Original Research Article

Spectrum of pediatric kidney diseases in a tertiary care nephrology unit from south India: A retrospective analysis

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Abstract

Introduction: The spectrum of pediatric kidney diseases is vast and varies from place to place.
Materials and methods: This was a hospital-based retrospective descriptive study done from 2016-2019 in a tertiary care nephrology unit from south India.
Results: We saw a total of 406 children in these four years. The most common diagnosis in this series was Nephrotic Syndrome (NS) in 32%, followed by Congenital Anomalies of Kidney and Urinary Tract (CAKUT) in 30.3%, acute nephritic syndrome in 9.6%, isolated urinary abnormalities in 7.63%, renal tubular disorders in 7.38%. Chronic Kidney Disease (CKD) was in 6.64%, and Rapidly Progressive Renal Failure was in (RPRF) 6.45%. Children less than ten years constituted 57.38% and mostly had CAKUT and NS. Older children had other presentations more commonly. We found that the majority of NS was due to minimal change disease (MCD). Congenital pelvi ureteric junction obstruction (PUJO) was the most common CAKUT. Acute nephritic syndrome was mostly due to post-infectious glomerulonephritis (PIGN). Isolated urinary abnormalities were mostly due to IgA nephropathy and urolithiasis. The most common renal tubular disorder was hypophosphatemic rickets presenting as rickets, followed by distal renal tubular acidosis (dRTA), presenting as failure to thrive and rickets. CKD was mostly due to 'undetermined causes,' and RPRF was mainly due to crescentic glomerulonephritis.
Conclusions: Pediatric kidney diseases have a varied presentation, of which the two most common manifestations are NS and CAKUT.

Key words

Kidney diseases, Nephrotic syndrome, Cakut, Chronic kidney disease, Children.

Introduction

Children of all age groups can have kidney problems either due to anatomical (congenital anomalies of kidney and urinary tract-CAKUT), immunological (nephrotic syndrome, nephritic syndrome), Infectious (urinary tract infections (UTI), including pyelonephritis), or genetic (syndromic) causes. In addition to these, adolescents develop kidney problems from acquired causes like diabetes mellitus (DM), hypertension, and metabolic syndrome [1, 2]. Whatever may be the cause, a sizeable young population is vulnerable to develop chronic kidney disease and ESRD by their adulthood if these diseases are not diagnosed on time or treated appropriately. It is evident that these chronic diseases will burden the parents, caregivers, and society [3] and additionally, caregiver burnout sets in disrupting the family's mental peace, indirectly affecting the siblings [4]. In addition to the medical burden, these chronic kidney problems lead to psychological and economic stress.

India has a relatively young population among the world nations. Children and adolescents (0-19 years) form 45 % of the whole population, and children less than five years account for nearly 10.7% [5]. This means that the absolute number of children with kidney problems will also increase eventually and need specialized care. In India, exclusive pediatric nephrology services are provided in only some centers, and in the majority part of the country, these children are managed by adult nephrologists only. In one study, it was seen that the proportion of adult nephrologists involved in pediatric kidney transplantation were comparable to pediatric nephrologists who did pediatric transplants [6]. Other than transplantation data, there is a lack of information regarding the pattern of pediatric kidney diseases seen by general nephrology units from India. Also, there is considerable variability of pediatric kidney diseases across the globe [7]. Here, we present the data regarding the pediatric kidney diseases seen in a tertiary care nephrology unit. This, we hope, will help in a better understanding of the demographics of the pediatric kidney diseases from south India.

Materials and methods

This was a retrospective descriptive analysis of children and adolescents (birth to 19 years) seen by us from 2016 to 2019. The data was collected from out-patient, in-patient, renal biopsy, and discharge summary records. We documented the child's age, appropriate anthropometry, diagnosis, duration of the diagnosis, any procedure done (renal biopsy/ dialysis/ surgery), and treatment given. The data was collected in MS excel using descriptive statistics, including mean, SD. Children were segregated into various cohort of diseases and analyzed.

We excluded neonates who were sick, as we did not have facilities to admit and manage them. But those who were stable and came for a second opinion were included. Children with acute kidney injury (AKI) (transient drug-induced AKI, multi-organ failure with AKI, malignancy/chemo-induced AKI, post-cardiac surgery AKI) were also excluded from the study as the complete data of these children was not available and as they were from multiple departments. We did not evaluate outcome measures like recovery from the disease or mortality in this study.

Definition of terms and standard of care:

CAKUT- comprise a wide range of structural malformations that result from a defect in morphogenesis of the kidney and urinary tract. These include renal agenesis, renal hypodysplasia, multicystic dysplastic kidney, hydronephrosis, pelvi ureteric junction obstruction (PUJO), megaureter, duplex ureter, vesico-ureteric reflux (VUR), and posterior urethral valves (PUV) [8]. The diagnosis was

aided with ultrasound, micturating cystourethrogram (MCUG), Diuretic renogram, renal cortical scintigraphy, and CT scan when required.

