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Clinical Signs, Causes, and Risk Factors of Pediatric Chronic Kidney Diseases: a Hospital-based Case-control Study

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Abstract

Background

This retrospective study aimed to determine the epidemiologic characteristics and risk factors of chronic kidney diseases (CKD) in patients < 18 years old at a single referral center.

Materials and Methods

In a hospital-based case control study, 66 CKD patients less than 18 years old were compared to 81 control patients (also under 18) without CKD. A patient was defined as a CKD case with renal injury and/or had a glomerular filtration rate (GFR) of <60 ml/min/1.73 m2 for more than 3 months. Required information for the study was collected using a questionnaire and conducting clinical tests. Data analysis was performed by using univariate and multivariate logistic regression, as well as a Chi-square test.

Results

Fever, chills, and urinary tract infections were the most common clinical signs in the referred patients. Urinary tract infection (39.5%) and growth failure (12.9%) were the most important causes in referred pediatric CKD. After controlling the effect of confounding variables, household income, using packed water for drinking, percentile of body mass index (BMI), and gestational age were the significant predictors of pediatric CKD (P<0.05).

Conclusion

The most common presentations of the disease were Urinary Tract Infection (UTI) and fever. Reflux nephropathy was the leading cause of CKD in children. Therefore, more attention to children with these signs is essential for early diagnosis. High household income and preterm delivery were the risk factors for CKD in children.

Key Words: Children, Kidney disease, Pediatric, Renal Insufficiency.

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1- INTRODUCTION

Chronic kidney disease (CKD), a major health problem, is increasing worldwide (1-3). The disease is defined as a condition related to irreversible kidney damage and can progress to end-stage renal disease (ESRD) (4, 5). The importance of CKD is in ESRD which increases the excessive risk of mortality, higher cardiovascular morbidity, and the need for specialized health care (5, 6). However, specific problems of ESRD in children occurs including impaired growth and psychosocial disorders that are related to their quality of life (6, 7). Moreover, due to the devastating effects of CKD in children, the mortality rate of ESRD patients receiving dialysis increases between 30 and 150 times more than the general pediatric population and their life expectancy is less than 20 years (8, 9). These complications, as a results of disabilities in children with ESRD, increase the burden of disease (8).

Studies showed high prevalence of CKD in different countries. The prevalence varies between 6% in Europe and North American countries to 18.7% in Japan. (1, 2, 7, 10). In addition, the prevalence of CKD in Iranian adults over a 20 year span is reported to be from 11.6-18.9% (1, 11). This prevalence is responsible for 1,145,654 disability-adjusted life years (DALYs) (12). The economic costs for CKD care and an increasing trend in morbidity of diseases show that CKD is threatening to reach worldwide epidemic proportions over the next decade (2, 5, 8). Moreover, the burden of early CKD exceeding more than 50 times those reaching ESRD is due to patients undiagnosed in early stages (8). Therefore, there is an urgent need to identify the risk factors of pediatric CKD and develop new methods to halt the progression of CKD in children (9).

Today, pediatric CKD epidemiology is at a disadvantage compared to adult data as limited studies exist and generally only reflect the status of children in developed nations (4-6, 11, 13-16). Furthermore, most of the available epidemiological data is gathered from ESRD patients; therefore, information concerning the earlier stages of pediatric CKD is further limited. Because of this lack of knowledge, CKD is often undiagnosed in patients in early stages, especially children, and its complications are often left untreated (1). Better understanding of the epidemiology of pediatric CKD is essential in decision-making and early diagnosis, as well as in identifying modifiable causes of progression, predicting prognosis, and aiding in the counseling of the children and their families. Therefore, the current study has been conducted to find the epidemiologic characteristics of CKD in children for the appropriate management of the disease.

2- MATERIALS AND METHODS2

2-1. Study setting

In a hospital-based case control study, a representative sample was taken from all children between 3 months to 18 years with CKD who were referred to Amirkabir hospital at 2014, the only nephrology clinic for children in Arak.

