Epidemiology of Pediatric End Stage Renal Disease in Southwest of Iran

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Abstract- Chronic kidney disease is a devastating disorder, which complicated the quality of life in affected patients. Determination the epidemiology of end stage renal disease (ESRD) seems necessary to decrease the occurrence of progressive renal damage in at risk patients. This study was performed to investigate the epidemiologic characteristics and treatment modalities of children with ESRD. A cross-sectional study was conducted on 115 children with ESRD admitted during 2020-2022 in a pediatric nephrology center in Southwest of Iran. All children were younger than 18 years and referred for renal replacement therapy (RRT). ESRD was defined as glomerular filtration rate less than 10-15 ml/min/1.73 m^2 for at least 3 months. Information such as age of ESRD, gender, etiology of ESRD and type of RRT were obtained from their medical records. A total of 115 patients (53% male) were included. Mean age at the time of ESRD was 8.47 years. Males outnumbered females. The most common cause of ESRD was congenital abnormality of kidney & urinary tract (CAKUT) in 36.5% of patients, followed by hereditary disorders. The majority of patients were older than 5 years at the time of ESRD, with a significant correlation to the underlying disorder (P<0.001). Parental consanguinity was detected in 77% of patients, especially in hereditary disorders. RRT was performed in all patients, including hemodialysis in 71.3% and chronic ambulatory peritoneal dialysis in 28.7%, respectively. In conclusion, CAKUT was the most common cause of ESRD in our patient population. was the most common cause of ESRD in our patient population. Prenatal evaluation of all fetuses along with early neonatal screening of susceptible cases is suggested for preventing practice or slowing the progression of chronic kidney disease.

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Keywords: Glomerular filtration rate (GFR); Chronic renal failure; End stage renal disease; Children; Congenital abnormality of kidney & urinary tract (CAKUT)

Introduction

The prevalence of end stage renal disease (ESRD) and the incidence of renal replacement therapy (RRT) in children has been increased during the recent years (1,2). Children with ESRD constitute a small group of all patients with ESRD in different age groups (3).

The etiology of ESRD is different in children compared with adults (4-8), as congenital and hereditary disorders are more common in the pediatric population. The etiology of ESRD in children varies in different parts of the world for the genetic, racial, cultural and environmental risk factors. However, data on the epidemiology of ESRD among children is limited and is often dependent to the information of RRT centers (1,3,9). Congenital abnormality of kidney & urinary tract (CAKUT) including renal aplasia, renal hypo/dysplasia, reflux nephropathy and obstructive uropathies followed by hereditary disorders constitute the majority of children with ESRD in many developed countries, respectively. However, infectious and acquired renal diseases such as chronic glomerulonephritis or chronic tubulointerstitial nephritis are more common in developing countries (3-5,10).

Progression to ESRD is slower in congenital urologic malformations than glomerular disorders, in which

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advanced CKD is more common. Early diagnosis and appropriate management of these patients might prevent or slow the progression to ESRD (2,4). Identification the epidemiologic and clinical characteristics of children with ESRD seems necessary to individualize the clinical course and follow up of these patients (11). This study was performed to identify the most common epidemiologic characteristics of children with ESRD in South of Iran, compared to the previous studies.

Materials and Methods

A cross-sectional study was performed in all patients with ESRD admitted to a referral hospital in Southwest of Iran between 2020 and 2022. Inclusion criteria consisted of all children younger than 18 years with ESRD, admitted for renal replacement therapy. ESRD was defined as glomerular filtration rate (GFR) <15 cc/min/1.73m^2 BSA for at least 3 months, according to the K-DIQO guidelines. Alternatively, serum creatinine values >2 mg/dl for age 0-2 years, 2.5 mg/dl for 3-10 years, and >3 mg/dl for 10-15 years old were also used. Glomerular filtration rate was calculated by the Schwartz's formula (K.L/Cr), in which K was 0.33 in preterm infants, 0.45 in full term infants, 0.55 in children and adolescent girls, and 0.70 in adolescent boys. Serum creatinine was measured by the modified Jaffe method in all patients. Demographic data such as age at diagnosis of ESRD, gender, etiology of renal failure and the modality of RRT were determined.