Children were diagnosed with NS, if they had edema with hypoalbuminemia (Serum albumin< 3 gm.dl), hypercholesterolemia (Serum cholesterol> 200 mg/dl), and proteinuria > 50 mg/kg/day or 40 mg/m^2/hour [9]. Based on the complete response to steroids, children who respond to four weeks of full dose steroid and those who do not are labeled as steroid-sensitive NS (SSNS) and steroid-resistant NS (SRNS), respectively [10]. This distinction is significant as 36-50% of SRNS children will progress to ESRD by ten years [11].

Acute nephritic syndrome is a clinical syndrome that presents as hematuria, elevated blood pressure, decreased urine output, and edema. The primary underlying pathology is inflammation of the glomerulus that results in nephritic syndrome. It causes a sudden onset of the appearance of red blood cell (RBC) casts and blood cells, a variable amount of proteinuria, and white blood cells in the urine [12].

This is usually caused by post-infectious glomerulonephritis (PIGN) due to streptococcal skin infection [13], however, it can also be caused by other bacterial, viral, and parasitic infections [14, 15].

Another cohort of children has RPRF, a group of heterogeneous diseases leading to progressive renal impairment over few weeks. RPRF may be considered a 'renal emergency' as these children may progress to ESRD if not diagnosed timely or treated appropriately. The renal histology may show lesions affecting the three components of the kidney, i.e., glomerular, tubulointerstitial, or vascular [16]. Included in this are glomerular diseases like vasculitis, tubulointerstitial diseases like acute tubular necrosis and vascular, renal vein thrombosis, and renal limited hemolytic uremic syndrome (HUS). In addition to standard care, these children underwent appropriate investigations, including renal biopsy and treatments, including dialysis, plasma exchange, and immunosuppression.

Isolated urinary abnormalities included children presenting with sub-nephrotic proteinuria ± microscopic hematuria. These were usually picked up in incidental health screening tests.
Renal tubular disorders included those affecting the proximal tubule, like Fanconi syndrome (FS) and hypophosphatemic rickets (XLH or Vitamin D resistant rickets), disorders effecting of Henle' loop and distal tubule (Bartter's syndrome, Gitelman syndrome (GS), and distal renal tubular acidosis (dRTA)), and others such as vitamin D dependent rickets (VDDR) [17]. All the children received standard care based on their diagnosis.

Results

Data of 406 children was recorded from the study period. The most common diagnosis was nephrotic syndrome (n=130, 32%), followed by CAKUT (n=123, 30.3%), acute nephritic syndrome (n=39, 9.6%), isolated urinary abnormalities in (n=31, 7.63%), renal tubular disorders (n=30, 7.38%), RPRF (n=27, 6.65%), and CKD (n=26, 6.64%), in that order of frequency. **Table - 1** showed the spectrum of pediatric kidney diseases and their etiology.

Age Group-wise: Children less than ten years, accounted for 57.38 % (n=233). And among them, the most common diagnosis was CAKUT (47%), followed by nephrotic syndrome (36.5%). In contrast, acute nephritic syndrome, RPGN, isolated urinary abnormalities, and tubular disorders were more common in children older than ten.

Etiology wise: Nephrotic syndrome was the most common presentation in this series (32%). Out of these 130 children with NS, 89 had atypical features and subjected to a renal biopsy (SRNS=70, SDNS=19). Our SRNS incidence was 53.8% of childhood NS. Rest was steroid-responsive and did not require biopsy. On histopathology, minimal change disease (MCD)

was the most common biopsy finding (n=50, 58.8%), followed by focal segmental glomerulosclerosis (FSGS) (n=18, 20.2%), IgM nephropathy in 10 (12.2%), mesangio-proliferative GN (MeSPGN) in 6, C1Q nephropathy in two, membranous nephropathy (MN) in two and diffuse mesangial sclerosis (DMS) in one.

Table – 1: The spectrum of pediatric kidney diseases.

Syndromic presentation	Total number of children (%)	Biopsy done (% of total biopsies)	Two most common biopsy finding
Nephrotic syndrome	130 (32%)	89 (52%)	MCD (n=50), FSGS (n=18)
CAKUT	123 (30.30%)	-	
Acute nephritic syndrome	39 (9.6%)	31 (18.1%)	PIGN (n= 20), LN (10)
Isolated urinary abnormalities	31 (7.63%)	15 (8.7%)	IgAN (n=11), Alport (n=2)
Renal tubular disorders	30 (7.38%)	-	
RPRF	27 (6.65%)	27 (15.7%)	Crescentic GN (n=16), LN (n=10)
CKD	26 (6.4%)	9 (5.2%)	Unclassified (n=5), Nephronophthisis (n=1)
	283	171	

Among the acute nephritic syndrome cohort, 31 out of 39 required a renal biopsy due to atypical features. The most common lesion was PIGN (n=20), followed by lupus nephritis (LN) in ten, and one child had C3GN (MPGN pattern with low C3).

