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Pathologic findings of renal biopsies in children; an 11-year experience from a single center in west of Iran

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ABSTRACT

Background: Renal biopsy is an important diagnostic procedure in pediatric nephrology. Although considered as an invasive method, numerous renal diseases cannot be definitively diagnosed and treated without it.

Objectives: The aim of this study was histopathological study of renal biopsy results in children of 6 months to 18 years old.

Patients and Methods: In this retrospective cross-sectional study, the available data from children who had undergone kidney biopsy between 2007 and the end of 2017 were evaluated. Demographic data, indications of biopsy, the outcome of patients, biopsy complications and histopathologic findings were collected using a checklist. Finally, data were presented as frequency and percentages.

Results: The most common cause of biopsy in children was nephrotic syndrome (43.7%). Focal segmental glomerulosclerosis (FSGS) with 39 cases (32.7%) had the highest frequency in examined biopsies. In the long-term follow-up, 71 children (59.7%) cured, 7 (5.9%) died, 25 (21.0%) continued treatment, 6 (5.0%) underwent a kidney transplant surgery, and the outcome of 10 children (8.8%) was unknown. While 6.7% of patients were diagnosed with complications of biopsy, the most frequent of them was hematuria. There was no case of death or nephrectomy and only one patient needed packed RBC transfusion.

Conclusion: Nephrotic syndrome was the most common indication for kidney biopsy. FSGS had the highest frequency in examined biopsies.

Implication for health policy/practice/research/medical education:
Kidney biopsy is an invaluable method in pediatric nephrology practice, shedding a light on diagnosis and is a guide for proper treatment.

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Original Article

Introduction

Chronic kidney disease (CKD) with the prevalence of 12.5 per million in children has devastating effects on various body systems including cardiovascular, endocrine, central nervous system, and gastrointestinal. The disease is asymptomatic at the beginning. However, symptoms including fatigue, hypertension, and growth failure are observed when the function of the kidney decreases gradually (1).

Despite the type of disease, CKD results in kidney failure and causes cardiorespiratory diseases. It was shown that the diagnosis and treatment of CKD might prevent the complications arisen from the disease as well as advanced kidney failure. Congenital anomalies of kidney and urinary tract constitute about 50 percent of causes of CKD in infancy, since hereditary nephritis and glomerulonephritis are among other causes of CKD in children (2).

The frequency of glomerular diseases is differing based on geographical area, socioeconomic status, ethnicity and age. For instance, IgA nephropathy has a higher prevalence in eastern Asia including Japan, Singapore, and South Korea than North America (3). In areas with a high prevalence of hepatitis B such as Southern Africa, membranous nephropathy is the main cause of kidney biopsy, while it is rare in other areas (4). Furthermore, the

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frequency of other glomerulopathies such as membranous nephropathy and focal segmental glomerulosclerosis (FSGS) varies based on the geographic variability and access to medical care (5).

Children all over the world are susceptible to various types of kidney diseases. These diseases or their manifestations encompass a wide range of presentations including acute kidney injury, urinary tract infection, hematuria, vesicoureteral reflux, acute glomerulonephritis, nephrotic syndrome and kidney involvement in metabolic diseases (6,7). Detection of many of these diseases is possible by taking complete history, thorough examinations and performing available diagnostic tests. However, in some cases, the accurate diagnosis of kidney disease, its treatment, and the prognosis of the disease requires biopsy of the kidney (8).

In recent years, some non-invasive methods to detect early renal complications have been proposed which mostly are based on evaluating plasma and urinary biomarkers via omics technologies (genomics, proteomics and metabolomics) (9). However, the value of these biomarkers in the diagnosis and treatment of patients is not well established (10). Numerous studies have shown that biopsy improves clinical processes in patients with renal problems (11,12). Therefore, renal biopsy is the gold standard method to diagnose, treat and predict treatment outcomes in patients with renal problems (13).