Glomerular disorder was defined as chronic glomerulonephritis, which presents with hematuria and/or proteinuria, decreased renal function and hypertension. Vesicoureteral reflux was shown by voiding cystourethrography or radionuclide cystography. Obstructive uropathy was diagnosed by renal ultrasound and complementary radiologic or isotopic investigations. Primary hypoplasia/dysplasia was defined as small kidney without a history of previous renal damage, with regular outline±renal cysts. Hereditary disorders were identified based on clinical manifestations, laboratory exams, tissue sampling or genetic analysis in some patients. Reflux nephropathy was shown as bilateral small scarred kidney (proved by TC^{99}-DMSA renal scan) with a history of previous UTI. RRT was performed in all patients, using continuous ambulatory peritoneal dialysis (CAPD) or hemodialysis (HD) of 3-4 hours at 3-4 sessions per week, using a permanent vascular access.

Statistical analysis was performed using SPSS version 23. Data was described as frequency and percentage for categorial variables or median and interquartile range (IQRs) for continuous variables. Comparison between parametric variables was done by the sample t-test, while the proportions were compared with Chi-2 test. *P* less than 0.05 was considered significant.

Results

Totally, 115 children with ESRD were enrolled in this study. Of them, 61(53%) were males. Mean age at the time of dialysis was 73 months in males and 78 months in females, with no significant difference (P>0.05). The majority of patients were older than 5 years at the time of ESRD (Table 1), with a significant correlation to the underlying disorder (P<0.001). ESRD occurred earlier in patients with hyperoxaluria (8 months) and congenital nephrotic syndrome (18 months). However, those with Diabetic nephropathy and polycystic kidney disease had the oldest age at the time dialysis.

Table 1. Age distribution of renal replacement therapy

Mean age (y)	All (n,%)	CAPD (n,%)	HD (n,%)
≤1	16 (13.9)	14 (42.5)	2 (2.5)
1-5	30 (26.1)	14 (42.5)	16 (19.5)
5-10	30 (26.1)	3 (9)	27 (33)
10-15	33 (28.7)	2 (6)	31 (37.5)
15-20	6 (5.2)	----	6 (7.5)
Total	115	33	82

CAKUT complex (renal hypo/dysplasia, obstructive uropathy and vesicoureteral reflux) was the most common cause of ESRD followed by congenital nephrotic syndrome, focal segmental glomerulosclerosis, Juvenile nephronophthisis, cystinosis, chronic glomerulonephritis, hyperoxaluria, polycystic kidney disease and diabetic nephropathy, respectively. Parental consanguinity was detected in 77% of patients, with no significant correlation to the underlying disorder (P=0.23). About 66% of patients with CAKUT complex had relative parents (Table 2). About 79% of patients had anemia, followed by hypocalcemia (59%), hyperphosphatemia (42.6%), hyponatremia (23.5%) and hyperkalemia (15.7%) (Table 3).

RRT was performed in all patients, including hemodialysis (HD) in 82 cases and continuous ambulatory peritoneal dialysis (CAPD) in 33 cases (Table 2). The majority of patients in both groups with RRT were male (58.34% in HD vs 54.66% in CAPD), with no significant correlation between gender and type of dialysis (P=0.83). There was a significant correlation between age and weight with type of dialysis (P<0.001). CAPD was performed more commonly in children younger than 5 years with lower weight (P<0.001) (Table 4).

Table 2. Epidemiologic characteristics of patients with end stage renal disease

Primary disease	Number (n,%)	Mean age (y)	Age <5 (y)	Male (n,%)	Consanguinity (n,%)	CAPD (n,%)	HD (n,%)
CAKUT	41(35.65)	6.3	18(43.9)	22(53.6)	27 (65.8)	15(36.5)	26(63.5)
CNS	19(16.52)	1.5	18(94.7)	9(47.4)	14 (73.7)	12(63.2)	7(36.8)
JNPH	16 (13.92)	7.8	1(6.2)	9(56.2)	16(100)	1(6.2)	15(93.8)
FSGS	16(13.92)	7.8	6(37.5)	12(75)	11(68.8)	2(12.5)	14(87.5)
Cystinosis	11(9.56)	7.7	1(9.1)	6(54.5)	9(81.8)	-----	11(100)
CGN	5(4.33)	11.4	0	----	4(80)	-----	5(100)
Hyperoxaluria	3(2.64)	0.68	3(100)	2(66.7)	3(100)	3 (9.09)	----
PCKD	2(1.73)	15.6	0	1(50)	2(100)	-----	2(100)
DNP	2(1.73)	17.5	0	0	2(100)	----	2(100)
Total	115 (100)	8.47	47(40.8)	61 (53)	88 (76.5)	33 (28.7)	82 (71.3)
P	----	----	<0.001	0.165	0.23	<0.001	<0.001

