 2009;24:1113–20.
111. Oshima K, Miyazaki Y, Brock III JW, et al. Angiotensin type II receptor expression and ureteral budding. J Urol. 2001;166:1848–52.
112. Nishimura H, Yerkes E, Hohenfellner K, et al. Role of the angiotensin type 2 receptor gene in congenital anomalies of the kidney and urinary tract, CAKUT, of mice and men. Mol Cell. 1999;3:1–10.
113. Hohenfellner K, Hunley TE, Brezinska R, et al. ACE I/D gene polymorphism predicts renal damage in congenital uropathies. Pediatr Nephrol. 1999;13:514–18.
114. Hahn H, Ku SE, Kim KS, et al. Implication of genetic variations in congenital obstructive nephropathy. Pediatr Nephrol. 2005;20:1541–4.
115. Rigoli L, Chimenz R, di BC, et al. Angiotensin-converting enzyme and angiotensin type 2 receptor gene genotype distributions in Italian children with congenital uropathies. Pediatr Res. 2004;56:988–93.
116. Stankovic A, Zivkovic M, Kostic M, et al. Expression profiling of the AT2R mRNA in affected tissue from children with CAKUT. Clin Biochem. 2010;43:71–5.
117. Cordell HJ, Darlay R, Charoen P, et al. Whole-genome linkage and association scan in primary, nonsyndromic vesicoureteric reflux. J Am Soc Nephrol. 2010;21:113–23.
118. Peruzzi L, Lombardo F, Amore A, et al. Low renin-angiotensin system activity gene polymorphism and dysplasia associated with posterior urethral valves. J Urol. 2005;174:713–17.
119. Bianchi D, Vespasiani G, Bove P. Acute kidney injury due to bilateral ureteral obstruction in children. World J Nephrol. 2014;3:182–92.
120. Thom RP, Rosenblum ND. A translational approach to congenital non-obstructive hydronephrosis. Pediatr Nephrol. 2013;28:1757–61.
121. Rodriguez MM. Developmental renal pathology: its past, present, and future. Fetal Pediatr Pathol. 2004;23:211–29.
122. Casella DP, Tomaszewski JJ, Ost MC. Posterior urethral valves: renal failure and prenatal treatment. Int J Nephrol. 2012;2012:351067.
123. Morris RK, Malin GL, Quinlan-Jones E, et al. Percutaneous vesicoamniotic shunting versus conservative management for fetal lower urinary tract obstruction (PLUTO): a randomised trial. Lancet. 2013;382:1496–506.
124. Klein J, Lacroix C, Caubet C, et al. Fetal urinary peptides to predict postnatal outcome of renal disease in fetuses with posterior urethral valves (PUV). Sci Transl Med. 2013;5:198ra106.
125. Crombleholme TM, Harrison MR, Golbus MS, et al. Fetal intervention in obstructive uropathy: prognostic indicators and efficacy of intervention. Am.J. Obstet Gynecol. 1990;162:1239–44.
126. Glick PL, Harrison MR, Golbus MS, et al. Management of the fetus with congenital hydronephrosis II: prognostic criteria and selection for treatment. J Pediatr Surg. 1985;20:376–87.
127. Lipitz S, Ryan G, Samuell C, et al. Fetal urine analysis for the assessment of renal function in obstructive uropathy. Am J Obstet Gynecol. 1993;168:174–9.
128. Morris RK, Quinlan-Jones E, Kilby MD, Khan KS. Systematic review of accuracy of fetal urine analysis to predict poor postnatal renal function in cases of congenital urinary tract obstruction. Prenat Diagn. 2007;27:900–11.
129. Lissauer D, Morris RK, Kilby MD. Fetal lower urinary tract obstruction. Semin Fetal Neonatal Med. 2007;12:464–70.
130. Ismaili K, Avni FE, Wissing KM, Hall M. Long-term clinical outcome of infants with mild and moderate fetal pyelectasis: validation of neonatal ultrasound as a screening tool to detect significant nephrouropathies. J Pediatr. 2004;144:759–65.
131. Riccabona M. Obstructive diseases of the urinary tract in children: lessons from the last 15 years. Pediatr Radiol. 2010;40:947–55.
132. Arthurs OJ, van Rijn RR, Sebire NJ. Current status of paediatric post-mortem imaging: an ESPR questionnaire-based survey. Pediatr Radiol. 2014;44:244–51.