Most studies on kidney biopsies in Iran are conducted in adults while the number of articles related to children is limited. Due to differences in renal biopsy indications between adults and children, the results of these studies cannot be generalized to children. For example, almost all cases of nephrotic syndrome in adults require biopsy, while most cases in children respond to steroids and do not require biopsy. In addition, kidney biopsy in children is more difficult than those performed on adults because the kidneys are smaller, patient's co-operation is not optimal and complications following biopsy may be higher (14). Nevertheless, ultrasonography guided kidney biopsy is safe and reliable in children to confirm or rule out clinical diagnosis and to choose the most appropriate treatment(15).

Objectives

This study was designed to evaluate the results of renal biopsy, indications and its role in the diagnosis and treatment of glomerular diseases in children admitted in Besat hospital in Hamadan, Iran during a period of 10 years.

Patients and Methods

Study design

This retrospective cross-sectional study was conducted in pediatric nephrology center of Besat hospital. Data were collected from children who underwent kidney biopsy between 2007 to 2017. Demographic information including gender and age, clinical symptoms before kidney biopsy, clinical diagnosis, indications for renal biopsy, histopathological findings, and the follow up of patients were documented in predesigned forms.

The indications for renal biopsy were as follows: in patients with nephrotic syndrome, steroid resistance, age of below one year and higher than 10 years old, steroid dependence, low levels of complements, renal failure, gross hematuria, hypertension, and the need for starting cyclosporine treatment for steroid resistant nephritic syndromes. In children with acute nephritic syndrome, the existence of nephrotic syndrome along with gross hematuria, severe proteinuria, reduced kidney function, and persistence of low level of C3 more than two months were considered as the indications for kidney biopsy. Moreover, patients with acute and chronic renal failure with unknown causes, as well as patients with persistent hematuria with proteinuria underwent kidney biopsy.

After taking informed consent from their parents, kidney biopsy was conducted in children who had indications for renal biopsy. In patients younger than one-year old, open renal biopsy was done by a surgeon. In other patients, a pediatric nephrologist performed real time sonography guided needle biopsy. Two samples were taken from each patient. Immunofluorescence study was conducted for some of the samples but all of them were stained for hematoxylin and eosin (H&E) and periodic acid-Schiff (PAS). After staining, these samples were evaluated by a pathologist. All of the patients were followed up by a pediatric nephrologist after kidney biopsy.

Ethical issues

Human rights were respected in accordance with the Helsinki Declaration 1975, as revised in 1983. The ethical committee of Hamadan University of Medical Sciences approved the study with the ethical code of IR.UMSHA.REC.1397.665. The informed consent was taken from the patients as well as from parents and first relatives. This study was extracted from M.D thesis of Amir Fazeli (Thesis #9710045756).

Statistical analysis

Because of descriptive nature of the study mean and percent were assessed.

Results

In this study period, 119 renal biopsies were performed on children, 56 were boys and 63 girls, with the mean age of 10.3 years. Renal biopsy was taken through real time sonography guided needle biopsy by a pediatric

nephrologist in 116 patients and by a pediatric surgeon by open biopsy in only three patients. Gross hematuria following biopsy was observed in 6.7% of patients. There was no case of nephrectomy or death following biopsy.

Of 119 patients, 71 (59.7%) cured, 25 (21%) are still under treatment, 7 patients (5.9%) died due to underlying disease, 6 (5%) undergone a kidney transplant surgery, and 10 patients (8.4%) had incomplete follow up to determine their outcome.

Nephrotic syndrome was the most common cause of kidney biopsy with 52 (43.6%) cases. It was followed by hematuria (28 cases, 23.5%) and acute nephritic syndrome (19 cases, 16%), respectively. The frequency of causes of renal biopsies in studied children was listed in Table 1.