In children presenting with *RPRF*, a biopsy was done in all the cases. Crescentic glomerulonephritis was the most common (n=16) lesion, followed by LN (n=10). The reason for crescents was ANCA-associated vasculitis in six, IgA nephropathy in two, C3GN in three, anti-GBM in one, and unknown etiology in the other four. One child had HUS. In children presenting with *CKD* of unknown etiology, a biopsy was done in 9 out of 26 since they had normal sized kidneys and no apparent cause for CKD. The biopsy lesions were unclassified in five children, and one each of nephronophthisis, early DM, glomerulocystic kidney disease, IgA CGN.

CKD/ESRD: A total of 59 children had CKD. Those who presented to us directly with CKD were 26 (6.4%) (previously mentioned) the rest 33 children were those with other kidney diseases and under our follow up. Out of the former group, 17 had contracted kidneys at presentation itself (65.38 % of new CKD children).

In children with isolated urinary abnormalities, a renal biopsy was done in 15 out of 31 children, which showed IgAN (n=11) and Alport syndrome (n=2), membranous nephropathy, lupus nephritis, and normal histology one each, respectively. Out of the remaining 16, 9 had urolithiasis, and in the rest, no specific etiology was identified.

Renal tubular disorders: The most common was Hypophosphatemic rickets (XLH) (n=11) presenting as rickets in children >10 years. Second was distal renal tubular acidosis (dRTA) (n=9), Bartter's syndrome (n=4), medullary sponge kidney (n=2), Fanconi syndrome (n=2), Gitelman syndrome (n=1), vitamin D dependent rickets type 1 (n=1).

Anatomical causes: CAKUT; This formed the second most common kidney disorder in our series. The most common CAKUT was

congenital pelvi-ureteric junction obstruction (PUJO), either unilateral or bilateral (n=46, 37.4%). Followed by posterior urethral valves (PUV) (n=23, 18.7 %), neurogenic bladder (n=17, 13.8%), renal dysplasia (including multicystic dysplastic kidney-MCDK) (n=16, 13%), primary VUR (n=12, 9.75%), crossed fused ectopia seen in four children, ARPKD in three children, and one child each with anorectal malformation and medullary sponge kidney. We did not encounter any children with Wilms's tumor or any renal malignancy.

Table – 2: Summary of studies on the pattern of pediatric kidney diseases around the world.

Study	Country	Year	Number of children	1st Most common	2nd	3rd	4th
Eke, et al. [18]	Nigeria	1994	699	UTI (68.9%)	NS (14.6%)	AGN (11.4%)	-
Mola, et al. [19]	Ethiopia	2016	381	CAKUT (33.3%)	NS (21%)	AGN (12.2%)	Urolithiasis (6.7%)
Yadav, et al. [20]	Nepal	2106	206	AGN (37.7%)	NS (26.1%)	UTI (21.3%)	AKI (17.9%)
Barman, et al. [21]	Eastern India	2018	326	AGN [31.6%]	NS [30.1%]	UTI (11%)	CKD (8%)
Kanodia, et al. [22]	Western India	2015	335 biopsies	NS (46.2)	Urinary abnormalities (41.19%)	Acute nephritic syndrome (10.74%)	CKD (1.79%)
Bazina, et al. [23]	Croatia	2107	65	NS (41.2%)	Urinary abnormalities (35%)	-	-
This study	South India	2020	406	NS (32%)	CAKUT (30.30%)	AGN (9.6%)	Isolated urinary abnormalities (7.63%)

Discussion

Children are not miniature adults. The kidney issues affecting them are more diverse and complex than those of adults. The spectrum of renal diseases in them varies by geographical location, race, genetic and environmental factors. The most common diagnosis seen in our study was nephrotic syndrome (32%), closely followed by CAKUT (30.30%). **Table – 2** showed comparison with other studies [18-23].

