Pediatric Chronic Kidney Disease and Urological Disorders: Exploring the Association

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Chronic kidney disease in children: Overview

Chronic kidney disease (CKD) is a clinical condition marked by a progressive irreversible loss of kidney function, which can gradually advance to end stage renal disease (ESRD). Although CKD is more common in adults, its true burden in children, especially in developing nations is poorly acknowledged.[1,2] Research in this context has revealed that children with CKD pose unique challenges to the healthcare system, likely due to the primary renal disorder per se as well as the associated extra-renal symptoms. Moreover, since the majority of children with CKD in its early stages remain undiagnosed and a large number of others die without receiving adequate medical assistance, the true impact of the disease on children in developing nations remains uncertain.[1]

Majority of children with CKD in developing nations have ESRD, which has an age-specific mortality rate that is 30- to 150-fold higher than that of healthy children. Moreover, ESRD also augments the risk of CV death by 100- to 1000-time as compared to the general pediatric population. This underscores the fact that in low resource settings, preventing CKD and its progression will not only save lives but also improve health outcomes and conserve valuable resources.[1,3]

The definition and classification of CKD include patients with normal kidney function but with persistent renal impairment, most notably persistent proteinuria, because these patients are more likely to experience the negative outcomes of CKD. CKD is further categorized based on severity of renal dysfunction in patients ≥2 years of age, regardless of the underlying diagnosis (Table 1).[3]

Table 1: Stages of CKD in children ≥2 years of age

Stage	GFR (ml/min/1.73 m²)
1	≥90
2	60–89
3	30–59
4	15–29
5	≤15

Adapted from: Claes DJ, Devarajan P. Chapter 14: Clinical Consequences of Congenital Anomalies of the Kidney and Urinary Tract. In: Barakat AJ, Rushton HG (eds.), Congenital Anomalies of the Kidney and Urinary Tract. Springer. Switzerland; 2016: 287-302.

Chronic kidney disease in adults versus children: Epidemiologic differences

As mentioned earlier, children are significantly less likely than adults to have CKD. With a global adult prevalence of 8–18% and a pediatric prevalence of 15–74.7 cases per million children, CKD is a significant public health issue on a global scale. According to data from the European Renal Association-European Dialysis and Transplant Association registry, the Australia and New Zealand Dialysis and Transplant Registry, and the United States Renal Data System database, the incidence of ESRD in children ranged between 7 and 11.4 per million people in 2018. On the other hand, in 2018 there were 390.2 cases of ESRD for every million individuals in the United States population.[2]

Chronic kidney disease in adults versus children: Etiological differences

The primary factors that lead to the development of CKD in children are significantly different from those that trigger the disease in adults. In adults, diabetes, hypertension, and heart disease are the main risk factors for CKD, with autosomal dominant polycystic kidney disease being the most common hereditary cause of ESRD.[2,4,5]

However, unlike adults in whom diabetes and hypertension predominantly cause CKD, congenital causes account for the majority of CKD cases in children.[6] Congenital abnormalities of the kidney and urinary tract (CAKUT) are the

leading causes of the disease, accounting for up to 50% of pediatric CKD cases.[5] Other major etiological factors of CKD in children include steroid-resistant nephrotic syndrome (SRNS), chronic glomerulonephritis (e.g. lupus nephritis, Alport syndrome) and renal ciliopathies, accounting for approximately 10%, 8% and 5% of all pediatric CKD cases. Less frequent causes of CKD in children include thrombotic microangiopathies (particularly atypical hemolytic uremic syndrome), nephrolithiasis/nephrocalcinosis, Wilms tumor, and infectious and interstitial diseases (Table 2).[4]

The etiology of CKD differs by age and race with children under the age of 12 years being more likely to have CAKUT. While anatomical causes, such as renal hypoplasia or posterior urethral valves, predominate in younger patients, the incidence of glomerulonephritis increases in those over 12 years of age. Moreover, minor reductions in nephron numbers that are observed in low-birth weight and small for gestational age newborns are now emerging as significant risk factors for CKD. Pediatric obesity is a growing burden worldwide, and recent researches have revealed early renal dysfunction and CKD risk in obese children. Thus, with the growing problem of pediatric obesity and aging of low birth weight babies, there might be a potential shift in the epidemiology of pediatric CKD.[4,5]