Of 52 patients with nephrotic syndrome, 15 cases (28.84%) were steroid-resistant, 25 cases (48.07%) steroid-dependent and 12 cases (23.07%) had age of <1 and >10-year-old. The frequency of indications for renal biopsy in patients with nephrotic syndrome was shown in Table 2.

The results showed that primary glomerular disease was seen in 96 cases (80.7%) of all 119 biopsied patients. It was followed by secondary glomerular diseases and tubulointerstitial involvement which were seen in 18 cases (15.1%) and five cases (4.2%), respectively.

The histopathological findings in kidney biopsied patients were listed in Table 3. As it was seen, FSGS with 39 cases (32.7%) had the highest frequency in examined biopsies. It was followed by minimal change disease (MCD), mesangioproliferative glomerulonephritis (MsPGN), and IgA nephropathy (IgAN) which were seen in 20 (16.8%), 16 (13.4%), and 13 (10.9%) of samples, respectively. Other samples were diagnosed as systemic lupus erythematosus (SLE), congenital nephrotic syndrome (Finnish type), membranous glomerulonephritis (membranous GN), crescentic glomerulonephritis, and acute post-streptococcal glomerulonephritis.

Of 119 biopsies, immunofluorescence microscopy was done on 87 cases. Fifty-eight cases (66.7%) were positive in immunofluorescence imaging and 29 cases (33.3%) were negative. The immunofluorescence microscopy findings in kidney biopsies were shown in Figure 1. The high frequency of IgG, C3, and IgM was seen in positive samples, which were 29.4%, 26.9%, and 21%, respectively.

Table 1. Clinical presentations of patients

Indication	No.	%
Nephrotic syndrome	52	43.6
Hematuria	28	23.5
Acute nephritic syndrome	19	16
Henoch-Schönlein nephritis	8	6.7
SLE	6	5.1
Renal failure	6	5.1
Total	119	100

Abbreviation: SLE, systemic lupus erythematosus.

Table 2. Indications of renal biopsy in patients with nephrotic syndrome

Nephrotic syndrome	No.	%
Steroid-resistant nephrotic syndrome	15	28.84
Age: <1 and >10-year-old	12	23.07
Low level of complement	6	11.53
Renal failure	4	7.69
Gross hematuria	3	5.76
Hypertension	6	11.53
Recurrent and need for cyclosporine therapy	6	11.53
Total	52	100

Discussion

Kidney biopsy is an important diagnostic method with high predictive value in many kidney diseases in children and adults (14,16). Kidney biopsy in children is difficult due to the lack of cooperation of the child and the different kidney size. However, use of ultrasound-guided

Table 3. Histopathological findings of renal biopsy samples

Histopathological fndings	No.	%
FSGS	39	32.7
MCD	20	16.8
MsPGN	16	13.4
IgAN	13	10.9
SLE	8	6.7
Congenital nephrotic syndrome, Finnish type	7	5.9
Membranous GN	6	5.1
Crescentic GN	6	5.1
Acute post-streptococcal GN	4	3.4
Total	119	100

Abbreviation: FSGS, Focal segmental glomerulosclerosis; MCD, Minimal change disease; MsPGN, mesangioproliferative glomerulonephritis; IgAN, IgA nephropathy; SLE, Systemic lupus erythematosus; GN, glomerulonephritis.

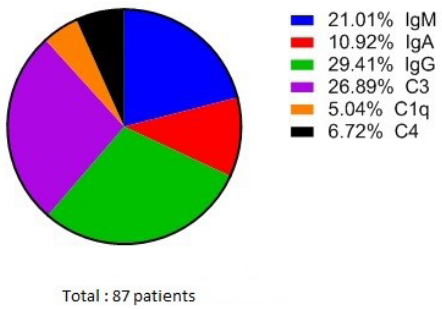

Figure 1. Immunofluorescence microscopy findings in renal biopsy samples.

biopsy and with the improvement in surgical techniques, performing biopsy by physicians is facilitated. Therefore, it can be said that technological innovations have made kidney biopsy a reliable and accurate diagnostic method (17).