Glomerular lesions: Nephrotic syndrome; NS is the most common glomerular disease in children worldwide [24] and our data, too, confirms this. According to the International Study of kidney disease in children (ISKDC), only 10-20% have steroid-resistant course [25]. But we found that more than half of our NS children were steroid-resistant. The reason for higher SRNS in our series would be because ours is a tertiary care referral hospital, and the children referred to us are those who could not be managed outside by primary pediatricians. Hence this could be a referral bias. We found that these SRNS children had MCD (58.8%) predominantly on renal biopsy, which is contrary to the ISDKC study, which showed SRNS had predominant FSGS (47.5%) [26] but in line with another study from Bosnia showed SRNS to have MCD more

common than FSGS [27]. This may indicate that histopathology in SRNS children varies widely.

Acute nephritic syndrome cohort: This group formed the second most common glomerular disease (9.6%) of our pediatric patients, which was similar to Kanodia et al., who found this in 10.74% of the renal biopsies from children [22]. Worldwide the most typical cause of this syndrome is PIGN [28], which is seen in this series.

RPRF: Our incidence of RPRF was 15.7%. Understandably, all these patients required a renal biopsy. Among them, we found that crescentic glomerulonephritis (majority due to ANCA vasculitis) and lupus nephritis to be the most common lesions. These are similar to a study from north India that showed 10.1% of children (n=18) had RPRF presentation, and the most common cause was crescentic GN, followed by IgA nephropathy [29].

CKD: Again, the etiology of CKD in children varies from one location to another. There is a lack of knowledge about the exact etiology of childhood CKD in India. In a series of 305 children, the most common cause of CKD was obstructive uropathy, reflux nephropathy, or CGN in 75% [30]. In adolescents, CGN is more common, leading to CKD [31]. A similar trend has been seen in other developing countries [32]. Our experience is a bit different. We had more CKD of unknown etiology (CKDu) and on biopsy had nonspecific lesions. This may be because of a high incidence of CKDu in this part of India [33, 34].

Whatever may be the reason, by the time they present with ESRD, they may have contracted kidneys and none of the features of the primary disease. In our series, 65% had a similar picture. Hence emphasis should be on early diagnosis of pediatric CKD via mass screening of children in schools as validated by Japanese studies, [35] or aggressive ultrasound screening [36].

Isolated urinary abnormalities: Studies from Japan, where the program of screening school children is a norm, have found that abnormal urine analysis can be seen in 1- 14% of healthy school children [37]. A study by Fouad et al. from Egypt found that in adolescents, isolated asymptomatic hematuria was seen in 9.8% and isolated proteinuria in 2.6% [38]. In our study, the prevalence of these asymptomatic abnormalities was 7.63%, and the most common underlying lesion was IgA nephropathy and urolithiasis for isolated proteinuria and microscopic hematuria respectively. Data from the US by Chandar et al. found in their retrospective analysis that hypercalciuria and orthostatic proteinuria was the main reason for isolated microhematuria and isolated proteinuria respectively [39].
This emphasizes the importance of thoroughly evaluating these abnormalities so that treatment and follow up is started on time.

Renal tubular disorders: We had many elderly children come to us with failed vitamin D treatment for rickets and found to have hypophosphatemic rickets. This was our most common tubular disorder. A study from a center from south India found dRTA to be the most common renal tubular disorder [40]. dRTA in our study was the second common tubular disorder.

CAKUT: This was the second most common disease noted in this series. CAKUT accounts for most cases of pediatric ESRD and predisposes the child to hypertension and cardiovascular disease throughout life [41]. According to the NAPRTCS registry, CAKUT is responsible for 48% of CKD in children. With the availability of ultrasound and trained fetal sonologists, the incidence of these lesions is increasing. The prevalence of CAKUT has been reported to be 0.1% on prenatal scans [42] and over 1% on Post-natal scans [43]. The most common CAKUT in our series was PUJO (presenting as either antenatal or post-natal hydronephrosis ± UTI), which accounted for 37%. In a study from a pediatric center in South India, the commonest

CAKUT was Primary VUR (27.3%), followed by PUJO (20%) [44]. In another study from the same institute published by the pediatric surgery department showed that 40% of children had PUJO, 32% had PUV, and 19% had VUR [45]. In another study from Egypt, PUV formed the most common CAKUT (36.4%) [46]. These studies emphasize that causes of CAKUT are not uniform and vary from center to center and interestingly among the same geographic location, they vary upon the departments managing them. Pediatric surgeons seen more PUJO, and physicians see more primary VUR. This underscores the need for knowing patterns in our place of work.

Limitations of the study

Being a retrospective study, some of the data may have been missed during entry or data retrieval. We have excluded children with AKI in the study, and in doing so, we may have missed its incidence among children in the society. We have not assessed the outcome measures of these children and hence cannot comment upon their recovery or deterioration.

Summary

Pediatric kidney diseases have a varied presentation depending upon geographical location and age. Two thirds of these children present either with nephrotic syndrome or CAKUT. The former it is usually due to MCD and the latter is due to PUJO.

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