2-2. Study population and measurements

The patients were selected by convenience sampling and recruited as cases. In these patients, according to the updated modified Schwartz equation (17), CKD cases were defined as irreversible renal injuries (such as proteinuria, the presence of abnormal quantities of protein in the urine, after treatment) and/or a glomerular filtration rate (GFR) of <60 ml/min/1.73 m2 for more than three months according to the K/DOQI classification system (4, 18-20). All cases were type I or II of CKD and selected based on Furth recommendations (21). The control group was comprised of children referred to that hospital without a CKD diagnosis. For all the subjects in the

control group, GFR and renal failure was normal. Sample size was determined based on sample size formula for comparing two proportions and 80% power assuming and type one error 0.05; therefore, we included 66 children with CKD in case group and 81 children without CKD in control group. Affecting to the type I or II of CKD and consent for cooperation for entering to the study were inclusion criteria. Moreover, subjects with a history of prior kidney transplant, dialysis, or those who were less than 2 years of age were excluded from the study (22).

All tests and sonographies conducted and assessed by pediatric nephrologist for all participants for detection of CKD. In addition, demographic data was collected by questionnaire. For all subjects, a complex of laboratory tests was conducted the day after the interview to collect fasting blood samples. Laboratory assessment (4) included urine analysis, complete blood count, creatinine, serum electrolytes, kidney and bladder sonography, and stone biochemical analysis. Creatinine clearance is estimated as the rate of filtration of the kidneys by GFR (17). Moreover, demographic characteristics of patients including age, sex, type of drinking water, parents' employment and education, family income, birth history (premature, small for gestational age, low birth weight) and primary CKD diagnosis (glomerular or non-glomerular), and anthropometric measurements were recorded in the checklist. In addition, according to the growth curve of study subjects, the status of growth including appropriate, lagged, stopped, and declined growth were checked by a children's specialist physician and was added to the data.

2-3. Ethical consideration

The study objectives were described for all study subjects and their parents before their recruitment and informed consent was taken. In addition, the study protocol was approved by the ethical committee of Arak University of Medical Sciences, Iran.

2-4. Statistical analysis

Data analysis was conducted by chi-square, Fisher's exact test, and logistic regression model on SPSS (IBM, Armonk, NY, United States of America) software was used and significance level considered as 0.05.

3- RESULTS

The most common cause of referring to a nephrology clinic was UTI and growth problems, 39.5% and 12.9%, respectively. In addition, the more common signs in studied subjects were UTI, fever, and chills. The highest cause of referring CKD cases to the nephrology ward was reflux nephropathies (16.7%). Of these cases, the most common (12.1%) reason for entering to clinic was resistance to treatment syndrome. Children who have 2+ proteinuria are classified as having resistance to treatment syndrome (17). Slightly less commonly found in the reflux nephropathy cases in our study was the occurrence of renal tubular acidosis (9.1%), autosomal polycystic kidney disease and hemolytic uremic syndrome (7.6%), and Bartter syndrome (4.5%).

Table.1 shows the demographic and family characteristics of cases and controls. According to these results, there was no significant difference in the two groups based on gender, family history of CKD, normal growth trend, parents' education, and birth weight ($P>0.05$). Nevertheless, significant differences were observed in cases and controls regarding household income and the type of drinking water consumed ($P<0.05$). Univariate logistic regression was used to find the relationship of related factors of CKD and the results are shown in (**Table.2**).

Univariate logistic regression showed that age, not being exclusively breastfed, term pregnancy age, undesirable growth, and

having high household income are risk factors of CKD. Nevertheless, using packed water as the main source of drinking were the protective factors of CKD. After using univariate logistic regression, all variables with a significance level lower than 0.15 were entered in multivariate logistic regression. Therefore, household income, use of packed water, percentile of BMI, and gestational age were determined as the most important predictors of CKD. In a way, being in high-income households and preterm delivery can increase the odds of CKD to more than four fold.

