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Original Article

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Membranoproliferative Glomerulonephritis: The Most Common Pediatric Renal Pathology at a Tertiary Center in Turkey

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Abstract

Objective: This study aimed to assess the histopathological diagnosis of pediatric renal biopsies performed at the tertiary referral center in the city and to compare the ultrasound (USG) -guided biopsy and percutaneous renal needle biopsy (PRNB) in terms of safety.
Materials and Methods: All pediatric cases who underwent percutaneous renal biopsy at the center from January 2004 to December 2016 were reviewed retrospectively. The biopsy methods were compared in terms of complications.
Results: A total of 171 pediatric renal biopsies in 151 patients were included in the study. The most common renal pathology was primary glomerular disease (47.37%), and membranoproliferative glomerulonephritis (MPGN) was the most common glomerular pathology (19.30%). Systemic diseases (20.47%), tubulointerstitial diseases (8.77%), hereditary and congenital diseases (5.26%), chronic pyelonephritis (5.26%), and malignancy (0.58%) followed MPGN, respectively. The number of USG-guided biopsies performed by different radiologists was 79 (46.20%), and the number of PRNB performed by an experienced nephrologist was 92 (53.80%). No statistically significant difference was found between the two methods in terms of complications (p=0.50).
Conclusions: The MPGN was the most common pathology in the center. The PRNB is a safe diagnostic method for pediatric renal diseases when performed by an experienced nephrologist.
Keywords: Childhood, membranoproliferative glomerulonephritis, nephropathology, renal biopsy

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INTRODUCTION

Renal biopsy is a well-known diagnostic tool to assess renal diseases in children. It not only determines pathological features and prognosis of the renal disease, but it also contributes to the selection of treatment modality. Published reports demonstrate that the spectrum of renal diseases in the pediatric age is different in different geographical regions (1-3). It is known that the pattern of renal disease can be affected by various racial, ethnic, genetic, and environmental factors (4). Although Turkish nephrology registry data have been published in the literature (5), to the best of our knowledge, no literature reveals renal biopsy data in the south of Turkey. Determining the epidemiologic data on renal pathologies in an area contributes significantly to clinical practice in terms of preventive and therapeutic measures.

The ultrasound (USG) -guided percutaneous renal biopsy has been found to be an efficient and safe diagnostic tool to assess renal diseases in the literature (6-8). However, to the best of our knowledge, no study has compared the USG-guided biopsy and percutaneous renal needle biopsy (PRNB) in terms of safety.

This study evaluated the histopathological results of pediatric renal biopsies, performed at the center from 2004 to 2016, and compared the USG-guided biopsy and PRNB in terms of safety.

MATERIALS AND METHODS

Study Design

This study retrospectively reviewed all children who underwent percutaneous renal biopsy at the center, which is a unique reference center in the city, from January 2004 to December 2016. The Clinical Research Ethics Committee of the center approved the study on April 27, 2017 (approval number: 2017-144). The study was conducted in accordance with the principles of the Declaration of Helsinki. Written consent was obtained from parents. The indications for renal biopsy were steroid-resistant nephrotic syndrome, nephrotic syndrome developing before 2 or after 10 years of age, acute nephritic syndrome, persistent hematuria, acute/chronic renal failure, and complex renal manifestations of other systemic diseases. The clinical and laboratory protocol for percutaneous renal biopsy for all children comprised complete blood count, prothrombin, partial thromboplastin time, urinalysis, daily urinary protein excretion, creatinine clearance, and renal ultrasonography. Before the PRNB was performed, kidney's upper and lower poles and the lumbar vertebrae, which fall on these points, were marked by using abdominal radiography like in Demircin's (9) study. General anesthesia was preferred in children aged <8 years, whereas local anesthesia with mild intravenous sedation was used for older children and adolescents. For infants, an 18-G needle was used, and for older children, a 16-G needle was used. USG-guided percutaneous renal biopsies were performed by different radiologists, whereas percutaneous renal needle biopsies were performed by the same experienced nephrologist. In general, three cores were taken. Two of fresh biopsy specimens in saline were sent to the Pathology Department of the hospital within 15 min, where a piece of it was cut and laid on a moistened compress prior to sectioning for immunofluorescence microscopy. The part containing more glomeruli was fixed immediately in 10% formaldehyde, embedded in paraffin for light microscopy, and stained with hematoxylin and eosin, periodic acid-Schiff, Masson's trichrome stain, Congo red, and periodic acid methenamine silver. For immunofluorescence studies, cryostat sections were stained using polyclonal antisera against immunoglobulin A (IgA), IgG, IgM, C_3, C_{1q}, fibrinogen, albumin, kappa, and lambda. The other core was placed in 2.5% glutaraldehyde solution and sent to the Department of Histology and Embryology of the hospital for electron microscopic evaluation. Biopsy specimens containing at least 10 glomeruli were considered sufficient for diagnosis. The MPGN was diagnosed when cellular proliferation with lobular appearance in the glomeruli thickened and when double-countered glomeruli basement membrane was seen in light microscopy. The immunofluorescence microscopy findings of MPGN were granular to thick semi-linear (pseudolinear) patterns of immune deposits of either IgG and C3, or isolated C3 deposits with lesser degrees of IgA, IgM, and C1q. The diagnosis was confirmed by the presence of electron-dense deposits in subendothelial, intramembranous, or subepithelial areas by electron microscopy.