133. Arlen AM, Merriman LS, Kirsch JM et al. Early effect of American academy of pediatrics UTI guidelines on radiographic imaging and diagnosis of vesicoureteral reflux in the emergency room setting. J Urol. 2015;193(5 Suppl):1760–5.
134. Taylor AT. Radionuclides in nephrourology, Part 2: pitfalls and diagnostic applications. J Nucl Med. 2014;55:786–98.
135. Taylor AT. Radionuclides in nephrourology, part 1: radiopharmaceuticals, quality control, and quantitative indices. J Nucl Med. 2014;55:608–15.
136. Taylor AT, Blaufox MD, De PD, et al. Guidance document for structured reporting of diuresis renography. Semin Nucl Med. 2012;42:41–8.
137. Liu Y, Ghesani NV, Skurnick JH, Zuckier LS. The F + 0 protocol for diuretic renography results in fewer interrupted studies due to voiding than the F – 15 protocol. J Nucl Med. 2005;46:1317–20.

138. Piepsz A, Ham HR. Pediatric applications of renal nuclear medicine. Semin Nucl Med. 2006;36:16–35.
139. Kuyvenhoven J, Piepsz A, Ham H. When could the administration of furosemide be avoided? Clin Nucl Med. 2003;28:732–7.
140. Piepsz A, Colarinha P, Gordon I, et al. Guidelines for 99mTc-DMSA scintigraphy in children. Eur J Nucl Med. 2001;28:BP37–41.
141. Rossleigh MA. Renal infection and vesico-ureteric reflux. Semin Nucl Med. 2007;37:261–8.
142. Weyer K, Nielsen R, Petersen SV, et al. Renal uptake of 99mTc-dimercaptosuccinic acid is dependent on normal proximal tubule receptor-mediated endocytosis. J Nucl Med. 2013;54:159–65.
143. Johnston RB, Porter C. The Whitaker test. Urol J. 2014;11:1727–30.
144. Airik R, Kispert A. Down the tube of obstructive nephropathies: the importance of tissue interactions during ureter development. Kidney Int. 2007;72:1459–67.
145. Deng FM, Liang FX, Tu L, et al. Uroplakin IIIb, a urothelial differentiation marker, dimerizes with uroplakin Ib as an early step of urothelial plaque assembly. J Cell Biol. 2002;159:685–94.
146. Baker LA, Gomez RA. Embryonic development of the ureter and bladder: acquisition of smooth muscle. J Urol. 1998;160:545–50.
147. Lang RJ, Tonta MA, Zoltkowski BZ, et al. Pyeloureteric peristalsis: role of atypical smooth muscle cells and interstitial cells of Cajal-like cells as pacemakers. J Physiol. 2006;576:695–705.
148. Lang RJ, Hashitani H, Tonta MA, et al. Spontaneous electrical and Ca2+ signals in the mouse renal pelvis that drive pyeloureteric peristalsis. Clin Exp Pharmacol Physiol. 2010;37:509–15.
149. Metzger R, Schuster T, Till H, et al. Cajal-like cells in the human upper urinary tract. J Urol. 2004;172:769–72.
150. Di BA, Arena S, Nicotina PA, et al. Pacemakers in the upper urinary tract. Neurourol Urodyn. 2013;32:349–53.
151. Lang RJ, Hashitani H, Tonta MA, Parkington HC, Suzuki H. Spontaneous electrical and Ca2+ signals in typical and atypical smooth muscle cells and interstitial cell of Cajal-like cells of mouse renal pelvis. J Physiol. 2007;583:1049–68.
152. Weisschuh N, Wolf C, Wissinger B, Gramer E. A novel mutation in the FOXC1 gene in a family with Axenfeld-Rieger syndrome and Peters' anomaly. Clin Genet. 2008;74:476–80.
153. Yu S, Shao L, Kilbride H, Zwick DL. Haploinsufficiencies of FOXF1 and FOXC2 genes associated with lethal alveolar capillary dysplasia and congenital heart disease. Am J Med Genet A. 2010;152A:1257–62.
154. Astorga J, Carlsson P. Hedgehog induction of murine vasculogenesis is mediated by Foxf1 and Bmp4. Development. 2007;134:3753–61.
155. de WD, Dik P, Lilien MR, Kok ET, de Jong TP. Hypertension is an indication for surgery in children with ureteropelvic junction obstruction. J Urol. 2008;179:1976–8.
