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Research Article

Prevalence of Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) in the Greater Buffalo Region: A Retrospective Review

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Abstract

Background: Congenital anomalies of the kidney and urinary tract, also known as CAKUT, represents a spectrum of conditions from complete bilateral renal aplasia (i.e. agenesis), to unilateral aplasia, hypoplasia (defined as small kidneys < 2SD below the expected mean), and dysplasia where the kidneys fail to differentiate normally. CAKUT are present in 3 to 7 out of 1000 births, accounting for 20-30% of all anomalies detected in the prenatal period [1]. CAKUT represents the most common cause of chronic kidney disease (CKD) in pediatrics [2]. Because patients may be asymptomatic, early detection, close follow up, and proper treatment are paramount. We conducted a 5-year cohort study of CAKUT populations, with comparison to common causes of renal diseases in pediatric patients in the greater Buffalo region.

Design/Methods: We performed a retrospect study in patients who were referred and seen in renal clinic in the past 5 years (2014-2019). Based on our selection criteria described in Table 1, we selected 720 patients from Electronic Medical Record (EMR) and clinical log books. We divided patients into 4 different groups: group 1 urologic disease (55%); group 2 primary glomerular disease (30%); group 3 secondary glomerular disease (13%); group 4 tubular disease (2%). We further divided patients in CAKUT into 9 subgroups: 1) renal agenesis/hypoplasia/dysplasia; 2) multicystic dysplastic kidney (MCDK); 3) congenital posterior urethral valve (CPUV); 4) vesicoureteral reflux (VUR); 5) ectopic kidney; 6) ureteral pelvic junction obstruction (UPJ); 7) horse-shoe kidney; 8) duplicated collecting system; 9) megaureter (Table 1). The percentage of cases was subsequently calculated.

Results: CAKUT is the most common cause of CKD in pediatric patient population in the greater Buffalo region, accounting for 39% of cases (286 cases out of 720 total cases). Among the CAKUT patients, agenesis/dysplasia/hypoplasia accounted for 37%, MCDK for 23%, CPUV and VUR each for 11%. The prevalence of megaureter was least common accounted for 1% (Figure 1). Males more likely to have CAKUT compared to females in most CAKUT subgroups, except for duplication of the collecting system and UPJ during which female was predominant (Figure 2).

Among CAKUT, megaureter, duplicated collecting system and horseshoe kidney do not progress, and the most severe cases of CAKUT (VUR, CPUV) are the leading cause of CKD progression (Figure 3).

Conclusions: In the greater Buffalo region, CAKUT represents 39% of children who have renal diseases. Renal agenesis/dysplasia/hypoplasia is the most common CAKUT. VUR and CPUV are the leading causes of CKD progression. Future research attempts to focus on genetic etiology for the high prevalence and severity of CAKUT in the greater Buffalo region.

Keywords: Congenital anomalies of kidney and urinary tract (CAKUT); Chronic kidney disease (CKD); End stage renal disease ESRD; Pediatric kidney transplantation; Prevalence; Renal replacement therapy;

Introduction

More than 1 in 7, that is 15% of US adults or 37 million people, are estimated to have Chronic Kidney Disease (CKD) [3]. CKD progresses into End-Stage Renal Disease (ESRD), which is estimated to increase in the US by 11-18% by 2030 [4]. The leading causes of CKD are different between adults and pediatric populations in that diabetes and hypertension being the most common causes of CKD in adults [4], whereas CAKUT and primary Glomerulonephritis (GN) being the most common causes of CKD in pediatrics [2]. CKD is a silent epidemic. As many as 9 in 10 adults with CKD do not know they have CKD, and about 2 in 5 adults with severe CKD do not know they have CKD due to the lack of early diagnostic tools or methods [3].

Despite technological improvements, there are limited therapeutic options. Dialysis and transplantation are the only treatment options for patients with ESRD. Dialysis requires an average of four-hour treatment sessions three times a week, and kidney transplantation has a waitlist with a median time of 3.6 years to receive the first kidney [4]. In the field of regenerative medicine, kidney organoids model development and rebuilding a kidney in vitro have demonstrated potentials to restore failing kidney function, none of them is ready for clinical implication [5].