Table1: Comparing cases and controls regarding related factors of pediatric CKD in univariate analysis

Variables		Control n (%)	Case n (%)	P- value
Male gender		48(59.3)	46(69.7)	0.228
Family history of CKD		31(38.3)	25(37.9)	0.91
Mother's job (being homemaker)		48(59.3)	50(75.8)	0.037
Appropriate growth of child		39(48.1)	23(34.8)	0.018
Income level of family ($)	Lower 300	17(21)	2(3)	0.005
	300-600	26(32.1)	23(34.8)	
	More 600	38(46.9)	41(62.1)	
Type of drinking water commonly used	Urban	29(35.8)	29(43.9)	0.001
	Filtrated	27(33.3)	33(50)	
	Packed	25(30.9)	4(6.1)	
Birth weight	Normal	59(72.8)	46(69.7)	0.502
	LBW	13(16)	15(22.7)	
	VLBW	9(11.1)	5(7.6)	
Father's education	Under 8 years	4(4.9)	4 (6.1)	0.73
	8-14 years	19(23.5)	19 (28.8)	
	Over 14 years	5(6.2)	2 (3)	
Mother's education	Under 8 years	11(13.6)	8 (12.1)	0.270
	8-14 years	23(28.4)	29(43.9)	
	Over 14 years	3(2)	1(1.5)	

Table 2: Risk factors for CKD in Univariate analysis of logistic regression

Variables		OR	CI of OR	P- value
Age of children (Month)		1.022	1.002-1.042	0.032
No exclusive breastfeeding		3.26	1.51-6.9	0.003
Using packed water, commonly		0.16	0.05-0.52	0.002
Percentile of height		0.94	0.84-1.016	0.33
Percentile of weight		0.99	0.87-1.13	0.877
Percentile of BMI		0.61	0.49	0.77
Preterm pregnancy age		2.62	1.29-5.3	0.008
Inappropriate growth		5.79	3.12-11.48	0.001
Affected to growth stop		3.47	1.71-7.19	0.001
Appropriate growth		0.58	0.3-1.12	0.106
Father's education	Under 8 years	1		
	8-12 years	0.97	0.22-4.5	0.99
	12-14 years	0.4	0.05-3.42	0.403
	Over 14 years	0.77	0.18-3.28	0.728
Mother's education	Under 8 years	1		
	8-12 years	1.73	0.22-4.5	0.310
	12-14 years	0.69	0.05-3.4	0.775
	Over 14 years	0.86	0.18-3.28	0.766

Income level of family ($)	Under 300	1		
	300-600	3.01	1.3-9.33	0.019
	Over 600	4.97	1.6-12.1	0.007
Birth weight	Normal	1		
	LBW	1.48	0.64-3.42	0.36
	VLBW	0.71	0.22-2.27	0.57

OR= Odds Ratio; CI= Confidence Interval

Table 3: Multivariate regression of risk factors of chronic kidney diseases

Variables		OR	CI of OR	P- value
Income level ($)	Lower 300	1		
	300-600	2.5	1.2-4.5	0.033
	More 600	5.3	2.4-9.67	0.004
Water used	Urban water	1		
	Packed water	0.13	0.03-0.62	0.011
High percentile of body weight		0.61	0.44-0.83	0.002
Preterm pregnancy age		4.56	1.5-13.4	0.006

OR= Odds Ratio; CI=Confidence Interval.

4- DISCUSSION

According to our results, fever, chills, and UTI were the most common clinical symptoms of CKD in children. The most important causes of referral to the nephrologist were UTI in 39.5% and growth failure in 12.9%. After a full examination, we observed the following in studied CKD patients: secondary nephropathies due to reflux (16.7%), resistant to treatment syndrome (12.1%), renal tubular acidosis (9.1%), polycystic autosomal kidney and uremic hemolytic syndrome (7.6%) and barter syndrome (4.5%).

In another study in Iran by Ahmadzadeh et al. (18), scar nephropathy, hypo/dysplastic kidney, hereditary nephropathy, and obstructive uropathy were the most common causes of CKD in children. Hooman's study reported that inherited kidney disease, systemic kidney disease, primary nephropathy, and kidney dysplasia were the most important causes of pediatric CKD (23). Moreover, Boskabadi showed that oral aciphex medication, hyaline membrane, sepsis, dehydration, and congenital heart disease are the most important consequences of CKD in hospitalized children in the neonatal intensive care unit (NICU) (24).

