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Etiology of Pediatric Chronic Kidney Diseases in North-West of Iran

[1]F. Mortazavi and [2]A. Rafiee
[1]Department of Pediatric Nephrology, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Resident of Pediatrics, Tabriz University of Medical Sciences, Tabriz, Iran

Abstract: The aim of this study was to evaluate the etiology of pediatric Chronic Kidney Disease (CKD) in a tertiary care hospital in north-west of Iran. Medical records of admitted children with CKD in Children's Hospital of Tabriz from 1999 to 2009 were studied retrospectively. CKD was defined as GFR less than 60 mL min^{-1} 1.73 m^2 for more than 3 month. The etiology of CKD was determined by clinical, biological, radiological and histopathological examination. During 10 years 115 children including 61 boys (53%) and 54 girls (47%) were studied. The mean age of patients was 8.1±3.53 years (range: 4 months to 14 years). Urological abnormalities were the most common cause of CKD (36.5%) followed by acquired glomerular diseases (23.5%), hereditary nephropathies (21.7%), unknown etiology (9.5%) and systemic diseases (6%). The most common urologic anomaly was vesicoureteral reflux (VUR) that accounted for 24.3% of total etiologies followed by obstructive uropathies. Focal segmental glomerulosclerosis was the most frequent glomerular disease and was responsible for 13.9% of patients. Nephronophtisis, cystinosis, infantile polycystic disease and congenital nephrotic syndrome were the most frequent hereditary nephropathies in a descending order. Frequency of parental consanguinity in patients with hereditary nephropathy was significantly higher than other patients ($p = 0.001$). High frequency of VUR in present study compared with developed countries necessitates more efforts for improving the management and follow up of urinary tract infections.

Key words: Chronic renal failure, etiology, children, reflux nephropathy, glomerulonephritis

INTRODUCTION

Chronic kidney disease (CKD) is the major cause of morbidity and mortality and represents an important health problem world wide. Prevalence of CKD in children varies from 18-74 per million child population in different reports depending on the upper limit of age and Glomerular Filtration Rate (GFR) considered in each study (Vogt and Avner, 2007; Ardissino *et al*., 2003; Hattori *et al*., 2002; Hamed, 2002). Children are particularly susceptible to adverse effects of CKD because they have not completed their maturation. Metabolic derangements due to CKD affect the growth, development and quality of life in children. Furthermore CKD is associated with significant neurodevelopmental and cognitive impairment in children (Furth *et al*., 2006). In addition to medical problems, CKD is a huge social and economic problem (Jha, 2009). Since the cost of dialysis and kidney transplantation is increasing over time, the management policy should be changed from treatment to prevention (Prodjosudjadi and Suhardjono, 2009). Identification of CKD etiology is the first step for its prevention. Etiology of CKD in children varies from one geographic area to another, due to environmental, genetic, socio-economic and cultural differences (Warady and Chadha, 2007). Reflux nephropathy accounted for 15-20% of end stage renal failure in past years but recently its percentage has decreased in developed countries due to improved diagnosis and management of urinary tract infections (Vogt and Avner, 2007). In some studies from developing countries, glomerular diseases are the predominant cause of pediatric CKD (Hiep *et al*., 2008; Ali *et al*., 2009). Hereditary nephropathies are more frequent in countries that consanguinity is common (Hamed, 2002; Kamoun and Lakhoua, 1996). There is few data about the etiology of CKD in children in our area due to lack of a national registry system and most available data are from adults. However etiology of CKD in children is different from adults. Diabetes mellitus and hypertension are the two common causes of CKD in adults (Monfared *et al*., 2009). While in children, congenital urologic malformations are responsible for the majority of CKD etiologies followed by glomerulonephritis (Miller and Williams, 2009; Cruz *et al*., 2005; Mosawi, 2002). Knowledge about etiology of CKD in children is necessary for prevention of CKD. This study was conducted to evaluate the etiology of CKD in Children's Hospital of Tabriz which is the sole referral center for pediatric CKD in East Azerbaijan province/Iran.

Corresponding Author: Fakhrossadat Mortazavi, Children's Hospital of Tabriz, Sheshgelan Street, Tabriz, Iran
Tel: 0098411 5262280, 09141166729 Fax: 0098 411 5262279

The results of this study may suggest ideas for prevention of CKD and help with planning of health care programs in the north-west of Iran.