CAKUT are wide spectrum disorders including renal agenesis/hypoplasia/dysplasia, ureteral pelvic junction obstruction, posterior urethral valve, vesicoureteral reflux, multicystic dysplastic kidney, duplicated collecting system, megaureter, ectopic kidney, and horse-shoe kidney [6]. CAKUT constitute 20-30% of all congenital malformations [6] and it is a frequent cause of birth defects, i.e. about three to six per 1,000 live births [7]. CAKUT is estimated to be implicated in 30% to 60% of cases of childhood-onset chronic kidney disease (CKD) in different populations [8]. Data from the European Renal Association-European Dialysis and Transplant Association Registry showed that Renal Replacement Therapy (RRT) for ESRD occurred earlier in patients with CAKUT than those without [9]. CAKUT may also lead to multiple manifestations such as hypertension, proteinuria, infection, renal impairment into adulthood. Because patients with CAKUT are often asymptomatic, early detection and treatment are paramount. If left untreated, clinical manifestations are almost assured.

In this study, we set to evaluate prevalence of CKD and distribution of CAKUT in pediatric patients in the greater Buffalo region.

Materials and Methods

In this 5-year cohort study, we first set up selection criteria as described in Table 1. Based on selection criteria, we then selected patients by 2 methods: 1) retrospectively chart reviewed all patients in the Allscripts Electronic Medical Record (EMR); and 2) using clinic register books for all patients seen in renal clinic for urologic disease, primary glomerular diseases, secondary glomerular diseases, and tubular diseases. We then combined both data entry into one excel sheet in which we established a list of 720 total patients. For each patient essential information (MRN, full name, DOB, Gender, race/ethnicity, ICD10 code) was identified. We called this the Master sheet. From the Master sheet, patients were divided into 4 groups with each represents the most frequently identified renal diseases: group 1 urologic disease; group 2 primary glomerular diseases; group 3 secondary glomerular diseases; and group 4 tubular diseases. The patients in each group were further divided based on frequency of occurrence (Table 1). Of note, CAKUT patients were further divided into 9 subgroups (Table 1). From the Master sheet, the percentage of each group and some subgroups were calculated and presented in Table 2.

For all patients	• Age less than 21 • Has arrived at a clinic appointment ≤ 260 weeks ago • Not deceased • Not marked as inactive in Allscripts • One entrance for patient (avoid multi-entrance) • Has one of the following ICD10 codes
For each patient	• MRN • Full name • DOB • Gender • Race or ethnicity
Established most frequently identified renal diseases	Group 1 - Urologic disease • Congenital anomalies of the kidney and urinary tract (CAKUT) • Nephrolithiasis • Urinary tract infection (UTI)/Pyelonephritis • Enuresis • Renal tumors Group 2 - Primary glomerular diseases • Nephrotic syndrome • focal sclerosing glomerulonephritis (FSGS) • IgA, HSP, PSGN, MPGN, RPGN • ANCA vasculitis, C3GN, HUS Group 3 - Secondary glomerular disease • Diabetes • Hypertension • SLE • Crohn • Sickle cell disease Group 4 - Tubular diseases • Renal tubular acidosis ○ Bartter syndrome
Characteristics of CAKUT	• CAKUT subgroup 1. renal agenesis/hypoplasia/dysplasia 2. multicystic dysplastic kidney (MCDK) 3. congenital posterior urethral valve CPUV) 4. vesicoureteral reflux (VUR) 5. ectopic kidney 6. ureteral pelvic junction obstruction 7. horse-shoe kidney 8. duplicated collecting system 9. megaureter

Note: IgA nephropathy; HSP, Henoch-Schonlein purpura; PSGN, post-streptococcal glomerulonephritis; MPGN, membranoproliferative glomerulonephritis; RPGN, rapidly progressive glomerulonephritis; HUS, hemolytic uremic syndrome; SLE, systemic lupus erythematosus

Table 1: Selection criteria and characteristics for pediatric patients in the greater Buffalo region from EMR/Allscripts.

Urologic diseases • CAKUT **39%** • Nephrolithiasis **10%** • UTI/pyelonephritis **4%** • Enuresis • Renal tumor	**55%**
Primary glomerular disease • Nephrotic syndrome **9%** • FSGS **3%** • IgA, HSP, PSGN, MPGN, RPGN • ANCA vasculitis, C3GN, HUS	**30%**
Secondary glomerular disease • Diabetes **5%** • Hypertension **4%** • SLE **2%** • Crohn **1.5%** • Sickle cell disease **< 1%**	**13%**
Tubular disease • Renal tubular acidosis **1.5%** • Bartter syndrome **< 1%**	**2%**
Total patients: 732	**100%**

Table 2: The most frequently identified renal diseases in pediatric patients in the greater Buffalo region. Majority being in urologic diseases. Of those, 39% had CAKUT.