156. Farnham SB, Adams MC, Brock III JW, Pope JC. Pediatric urological causes of hypertension. J Urol. 2005;173:697–704.
157. Cheng AM, Phan V, Geary DF, Rosenblum ND. Outcome of isolated antenatal hydronephrosis. Arch Pediatr Adolesc Med. 2004;158:38–40.
158. Thom RP, Rosenblum ND. A translational approach to congenital non-obstructive hydronephrosis. Pediatr Nephrol. 2013;28:1757–61.
159. Chertin B, Pollack A, Koulikov D, et al. Conservative treatment of ureteropelvic junction obstruction in children with antenatal diagnosis of hydronephrosis: lessons learned after 16 years of follow-up. Eur Urol. 2006;49:734–8.
160. Lee RS, Retik AB, Borer JG, Peters CA. Pediatric robot assisted laparoscopic dismembered pyeloplasty: comparison with a cohort of open surgery. J Urol. 2006;175:683–7.
161. Olsen LH, Jorgensen TM. Computer assisted pyeloplasty in children: the retroperitoneal approach. J Urol. 2004;171:2629–31.
162. Peters CA. Pediatric robot-assisted pyeloplasty. J Endourol. 2011;25:179–85.
163. Sutherland RW, Chung SK, Roth DR, Gonzales ET. Pediatric pyeloplasty: outcome analysis based on patient age and surgical technique. Urology. 1997;50:963–6.
164. Chevalier RL. Biomarkers of congenital obstructive nephropathy: past, present and future. J Urol. 2004;172:852–7.
165. Carr MC, Peters CA, Retik AB, Mandell J. Urinary levels of the renal tubular enzyme *N*-acetyl-beta-D-glucosaminidase in unilateral obstructive uropathy. J Urol. 1994;151:442–5.
166. El-Sherbiny MT, Mousa OM, Shokeir AA, Ghoneim MA. Role of urinary transforming growth factor-beta1 concentration in the diagnosis of upper urinary tract obstruction in children. J Urol. 2002;168:1798–800.
167. Valles PG, Pascual L, Manucha W, Carrizo L, Ruttler M. Role of endogenous nitric oxide in unilateral ureteropelvic junction obstruction in children. Kidney Int. 2003;63:1104–15.
168. Bartoli F, Penza R, Aceto G, et al. Urinary epidermal growth factor, monocyte chemotactic protein-1, and beta2-microglobulin in children with ureteropelvic junction obstruction. J Pediatr Surg. 2011;46:530–6.
169. Taranta-Janusz K, Wasilewska A, Debek W, Filonowicz R, Michaluk-Skutnik J. Urinary angiotensinogen as a novel marker of obstructive nephropathy in children. Acta Paediatr. 2013;102:e429–33.
170. Decramer S, Wittke S, Mischak H, et al. Predicting the clinical outcome of congenital unilateral

ureteropelvic junction obstruction in newborn by urinary proteome analysis. Nat Med. 2006;12:398–400.
171. Drube J, Zurbig P, Schiffer E, et al. Urinary proteome analysis identifies infants but not older children requiring pyeloplasty. Pediatr Nephrol. 2010;25:1673–8.
172. Papachristou F, Pavlaki A, Printza N. Urinary and serum biomarkers in ureteropelvic junction obstruction: a systematic review. Biomarkers. 2014;19:531–40.
173. Alberti C. Congenital ureteropelvic junction obstruction: physiopathology, decoupling of tout court pelvic dilatation-obstruction semantic connection, biomarkers to predict renal damage evolution. Eur Rev Med Pharmacol Sci. 2012;16:213–19.
174. Boubaker A, Prior JO, Meyrat B, et al. Unilateral ureteropelvic junction obstruction in children: long-term followup after unilateral pyeloplasty. J Urol. 2003;170:575–9.
175. Han SW, Lee SE, Kim JH, et al. Does delayed operation for pediatric ureteropelvic junction obstruction cause histopathological changes? J Urol. 1998;160:984–8.
176. Bandin F, Siwy J, Breuil B, et al. Urinary proteome analysis at 5-year followup of patients with nonoperated ureteropelvic junction obstruction suggests ongoing kidney remodeling. J Urol. 2012;187:1006–11.
177. Mackie GG, Awang H, Stephens FD. The ureteric orifice: the embryologic key to radiologic status of duplex kidneys. J Pediatr Surg. 1975;10:473–81.