According to our results, CKD is associated with delay or impaired growth in children. On the other hand, as results of other studies of CKD in childhood, the disease is strongly associated with stunting of linear growth (9). This is because of an elevation of insulin-like growth factor and increased hepatic synthesis, the bioavailability of insulin-like growth factor decrease, and this leads to a decrease in the expression of growth hormone hepatic receptor and decreased production of insulin-like growth factor (25).

Nevertheless, these complications of CKD are dependent on access to health care resources and the income level of the household (8). Moreover, according to our results, some social and economic factors such household income, type of drinking water, and having homemaker's mother were the highest predictors of occurrence of pediatric CKD or its complications. This can be justified because children who are more affluent have higher access to healthcare, sanitary water and lower infant death rate due to availability of heath care services (26-28). Moreover, using packed water is more common highly socioeconomic/high income families.

Two factors primarily responsible for the increase in the incidence of CKD in adults

are hypertension due to an aging population and diabetic nephropathy due to the global epidemic of type-II diabetes mellitus (2, 8, 22). In addition, the CKD risk factors vary from one geographic area to another due to genetic and environmental factors (18). Causes of CKD are very different in children than they are in adults (29). Congenital or inherited kidney disorders and urinary tract abnormalities are the leading cause of ESRD in children (6, 30). The attributable risk of congenital anomalies for pediatric CKD is approximately 60 to 70% (22).

Also, compared to adults, additional allocation of funds and specialized care is needed for children with CKD in order to achieve better administration of patients (22). Nevertheless, a number of pediatric CKD that is diagnosed in its earlier stages in developed countries are due to congenital factors (8). Unlike developed countries, infectious and acquired etiologies are prominent causes of CKD in developing nations (8). Our results showed that body weight percentile in children, household income, type of water used, and preterm delivery in pregnancy are the greatest predictors of CKD in children. Moreover, according to the results of some studies, demographic characteristics such as the gender of the child, age and BMI are the causes of CKD in children (11, 31, 32).

Tohidi's study reported that a strong positive correlation was observed between different stages of CKD with age, female gender, and high body mass index (3). While, based on Mohkam's study, gender and age were not related factors for GFR at the time of admission (31). However, children in families with high-income levels are more commonly diagnosed by screening tests due to greater care.

Some studies have shown that the morbidity of CKD is increasing in developing countries and the incidence of disease increased 2 times in 6 years (33). Epidemiologic studies suggested that identifying the epidemiologic characteristics of CKD in children and adults worldwide is essential, especially in countries such as Iran that include different ethnicities (34). However, valid and widespread information about the epidemiology of pediatric CKD as well as its genetic, social, and environmental risk factors require additional studies at the national level via prospective studies and longitudinal follow-up. In addition, the effect of the packed drinking water and preterm delivery in pregnancy were significant in our study, but it is needed to be assessed in future studies.

5. CONCLUSION

Fever and UTI were the more common signs and reflux nephropathy was the highest cause of referring CKD cases to the nephrology clinic. Preterm pregnancy age of children and high percentile of body weight as well as high household income were the predictors of CKD in children. In a way, having a high household income and preterm pregnancy age can increase the odds of CKD to more than four fold. Nevertheless, the effect of these factors as cause of CKD need to be addressed in future studies.

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7- CONTRIBUTION OF AUTHORS

PY: Contributions to the conception and design of the research; analysis and interpretation of data; final approval of the manuscript

SR: Contributions to the acquisition and analysis of data; drafting of the manuscript and final approval of the manuscript

AM: Contributions to the conception and design of the research analysis; interpretation of data; final approval of the manuscript

MR: Contributions to the conception and design of the research; interpretation of data; final approval of the manuscript.

8- CONFLICT OF INTEREST

The authors had not any financial or personal relationships with other people or organizations during the study. So there was no conflict of interests in this article.

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