From the Master sheet, the number and percent of each CAKUT category (Figure 1), as well as the breakdown of sex (Figure 2) were determined. We also determined the percent number of CAKUT patients with CKD. Within this subset of patients, we then calculated the percent number of patients with each stage of CKD as a consensus and individually within each individual CAKUT category (Figure 3).

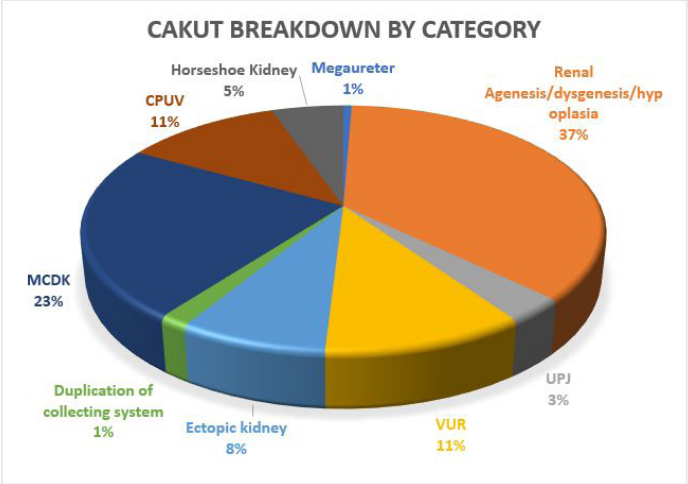

Figure 1: Percentage distribution of CAKUT patients in the greater Buffalo region. Among total of 286 CAKUT patients, 37% were shown to have renal agenesis/dysgenesis/hypoplasia, 23% with MCDK, and CPUV and VUR tied in third highest percentage with 11% each. The least prominent category was megaureter with 1%.