CNS: Congenital nephrotic syndrome, JNPH: Juvenile nephronophthisis, FSGS: Focal segmental glomerulosclerosis, CGN: Chronic glomerulonephritis, PCKD: Polycystic kidney disease, DNP: Diabetic nephropathy

Table 3. Laboratory findings of children with end stage renal disease

Etiology	Hyponatremia (n,%)	Hyperkalemia (n,%)	Hypocalcemia (n,%)	Hyperphosphatemia (n,%)	Anemia (n,%)
CAKUT	9 (22)	4 (9.8)	19 (46.3)	16 (39)	33 (80.5)
CNS	6 (31.6)	3 (15.8)	14 (73.7)	7 (36.8)	13 (68.4)
JNPH	3 (18.8)	5 (31.3)	9 (56.3)	10 (62)	11 (68.8)
FSGS	3 (18.8)	2 (12.5)	11 (68.8)	5 (35.7)	13 (81.3)
Cystinosis	3 (27.3)	1 (9.1)	6 (54.5)	5 (50.0)	10 (90.9)
CGN	1 (20.0)	1 (20.0)	3 (60.0)	3 (60.0)	5 (100.0)
Hyperoxaluria	0 (-)	1 (33.3)	2 (66.7)	1 (33.3)	2 (66.7)
PCKD	1 (50.0)	0 (-)	2 (100.0)	2 (100.0)	2 (100.0)
DNP	1 (50.0)	1 (50.0)	2 (100.0)	0 (-)	2 (100.0)
Total	27 (100)	18 (100)	68 (100)	53 (100)	91 (100)

CNS: Congenital nephrotic syndrome, JNPH: Juvenile nephronophthisis, FSGS: Focal segmental glomerulosclerosis, CGN: Chronic glomerulonephritis, PCKD: Polycystic kidney disease, DNP: Diabetic nephropathy

Table 4. Characteristics of renal replacement therapy in children with end stage renal disease

Variables	CAPD (n,%)	HD (n,%)	*P*
Mean age (y)	2.94 (3.2)	9.14 (4.04)	<0.001
Mean weight (Kg)	10.2 (5.65)	24.6 (11.2)	<0.001
(BMI<3th percentile)	7 (21.2)	18 (21.9)	0.93
Male (n, %)	18 (45.4)	43 (47.5)	0.83
Anemia	23 (69.6)	68 (82.9)	0.11
Hyperphosphatemia	8 (25.8)	41 (51.8)	0.013
Hyponatremia	11 (33.3)	16 (19.5)	0.11

BMI: Body mass index

Discussion

Chronic kidney disease (CKD) is a major public health problem (1,3). A substantial number of children develop CKD early in life for congenital, urologic and hereditary disorders. Determination the epidemiology of CKD seems necessary to prevent the progression to ESRD (4,7,8). Accordingly, multiple studies in different geographic parts of the world have been performed with different results, which are described as epidemiologic details.

Age

Etiology of chronic renal failure in children is age

dependent and vary in different regions and nationalities. The incidence of ESRD increases with age and is higher in 15-19 years old than the younger age (3). Patients younger than 5 years consisted of 8-40% of children with ESRD in AL-Eisa study (12). Most patients in our study were older than 5 years at the time of ESRD. Children with diabetic nephropathy, polycystic kidney disease and chronic glomerulonephritis had the highest age at the time of RRT. However, patients with congenital nephrotic syndrome and congenital anomalies had the youngest age at the time of ESRD. Our results were in accordance with the majority of previous studies, in which, the incidence of ESRD and RRT were higher in older than the younger children (0-4 years). (4,5,9,13-15). Similar to our results CKD occurs earlier in younger children with structural abnormality such as renal hypoplasia/dysplasia, obstructive uropathy, and hereditary nephropathy with the worse survival after RRT, while glomerulonephritis was more common in those older than 12 years in some studies and ERA-EDTA registration report (3,6,9).