MATERIALS AND METHODS

Medical records of all admitted children with CKD (under 14 years of age) in children's Hospital of Tabriz/Iran from October 1999 to October 2009 were reviewed retrospectively. CKD was defined as GFR less than 60 mL min^{-1} 1.73 m^2 for more than 3 months (Vogt and Avner, 2007). GFR was estimated by schwartz formula using height (cm) and serum creatinine (Vogt *et al*., 2007). The etiology of CKD categorized in six groups based on clinical, biological, radiological and histopathological examination as: (1) Congenital and urologic abnormalities including obstructive uropathies, reflux nephropathy and hypoplasia/dysplasia. This group of patients were diagnosed by imaging studies including ultrasonography, voiding cystourethrography (VCUG), intravenous urography, renal isotope scan (DMSA and DTPA) depending on the case. (2) Glomerular diseases: This category included the patients with acquired nephrotic and/or nephritic syndrome who underwent renal biopsy for histopathologic diagnosis. (3) Diseases with known inheritance pattern classified as hereditary nephropathies. In this group nephronophtisis and congenital nephrotic syndrome diagnosed based on renal biopsy. Diagnosis of cystinosis was made by ophthalmologic exam by slit lamp (presence of cystin crystals in cornea). Infantile polycystic kidney was diagnosed by sonographic and CT scan findings. Primary hyperoxaluria was diagnosed by measurement of 24 h urine oxalate in association with diffuse nephrocalcinosis and urolithiasis. (4) Diseases with both extrarenal and renal manifestations categorized as systemic diseases such as lupus erythematosus, hemolytic uremic syndrome and Henoch-Schonlein purpura. (5) Patients with small and atrophic kidneys at the time of first admission were categorized as unknown etiology if they had normal VCUG. (6) Patients with unclassified diseases categorized as miscellaneous group.

All diagnostic evaluations and renal biopsies were carried out by a pediatric nephrologist. Patients who had normal renal function at first admission but developed CKD during follow up period were included. Data for each patient including: sex, age, physical and laboratory findings, etiology of CKD and family history was collected in information forms. Patients with incomplete data were excluded. This study was approved by ethical committee of Tabriz University of Medical Sciences. The data were analyzed by statistical package for the social sciences (SPSS). Quantitative variables presented as Mean±SD. Chi-square test was used for comparisons and p-value <0.05 considered as significant.

RESULTS

During 10 years 115 children with CKD including 61 boys (53%) and 54 girls (47%) were studied. There was not any significant difference between frequency of girls and boys (p>0.05). The mean age of patients at the time of CKD diagnosis was 8.1±3.53 years (range: 4 months to 14 years). Twenty patients (17.4%) had positive family history as having a sibling with CKD. Urological abnormalities, the most common cause of CKD, detected in 42 patients (36.5%) including 22 boys and 20 girls. There was not any significant difference between frequency of urological abnormalities between girls and boys (p>0.05). Vesicoureteral reflux (VUR), as the most common urologic anomaly, was detected in 28 patients (28/115=24.3%) with a mean age of 9.4±1.5 years including 12 patients (10.4%) with primary VUR and 16 patients (13.9%) with secondary VUR. Vesicoureteral reflux secondary to neurogenic bladder accounted for 38% of total urologic abnormalities (Table 1).

Acquired glomerular disease, the second common cause of CKD, was diagnosed in 27 patients (23.5%). Focal segmental glomerulosclerosis (FSGS) was the most frequent glomerular disease that accounted for 13.9% of total etiologies and 59% of glomerular diseases.

Table 1: Etiology of chronic kidney disease in children's hospital of Tabriz/Iran

Etiology	Number (%)	Male	Female
Congenital malformations and urologic problems	42 (36.5)	22	20
Vesicoureteral reflux	28	12	16
Obstructive uropathies	9	7	2
Hypoplasia/dysplasia	5	3	2
Glomerular diseases	27 (23.5)	9	18
Focal segmental glomerulo sclerosis	16	6	10
Memranoproliferative glomerulonephritis	4	1	3
Rapidly progressive glomerulonephritis	3	1	2
Diffuse mesangial proliferation	2	-	2
Diffuse mesangial sclerosis	2	1	1
Hereditary nephropathies	25 (21.7)	18	7
Nephrononphthisis	7	5	2
Cystinosis	5	4	1
Infantile polycyctic kidney	4	2	2
Congenital nephrotic syndrome	4	2	2
Primary Hyperoxaluria	3	3	-
Laurence- Moon- Biedl syndrome	2	2	-
Systemic diseases	7 (6)	4	3
Lupus erythematosus	4	2	2
Hemolytic uremic syndrome	2	2	-
Henoch-Schonlein purpura	1	-	1
Miscellaneous kidney disease	3 (2.6)	2	1
Chronic tubulointerstitial nephritis	1	-	1
Urolithiasis	2	2	-
Unknown	11 (9.5)	6	5
Total	115	61	54

Hereditary nephropathies constituted 21.7% of causes of CKD. Nephronophtisis, cystinosis, infantile polycystic disease and congenital nephrotic syndrome were the most frequent hereditary diseases in a descending order (Table 1).