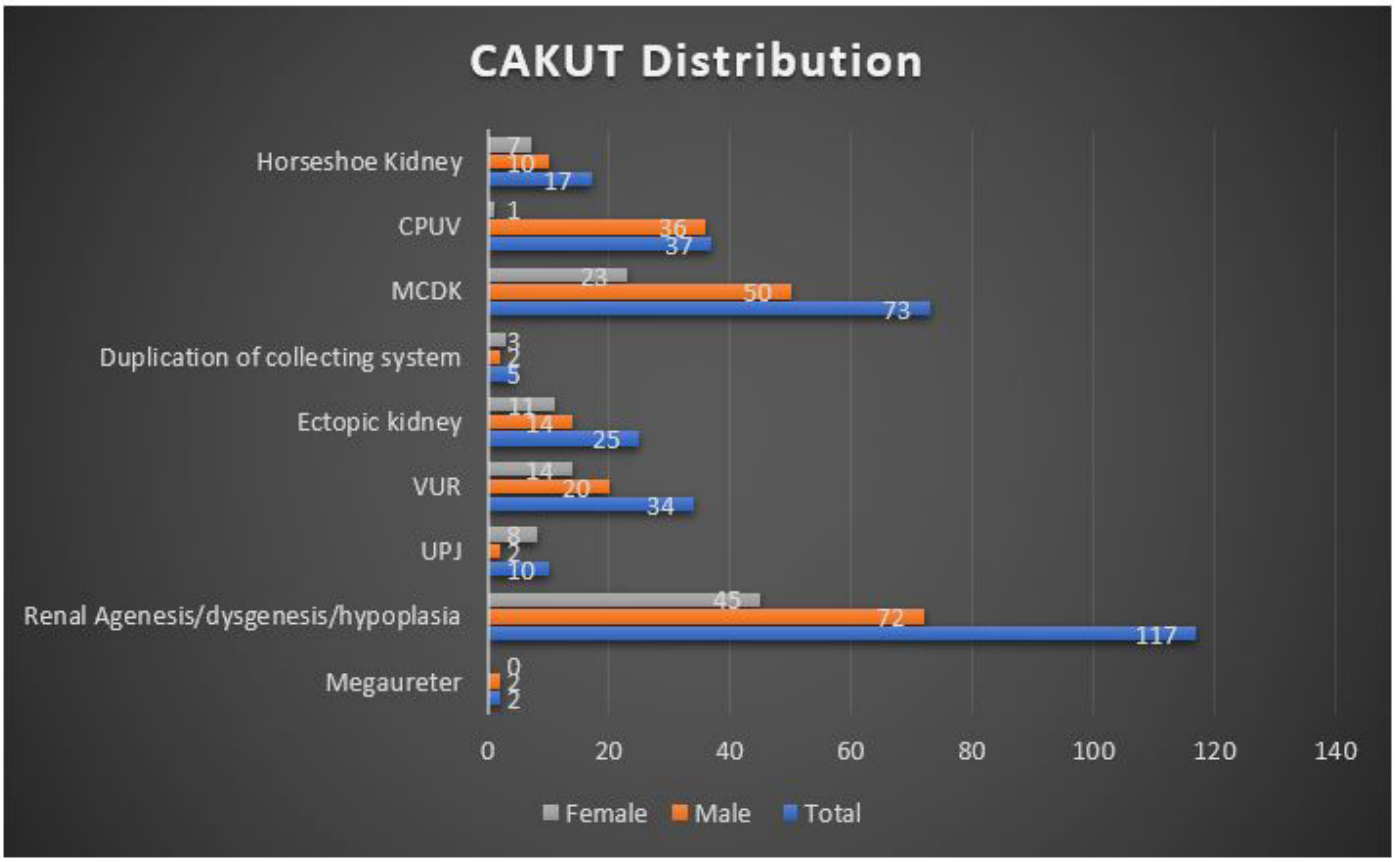

Figure 2: Gender distribution in CAKUT in the greater Buffalo region. Males were more likely to have CAKUT compared to females in most CAKUT subgroups, except for duplication of the collecting system and UPJ, during which female patients predominated.

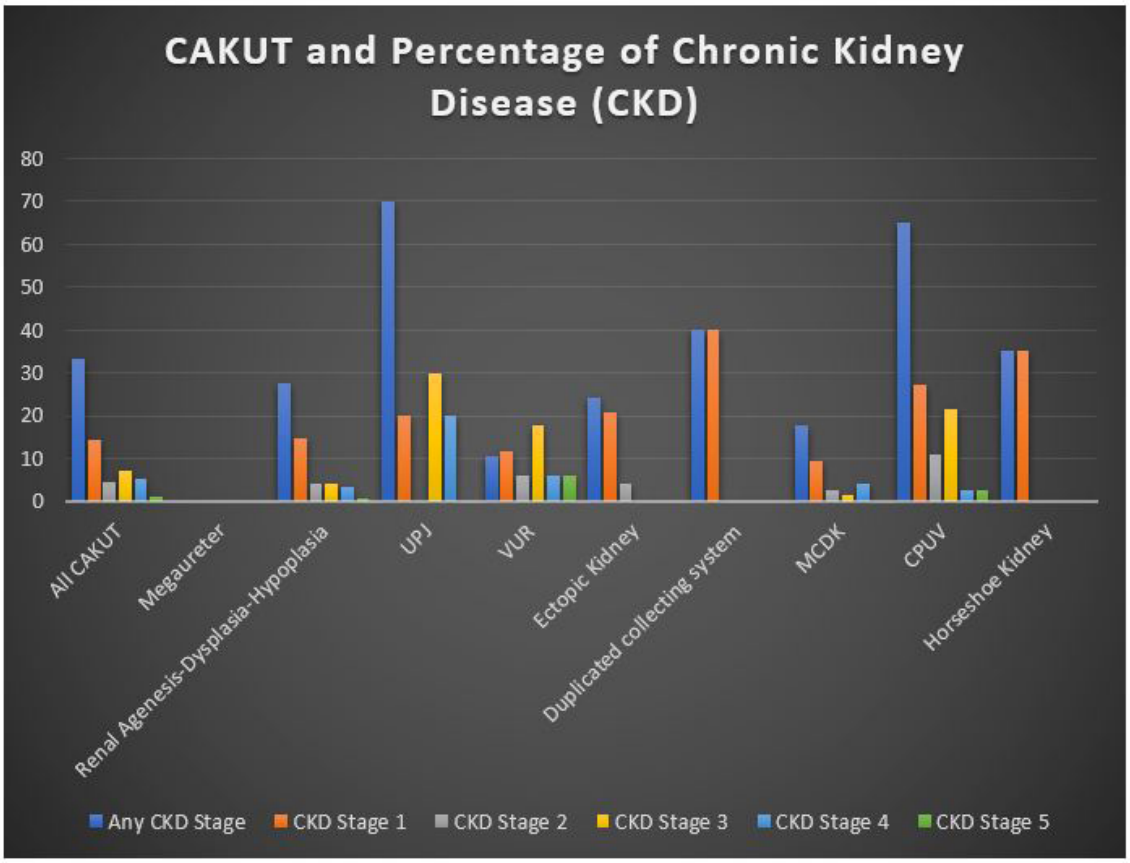

Figure 3: CKD staging in pediatric CAKUT patients in the greater Buffalo region. As indicated, megaureter, duplicated collecting system, and horseshoe kidney do not progress. The most severe cases of CAKUT (VUR, CPUV) are the leading cause of CKD progression.