178. Grieshammer U, Le M, Plump AS, et al. SLIT2-mediated ROBO2 signaling restricts kidney induction to a single site. Dev Cell. 2004;6:709–17.
179. Kume T, Deng K, Hogan BL. Murine forkhead/winged helix genes Foxc1 (Mf1) and Foxc2 (Mfh1) are required for the early organogenesis of the kidney and urinary tract. Development. 2000;127:1387–95.
180. Hains DS, Sims-Lucas S, Carpenter A, et al. High incidence of vesicoureteral reflux in mice with Fgfr2 deletion in kidney mesenchyma. J Urol. 2010;183:2077–84.
181. Murawski IJ, Gupta IR. Vesicoureteric reflux and renal malformations: a developmental problem. Clin Genet. 2006;69:105–17.
182. Wang H, Li Q, Liu J, et al. Noninvasive assessment of antenatal hydronephrosis in mice reveals a critical role for Robo2 in maintaining anti-reflux mechanism. PLoS One. 2011;6:e24763.
183. Uetani N, Bouchard M. Plumbing in the embryo: developmental defects of the urinary tracts. Clin Genet. 2009;75:307–17.
184. Routh JC, Huang L, Retik AB, Nelson CP. Contemporary epidemiology and characterization of newborn males with prune belly syndrome. Urology. 2010;76:44–8.
185. Hassett S, Smith GH, Holland AJ. Prune belly syndrome. Pediatr Surg Int. 2012;28:219–28.
186. Haeri S, Devers PL, Kaiser-Rogers KA, et al. Deletion of hepatocyte nuclear factor-1-beta in an infant with prune belly syndrome. Am J Perinatol. 2010;27:559–63.
187. Murray PJ, Thomas K, Mulgrew CJ, et al. Whole gene deletion of the hepatocyte nuclear factor-1beta gene in a patient with the prune-belly syndrome. Nephrol Dial Transplant. 2008;23:2412–15.
188. Weber S, Thiele H, Mir S, et al. Muscarinic acetylcholine receptor M3 mutation causes urinary bladder disease and a Prune-Belly-like Syndrome. Am J Hum Genet. 2011;89:668–74.
189. Farrugia MK, Woolf AS. Congenital urinary bladder outlet obstruction. Fetal Maternal Med Rev. 2010;21 (1):55–73.
190. Park JM. Normal development of the genitourinary tract. In: Weinberg A, editor. Campbell-Walsh urology. Philadelphia: Elsevier-Saunders; 2012. p. 2975–3001.
191. Woolf AS, Winyard PJ, Hermanns MM, Welham SJ. Maldevelopment of the human kidney and lower urinary tract: an overview. In: Vize PD, Woolf AS, Bard JBL, editors. The kidney: from normal development to congenital disease. London: Academic; 2003. p. 377–93.
192. Nasir AA, Ameh EA, Abdur-Rahman LO, Adeniran JO, Abraham MK. Posterior urethral valve. World J Pediatr. 2011;7:205–16.
193. Frohneberg DH, Thuroff JW, Riedmiller H. Posterior urethral valves: theoretical considerations on embryological development. Eur Urol. 1982;8:325–8.
194. Krishnan A, De SA, Konijeti R, Baskin LS. The anatomy and embryology of posterior urethral valves. J Urol. 2006;175:1214–20.
195. Lowsley OS. Congenital malformation of the posterior urethra. Ann Surg. 1914;60:733–41.
196. Borzi PA, Beasley SW, Fowler R. Posterior urethral valves in non-twin siblings. Br J Urol. 1992;70:201.
197. Golbus MS, Harrison MR, Filly RA, Callen PW, Katz M. In utero treatment of urinary tract obstruction. Am J Obstet Gynecol. 1982;142:383–8.
198. Morris RK, Kilby MD. Long-term renal and neurodevelopmental outcome in infants with LUTO, with and without fetal intervention. Early Hum Dev. 2011;87:607–10.
199. Freedman AL, Johnson MP, Gonzalez R. Fetal therapy for obstructive uropathy: past, present.future? Pediatr Nephrol. 2000;14:167–76.
200. Hennus PM, van der Heijden GJ, Bosch JL, de Jong TP, de Kort LM. A systematic review on renal and bladder dysfunction after endoscopic treatment of infravesical obstruction in boys. PLoS One. 2012;7: e44663.