Parental consanguinity was detected in 18 of 25 patients (%72) with hereditary nephropathy and in 18 of 90 patients (20%) with other causes of CKD. Frequency of parental consanguinity in patients with hereditary nephropathy was significantly higher than other patients ($p = 0.001$).

Systemic diseases accounted for 6% of patients and lupus erythematosus was the most frequent among them (Table 1). In 11 patients (9.5%) who were referred in an advanced stage of CKD, the etiology remained unknown.

DISCUSSION

In most studies, prevalence of CKD in boys is higher than girls (Warady and Chadha, 2007). The male to female ratio was 2:1 in Tunisia (Kamoun and Lakhoua, 1996), 1.7:1 in Iraq (Mosawi, 2002) and 1.5:1 in Vietnam (Huong *et al*., 2009). Male preponderance may be explained by higher prevalence of obstructive uropathy such as posterior urethral valve in boys. However there was not any significant sex preponderance in present study not only in total study population but also in patients with urologic anomalies which may be due to the high frequency of vesicoureteral reflux (VUR) in our female patients.

In studies performed in North America, Iran/Tehran and India congenital urologic anomalies were the predominant cause of pediatric CKD and accounted for 50, 52 and 47% of etiologies, respectively (Warady and Chadha, 2007; Madani *et al*., 2001; Gulati *et al*., 1999) that is in accordance with results of present study. In North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) report, VUR accounts for about 8% of chronic renal insufficiencies (Warady and Chadha, 2007). While in some developing countries VUR comprises a higher percentage. In Kuwait 30% (Reshaid *et al*., 1999) and in southwestern Iran 23.1% of CKD was due to VUR (Ahmadzadeh *et al*., 2009). In present study VUR is responsible for 24.3% of etiologies that is compatible with results from developing countries. Since urinary tract infection is the cardinal presentation of VUR and other urologic anomalies, more attention to management of UTI is needed in our area.

Glomerular diseases were the second cause of CKD and represented 23.5% of patients in present study. While in some reports from Vietnam, Nigeria and South Africa, glomerulonephritis accounted for 66.4, 58.3 and 56.4% of pediatric CKD respectively (Huong *et al*., 2009; Michael and Gabriel, 2004; Bhimma *et al*., 2008). This discrepancy may be due to higher prevalence of infectious diseases (such as HIV infection) in some countries that results in higher prevalence of post-infection glomerulonephritis. In Jamaican children with chronic renal failure half of the cases of glomerulonephritis was secondary to HIV associated nephropathy (Miller and Williams, 2009). In report of NAPRTCS, FSGS was the most frequent glomerular disease of childhood resulting in CKD (Warady and Chadha, 2007) that is in accordance with our results.

Hereditary nephropathies were determined in 21.7% of our patients that is similar to other studies from Iran (26%) (Madani *et al*., 2001), Tunisia (29%) (Kamoun and Lakhoua 1996), Iraq (21.36%) (Mosawi, 2002) and Jordan (29.7%) (Hamed, 2002) While in Vietnam only 2.6% of children with CKD had hereditary nephropathies (Huong *et al*., 2009). High frequency of hereditary nephropathies in our study may be explained by high frequency of consanguinity due to our cultural characteristics.

Percentage of unknown etiology in our study (9.5%) is similar to studies carried out in other parts of Iran such as Tehran (8.4%) (Madani *et al*., 2001) and Ahvaz (10.8%) (Ahmadzadeh *et al*., 2009). While in report of NAPRTCS only 2.6% of patients had unknown etiology (Warady and Chadha, 2007). High number of unknown etiology in our study, in comparison with developed countries, indicates late referral of patients because of a poor health care system.

CONCLUSION

Prompt diagnosis and treatment of UTI and its proper follow up for early detection of underlying urologic anomalies and VUR, is essential for prevention of pediatric CKD in our area. Improvement of health care system is needed for early detection and referral of patients who are at early stages of CKD. More studies are needed to evaluate the impact of changing the public opinion about consanguinity, in reducing the frequency of hereditary nephropathies.

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