Results

Among the 720 total pediatric patients studied, CAKUT is the most common cause of renal disease seen in pediatric patents, representing 39% of all patients studied in the great Buffalo region, followed by primary GN (30%), secondary GN (13%), and nephrolithiasis (10%). Among the 286 cases of CAKUT studied, renal agenesis/dysplasia/hypoplasia is the most common cause of CKD, accounting for 37% of CAKUT cases. This was followed by MCDK accounting for 23%, CPUV and VUR, with each accounting for 11%. The least common category was megaureter. It accounted for only < 1% of the population we studied and a miniscule 2 out of 286 patients. The other categories of CAKUT are depicted in Figure 1. Figure 2 showed gender distribution in CAKUT patients. Males are more likely to have CAKUT in general, except in subgroups of UPJ (8 female, 2 male) and duplicated collecting system (3 female, 2 male) in which females are more commonly seen. Figure 3 shows CKD staging in CAKUT patients. CAKUT patients with megaureter, duplicated collecting system and horseshoe kidney have preserved kidney functions and they do not progress, whereas CAKUT patients with VUR, CPUV are the leading cause of CKD progression, the majority of both UPJ and CPUV have CKD at 70.0% and 64.9%. CAKUT patients with unilateral renal agenesis/hypoplasia, UPJ obstruction and MCDK may also progress to ESRD eventually.

Discussion

In adults and children, one of major public health problems worldwide is CKD. CKD is characterized by a progressive decline in kidney function to the point of failure. Once failed, CKD then becomes end-stage renal disease, which is a devastating disorder associated with excessive mortality and morbidity. CKD complications, such as cardiovascular disease, infection, impaired growth and psychosocial adjustment have severe impact on the quality of life. Pediatric CKD represents a greater challenge due to the comorbidities, quick progression, increased mortality, and a higher cost than adult CKD care [10]. In the US, the annual incidence of end stage renal disease in the pediatric population has increased to 14-15 per million for CKD stages 3–5, and 8 per

million for CKD stages 4–5 [2]. The Global Burden of Disease (GBD) study reported that, in 2015, 1.2 million people died from kidney failure, an increase of 32% since 2005 [5]. To identify CKD patients at highest risk for complications of kidney failure and other co-morbid complications, a classification system was developed by the KDIGO (kidney disease: Improving Global Outcomes) initiative. This system was based on three domains: cause of kidney disease, glomerular filtration rate, and albuminuria [11]. CKD is now defined by a presence of kidney damage (for example, any structural or functional abnormality involving pathological, laboratory or imaging findings) for≥3 months or a GFR<60 ml/min/1.73 m2 for≥3 months.

Identifying patients with CKD is important as dialysis and organ transplantation are the only limited therapeutic options. It has shown that pediatric CKD has increased mortality with the average life expectancy of only 38 years for those with RRT/dialysis and 63 years for those with a kidney transplant [2]. Infants with severe renal disease are at higher risk of death in the first 2 years of life, but outcomes thereafter are comparable to those of older children [12]. Death rate in children with RRT is about 30 times higher than their healthy peers [13,14]. If a patient could obtain a transplant, transplant patients consistently have up to a 4-fold survival benefit compared with dialysis patients [13]. Outside of allograft transplantation, the field of regeneration medication, organoid development, and rebuilding kidney have made significant progress. We have seen the advent of human induced pluripotent stem cells, substantial advances in our capacity to both sequence and edit the genome, global and spatial transcriptional analysis down to the single-cell level [5], some approaches may well deliver outcomes in the future, whereas others remain in infancy. These could be possible avenues for additional treatment options for those with CKD.