Gender

The majority of patients in our study were male. Similarly, male predominance has been reported in the previous studies. Male gender consisted a large number of patients with CAKUT in our study, similar to the other reports (1,3,5,9,14-16). Totally, abnormality in embryogenetic organogenesis, such as obstructive uropathy or renal dysplasia have been reported more prevalent in male gender, especially those with ESRD, which reflects the higher incidence of CAKUT complex in male than female (1,3). However, no gender difference was reported in these patients in some studies (12).

Etiology

CAKUT complex was the most common cause of ESRD in our patients, followed by hereditary disorders such as congenital nephrotic syndrome, juvenile nephronophthisis, cystinosis, hyperoxaluria and polycystic kidney disease (Table 2).

The CAKUT complex accounts for 35% of all congenital malformations in Rahman *et al.*, study (17), and more common in developed countries (4). In the CRI registry of NAPRTCS, CAKUT (45-58%) was the most common cause of CKD [obstructive uropathy (22%), renal hypo/dysplasia (18%), and reflux nephropathy (8%)], followed by hereditary nephropathy (10-20%) and glomerulonephritis (14%) (4,8). In the Ital-kid Project hypo/dysplasia secondary to the urinary tract malformation and isolated renal hypo/dysplasia accounted for 54% and 14% of patients with CKD, respectively. Glomerular disorder was the second cause of CKD in about 7% of patients in Warady *et al.*, study (3). CAKUT complex constitutes 30-60% of all children with CKD in different geographic areas (1-3,7-9,11-13,16,18-21).

Hereditary disorders such as congenital nephrotic syndrome, juvenile nephronophtisis and cystinosis consisted of a large number of our patients in this study, which might be correlated to the high incidence of parental consanguinity. Hereditary nephropathies have been reported in 7-40% of the previous studies (5,8,9,18,21), more common in regions with high frequency of consanguinity (16).

FSGS was the most common glomerular disease in our patients, third to the CAKUT complex. Similarly, glomerular disorders such as FSGS have been accounted as an important cause of CKD in 10-52% of patients, mostly second to the urologic or hereditary problems (3,9,17).

However, glomerulonephritis was the most common cause of CRF in some studies followed by obstructive uropathies, hereditary disorder and renal dysplasia (10,15).

Etiology of CKD varies by age and race, in which CAKUT is more common in children younger than 12 years old. However, glomerular disorder such as focal segmental glomerulosclerosis is more likely in black adolescents in the other countries (4,6). In the ERA-EDTA registry, hypo/dysplasia, obstructive uropathy and hereditary disorder were the most common cause of ESRD in 0-4 year age group. However, chronic glomerulonephritis and chronic pyelonephritis were more common in older children, (3).

Consanguinity

About 77% of patients in our study had related parents, more in inherited disorders such as nephronophthisis, hyperoxaluria, polycystic kidney disease and cystinuria. Consanguinity was found in 66% of children with CAKUT complex. As has been reported hereditary disorders are more common in related parents.

Renal replacement therapy

Life expectancy of children receiving RRT has been significantly improved, especially in those younger than 5 years old. Survival rate is worse in children with glomerular disorder, advanced CKD and early onset CKD (6,9). HD was the most common modality of RRT in our patients and chronic ambulatory peritoneal dialysis was mostly performed in young children. HD has been

considered as the most prevalent modality of RRT in different studies (3,5,9,14,17,22). However, the prevalence of peritoneal dialysis has been increased gradually, especially in childhood (14,21).

Epidemiologic characteristics of our patients in Southwest of Iran was similar to the previous reports from the other parts of the world. According to the high incidence of CAKUT complex, early intrauterine ultrasound and proper management are recommended in at risk patients for preventing the progression to irreversible renal damage. In addition, prenatal diagnosis and appropriate management of hereditary disorders such as cystinosis, hyperoxaluria and nephronophthisis seems necessary to prevent further increase in the incidence of these disorders. Moreover, prenatal genetic counseling is recommended in familial consanguinity to prevent the occurrence of genetic disorders in susceptible populations.

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