Table 2: Etiological factors for CKD in children versus adults

Adults	Children
• Diabetes • Hypertension • Heart disease • Autosomal dominant polycystic kidney disease	• Congenital anomalies of the kidney and urinary tract (CAKUT) [≈50%] • Cystic or congenital kidney disease [10-19%] • Steroid-resistant nephrotic syndrome (SRNS) [10.4%] • Chronic glomerulonephritis (e.g. lupus nephritis, Alport syndrome) [8.1%] • Renal ciliopathies [5.3%] • Obesity • Low birth weight

Adapted from: 1. Lombel RM, Brakeman PR, Sack BS, *et al.* Urologic Considerations in Pediatric Chronic Kidney Disease. *Adv Chronic Kidney Dis.* 2022;29(3):308-317. **2.** Becherucci F, Roperto RM, Materassi M, *et al.* Chronic kidney disease in children. *Clin Kidney J.* 2016;9(4):583-91. **3.** Kaspar CD, Bholah R, Bunchman TE. A Review of Pediatric Chronic Kidney Disease. *Blood Purif.* 2016;41(1-3):211-7. **4.** Warady BA, Chadha V. Chronic kidney disease in children: the global perspective. *Pediatr Nephrol.* 2007;22(12):1999-2009.

Urological Disorders in pediatric Chronic Kidney Disease

Pediatric patients may experience urologic problems at any age, from before birth to late adolescence. Although some pediatric urologic conditions have little to no impact on kidney function, many urologic conditions can cause and contribute to the progression of CKD. In fact, urological disorders are the most common cause of pediatric CKD, accounting for up to 60% of underlying diagnoses in children 0 to 12 years old with CKD.[2,7]

Among the leading urological causes of CKD are obstructive uropathy, reflux nephropathy and kidney aplasia/hypoplasia/dysplasia. According to some patient registries, obstructive uropathy and aplastic/hypoplastic/dysplastic kidneys each account for 16% of patients undergoing renal transplantation and 8.5% of pediatric patients had vesicoureteral reflux as a cause of renal failure. Together with the pediatric nephrologist, pediatric urologists play a critical role in identifying children who are at risk for CKD. Renal function should be monitored through time in order to optimize the long-term outcome for these children.[7]

Congenital anomalies of the kidney and urinary tract (CAKUT)

Congenital anomalies of the kidney and urinary tract is a diagnostic term that refers to a group of congenital diseases which include renal anomalies, pelviureteric anomalies, vesicoureteric junction anomalies, and anomalies of the collecting system, ureters, bladder, and urethra.[8,9] CAKUT has an incidence of 3 to 6 per 1000 live births constituting 20-30% of all anomalies identified in the neonatal period.[10] Accumulating evidences suggest that CAKUT is a significant cause of morbidity in pediatric and adolescent patient populations.[11] If undetected in childhood, CAKUT can present with renal problems in adulthood. These include recurrent urinary tract infection (UTI), hypertension, proteinuria, CKD, and ESRD, which often require referral to adult nephrology.[8,11]