In this retrospective cohort study, we ascertained childhood CKD epidemiology in the greater Buffalo region. Among the most common causes of CKD in our pediatric patient population, CAKUT accounts for 39% of cases. Followed by primary GN for 30% of cases. The proportion of nephrolithiasis (10%) was the 3rd most cause of CKD in our study (Table 2). Causes of CKD are very different in children from those in adults. In the United States, the registry of the NAPRTCS has collected data on the early stages of CKD in children since 1994. The report showed that CAKUT (48%), glomerulonephritis (14%) and hereditary nephropathies (10%) are the most common causes of CKD in children aged under 21 years [2]. CAKUT causes about 40% of cases of ESRD in patients who develop it within the first three decades of life. It accounts for 20-30% of all congenital malformations. To understand the prevalence of the different categories of CAKUT, we showed that, in the current study, renal agenesis/dysplasia/hypoplasia was the most prevalent, accounting for 37% of the CAKUT cases. The second most common was multi-cystic kidney disease (MCDK, 23%), CPUV, and VUT tied in 3rd highest percentage with 11% each. The least common being megaureter (1%) (Figure 1). CAKUT had the greatest prevalence in male patients, with the exception of UPJ (8 female, 2 male) and duplicated collecting system. In both UPJ and the duplicate collecting system, female patients predominated (Figure 2). Among the CAKUT patients, CPUV and VUR are leading causes of CKD progression (Figure 3).

A similar study in Taiwan conducted by Tain et al in 2016 [8] showed a different spectrum of prevalence. Their study looked at the nation's birth registry from 2004 to 2011. They found that polycystic kidney disease was the most prevalent, accounting for 10.63% of CAKUTs. Ureteropelvic junction obstruction (10.22%), cryptorchidism (9.81%), and renal hypoplasia (9.73%) followed. In our population, ureteropelvic junction obstruction consisted of only 3% of our population. Similar to their study, our study found that males were more likely to have CAKUT compared to females [8]. Another study conducted by Li et al in 2019 [15], examined the prevalence of CAKUT in Zhejiang Province in China. Their study included stillbirths and early fetal losses, which were excluded in our study. They found that males also have a higher risk of CAKUT as well. The most prevalent CAKUT in their study was hydronephrosis at 31.90%. This was followed by polycystic kidney disease (19.10%), renal agenesis (18.96%), renal ectopia (4.34%), with the least common being renal duplication at 2.4%. Their results closely matched that of our study, with the exception of hydronephrosis which was not included as a phenotype for CAKUT.

CPUVs are the most significant lower urinary tract defect resulting in bladder outflow obstruction. Prenatally CPUV are suspected if there is bilateral hydroureteronephrosis and a distended bladder. Another common association is the "keyhole sign" – a dilated proximal urethra and a distended bladder. A Voiding Cystourethrogram (VCUG) is used to confirm the diagnosis. CPUV occurs exclusively in boys and is a leading cause of ESRD. In one study with the extensive follow up, the lifetime risk of stage 5 CKD due to CPUV has been demonstrated to be 28.5% with follow up over a median of 31 years, with one third of cases presenting over the age of 17 years, and progression to kidney failure decreasing with age and not seen over the age of 34 years [16]. In 2 studies, a median follow-up of approximately 7 years, 15-20% of patients with CPUV progressed to ESRD [17,18].

VUR is defined as the retrograde flow of urine due to poorly functioning vesicoureteral junction from the bladder towards the kidneys. This puts the patient at the highest risk of kidney scarring and CKD when VUR is associated with dysplastic kidneys and/or poorly functioning bladder. The time taken to develop kidney injury can be many years, as many as 15 years as seen by one study [19]. CAKUT is caused by a single gene mutation [20]. It is caused by mutation of a single gene in a high number of different monogenic CAKUT genes, involving different genes in different patients [21]. The notion that monogenic CAKUT is suggested by three findings: (1) CAKUT may appear with familial aggregation; (2) monogenic mouse models exhibit CAKUT phenotypes; (3)

human multi-organ monogenic syndromes may include CAKUT phenotypes. In 20%, a monogenic mutation can be identified. One such example is the mutations seen in HNF1B and PAX2, which have been described in patients with hypodysplasia [22,23]. Whole-Exome Sequencing (WES) has facilitated the discovery of these genes. CRISPR/Cas knock-in techniques have strong potential to conclusively define genotype-phenotype relations for patients with CAKUT. Outcomes of reconstructive surgery, rate of progression into renal failure, and the likelihood for the development of extrarenal complications will be reduced [24].

Limitations

Due to the retrospective design and inclusion criteria, children who underwent renal replacement therapy and kidney transplant were not included in this study.

Conclusion

In the greater Buffalo region, CAKUT represents 39% of those younger than 21 who have renal diseases and visited the clinic within 260 weeks of the initiation of the study. Moreover, renal agenesis/dysplasia/hypoplasia is the most common CAKUT whereas CPUV and VUR are the most severe type of CAKUT with fast CKD progress and decline kidney function within our study population.

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