In the present study, 6.7% of patients experienced complications related to the biopsy and the most frequent one was microscopic hematuria. Previous studies reported the frequency of complications between 4% and 36% following a kidney biopsy (18,19). The rate of complications was significantly lower when real time ultrasound guidance was performed compared to skin marking before biopsy (19). With regard to the size and age of the patient, the degree of complications can be reduced by selecting the appropriate needle size and the limiting biopsy attempts. Performing biopsies by radiologists or nephrologists is another cause of the difference in the frequency of the complications (20). The results of the meta-analysis by Varnell et al showed that biopsy in children is safe, since only 11% of patients had hematuria and less than 1% needed blood transfusions. In addition, no case of nephrectomy was reported (21). Therefore, kidney biopsy is considered as a safe diagnostic method, with minor side effects (22). In the study of Levart et al, no serious complications were observed following renal biopsy (23), which is consistent with the findings of our study which no case of death, nephrectomy after renal biopsy was observed.

Based on the findings of this study, the most common indication for biopsy in children was nephrotic syndrome and hematuria with or without proteinuria with a frequency of 43% and 23%, respectively. In most studies, nephrotic syndrome was the main indication of renal biopsy in children. In our study, steroid-resistant nephrotic syndrome accounts of 29% of indications of biopsy in children with nephrotic syndrome. The same result was seen in the study by Bakr et al in Egypt (24). In the study by Nammalwar et al in India, steroid-resistant nephrotic syndrome was the cause of about 65% of kidney biopsies (25). It was the most common cause of kidney biopsy reported by Paripović et al in Serbia (26).

In this study, the most common reported pathologic diagnosis was FSGS with a prevalence of 32.7%, which was followed by MCD with a prevalence of 16.8%. The prevalence of FSGS in children with nephrotic syndrome has increased in recent years (27, 28). Borges et al showed that the prevalence of FSGS as the cause of idiopathic nephrotic syndrome in children has almost doubled in recent years (29). Perhaps it is due to an increase in the prevalence of obesity (30). The incidence of FSGS can be affected by the socioeconomic status that predisposes children to tress and infection. The result of our study is consistent with the results of studies performed in Croatia, in which the most common finding was FSGS (31).

The pattern of glomerular diseases is different based on the geographical area. In the current study, the prevalence of MsPGN was in third place. The prevalence of MsPGN depends on socioeconomic status, environmental conditions, and health outcomes. Thereby, the higher prevalence of bacterial and parasitic infections and malnutrition in Iranian children can justify this high prevalence of MsPGN in this study. However, the prevalence of MsPGN has declined when compared to previous studies (32).

In a study by Chen and colleagues, the frequency of MsPGN was higher in children in Taiwan (33). The same result was found in a study by Abdullah et al in western Saudi Arabia (34). However, other studies showed that MCD and IgA nephropathy are more prevalent. Özkayın et al in Turkey and Lee et al in Korea showed a higher prevalence of MCD and IgA nephropathy was 70.1% and 24%, respectively (35,36).

Conclusion

Based on the results of this study, nephrotic syndrome was the most common cause of kidney biopsy. Most of the cases were primary glomerular diseases. In addition, based on histopathological findings, FSGS had the highest frequency in examined biopsies. The epidemiology of glomerular diseases in biopsied children was similar to the same studies conducted elsewhere. There was no mortality and nephrectomy after renal biopsy in our study and complications were limited to hematuria and pain of biopsy site.

Limitations of the study

Limitations of our study were loss of follow up of a few patients and unavailability of electron microscopy for examination of equivocal cases.

Authors' contribution

HEM performed renal biopsies, conducted research, helped in gathering data and editing the manuscript. AD reviewed and reported pathologic specimen. AF gathered the data from records and wrote the draft of manuscript.

Conflicts of interest

There is no conflict of interest in this study.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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