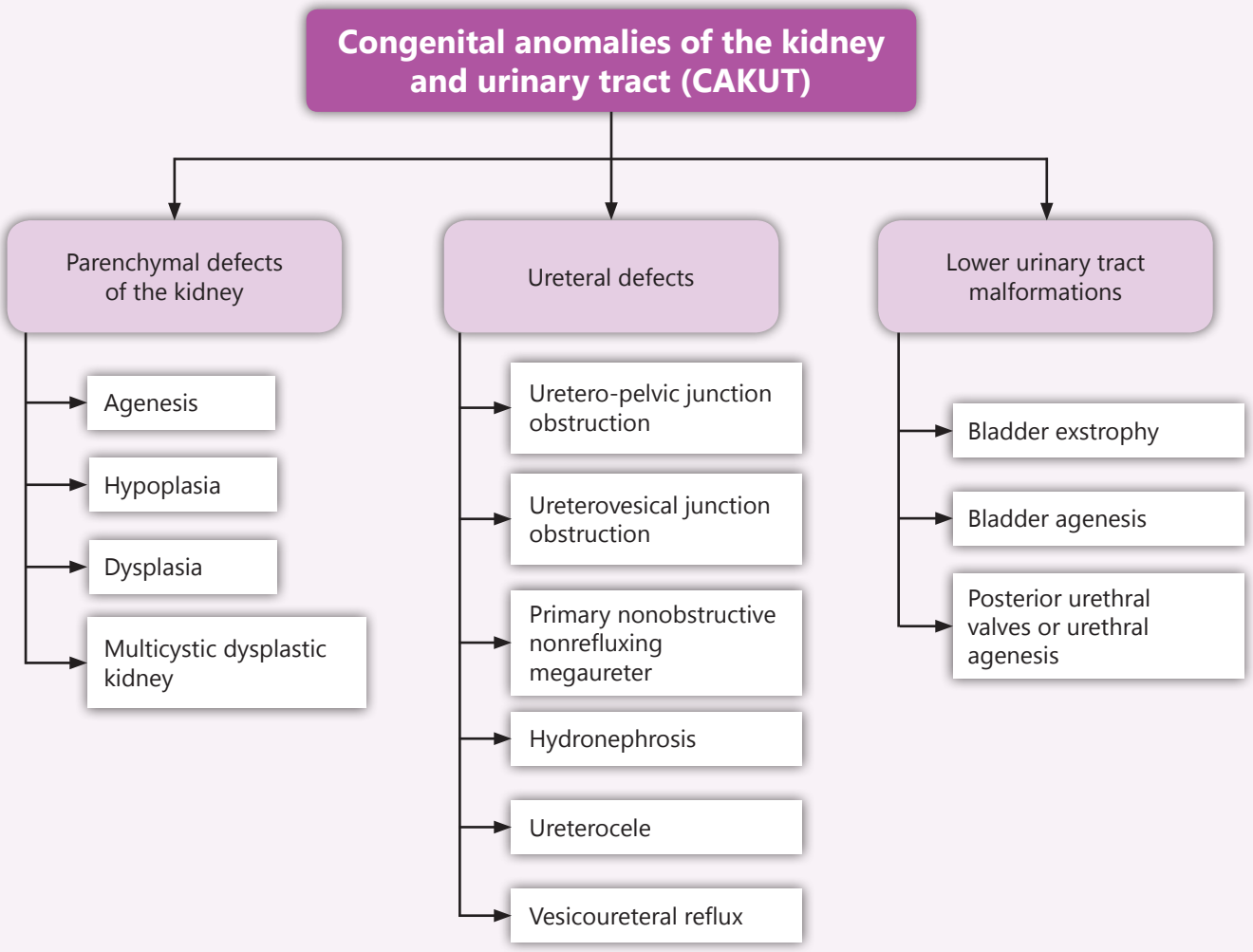
Clinical spectrum of phenotypes of CAKUT

CAKUT refers to a wide range of structural and functional malformations of the kidney and urinary tract. The phenotypic complexity of CAKUT is often clinically subdivided into anatomic order, as illustrated in Figure 1.[11-13]

Single functioning kidney

Solitary functioning kidney (SFK) is one of the most common anomalies of the CAKUT. An SFK can be the outcome of unilateral renal agenesis, renal dysplasia such as a multicystic dysplastic kidney, severe vesicoureteral reflux

Figure 1: General classification of the various types of CAKUT



Adapted from: 1. Stonebrook E, Hoff M, Spencer JD. Congenital Anomalies of the Kidney and Urinary Tract: A Clinical Review. *Curr Treat Options Pediatr*. 2019;5(3):223-235. **2.** Yosypiv IV. Congenital anomalies of the kidney and urinary tract: a genetic disorder? *Int J Nephrol*. 2012;2012:909083. **3.** Westland R, Renkema KY, Knoers NVAM. Clinical Integration of Genome Diagnostics for Congenital Anomalies of the Kidney and Urinary Tract. *Clin J Am Soc Nephrol*. 2020;16(1):128-137

(VUR) with episodes of pyelonephritis, a severely obstructed kidney, and/or surgical removal of a nonfunctional or poorly functioning contralateral kidney. Reduced kidney mass is usually associated with increased risk for progression of CKD and hypertension independent of the etiology of SFK. Nonetheless, the odds of CKD progression and hypertension may vary depending on the etiology. Some factors that contribute to increased risk of progression of CKD in patients with SFK are kidney size, acute kidney injury events, prematurity, presence of hyperfiltration, and genetic risk factors (Box 1). A considerable proportion of the children with SFK have early signs of renal damage, with an increased risk of progression to CKD and ESRD in adulthood.[2,14]

Box 1: Factors for increased risk of CKD progression in patients with SFK[2]

- Kidney size
- Acute kidney injury
- Prematurity
- Presence of hyperfiltration
- Genetic risk factors

Adapted from: Lombel RM, Brakeman PR, Sack BS, *et al.* Urologic Considerations in Pediatric Chronic Kidney Disease. *Adv Chronic Kidney Dis.* 2022;29(3):308-317.

Vesicoureteral reflux

Vesicoureteral reflux (VUR), the abnormal backflow of urine from the bladder into the ureters and kidneys, is a common urologic finding in the pediatric population. Depending on the presentation, the prevalence of VUR might range from up to 15% in cases of prenatal hydronephrosis (AH) to upwards of 45% in cases of febrile UTIs. There are five different levels of VUR, ranging in severity from I to V. Pyelonephritis relapses are common in patients with VUR, and available data point to a possible link between recurrent pyelonephritis and kidney scarring. Kidney scarring can be a causative factor for both CKD and hypertension. Severity of reflux increases the risk of scarring. Most patients with primary VUR recover on their own; however, those who have high-grade reflux and/or recurrent episodes of pyelonephritis need to be evaluated for bladder dysfunction and may eventually need surgical intervention.[2,14]

Posterior urethral valves

Posterior urethral valves (PUV) are the most prevalent congenital obstructive disorder of the urethra and are specific for boys. Prenatal presence of bilateral hydroureteronephrosis and a distended bladder point toward PUV. The "keyhole sign," which consists of a dilated proximal urethra and a distended bladder, is another common association. CKD is a common finding in boys with PUV considering the concomitant renal dysplasia, dysfunctional bladder, and infection, with one-half to one-third of the patients presenting with VUR. Evidences have shown that 15–20% of patients with PUV advance to ESRD over a period of approximately 7 years.[2]

Evaluation of obstructive uropathy

Early detection of congenital and acquired renal and urinary tract defects may enable the most appropriate medical or surgical intervention to delay the progression of CKD or ESRD. Ultrasonography is the primary examination for an early diagnosis of renal and urinary tract anomalies. It is economic, widely available, and promptly identifies the cause of obstructive uropathy in adult patients and in pregnant women. It is currently advised to perform a postnatal ultrasound and voiding cystourethrogram on all infants presenting with a renal pelvic diameter >5 mm.[14]

Conclusion

Congenital and acquired anomalies of the kidneys and urinary tract are common in both adults and children and frequently go undiagnosed. Many urologic problems in pediatric patients that contribute to CKD require continuous urologic surveillance and therapy. To achieve the best kidney outcome in adulthood, pediatric patients with CKD and chronic bladder dysfunction require comprehensive continuous urologic monitoring and treatment. To rule out urological disorders, non-invasive and affordable tests like cystourethrogram should be performed. If necessary, however, ultrasonography, urography, and scintigraphy might provide a correct and early diagnosis of these urological conditions in order to assess the most appropriate course of treatment. Ultimately, multidisciplinary care involving cooperation between nephrology and urology specialists is necessary to provide the optimal therapeutic outcome for pediatric and adult patients with CKD and urologic problems.

References

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