Post-biopsy patients were observed for 24 h in the hospital. Each urine sample voided was examined for gross hematuria for a day. Follow-up hemoglobin measurements were performed 2-4 h and 6-12 h after biopsy. The following day, repeat ultrasonographic examination was performed to evaluate the presence of perirenal hematoma or any other biopsy-related complication.

Until 2010, different pathologists evaluated biopsy specimens. After 2010, one nephropathologist began to evaluate biopsies.

Statistical Analysis

The data were processed and analyzed using the Stata MP/11 statistical package. The normality assumption was checked using the Shapiro-Wilk test. These variables were summarized as count (percentage), mean, standard deviation, median, minimum, and maximum values, and the comparisons between groups were performed using the Mann-Whitney U test and Fisher's exact test. A $p<0.05$ was accepted as statistically significant.

RESULTS

From January 2004 to December 2016, a total of 171 pediatric renal biopsies in 151 patients were performed at the center. Of these, 76 patients were female, and 75 were male. In 13 patients, repeated biopsy was done either due to the lack of adequate renal tissue or to assess the response to therapy. The mean age of the patients was 10.5±4.85 years (1-18). Direct immunofluorescence was performed in 129 of the cases (75.44%). The distribution of renal biopsies according to the years is presented in Figure 1. Indications for renal biopsy and histopathological diagnosis are shown in Table 1. Histopathological diagnoses are shown in Table 2. The MPGN was the most common pediatric pathology (n=33, 19.30%). Complement 3 (C3) deficiency was detected in 19 (57.57%) patients diagnosed with MPGN. Complement 4 deficiency was not seen in any of the patients. In terms of clinical findings, considering patients with MPGN, 14 patients (42.42%) had microscopic hematuria, 1 (3.03%) had acute renal failure, and 18 (54.54%) had nephrotic syndrome. In 2017, (until March), 9 USG-guided biopsies were performed. The

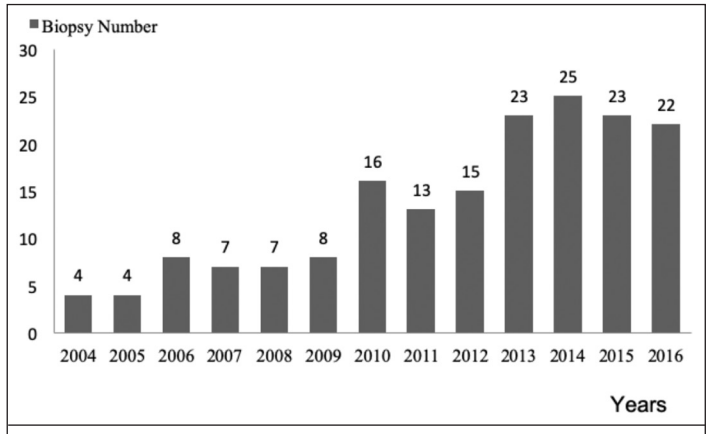

Figure 1. Distribution of renal biopsies according to the years.

Table 1. Indications for Biopsy and Histopathological Diagnosis

Indications for Biopsy and Histopathological Diagnosis	Number of Patients (%)	Indications for Biopsy and Histopathological Diagnosis	Number of Patients (%)
Nephrotic syndrome	59 (34.50)	Hematuria	18 (10.53)
MPGN	18 (10.53)	MPGN	14 (8.19)
MCNS	8 (4.68)	Alport Syndrome	3 (1.75)
FSGS	5 (2.92)	Thin membrane disease	1 (0.58)
SLE	17 (9.94)	Acute renal failure	24 (14.03)
HSP	6 (3.51)	MPGN	1 (0.58)
Congenital NS	1 (0.58)	Crescentic GN	6 (3.51)
Alport Syndrome	3 (1.75)	Acute TIN	2 (1.17)
DMS	1 (0.58)	Anti-GBM disease	1 (0.58)
Acute nephritic syndrome	29 (16.96)	SLE	3 (1.75)
FSGS	4 (2.34)	HUS	1 (0.58)
IgA nephropathy	10 (5.85)	Acute tubular necrosis	2 (1.17)
Diffuse proliferative GN	7 (4.09)	IgA nephropathy	4 (2.34)
Mesangial proliferative GN	5 (2.92)	Malignancy	1 (0.58)
C3GN	2 (1.17)	Alport Syndrome	3 (1.75)
HSP	1 (0.58)		
Complex renal manifestations	21 (12.28)	Chronic renal failure	20 (11.70)
HSP	8 (4.68)	Chronic TIN	11 (6.43)
SLE	13 (7.60)	Chronic pyelonephritis	9 (5.27)

MPGN: Membranoproliferative glomerulonephritis; MCNS: Minimal change nephrotic syndrome; FSGS: Focal segmental glomerulosclerosis; GN: Glomerulonephritis; C3GN: C3 Glomerulonephritis; SLE: Systemic lupus erythematosus; TIN: Tubulointerstitial nephritis; GBM: Glomerular basement membrane

histopathological diagnosis of these patients was the following: Alport syndrome in 2 patients, hemolytic uremic syndrome, focal segmental glomerulosclerosis, acute poststreptococcal glomerulonephritis (GN), crescentic GN, minimal change disease, transplant rejection, and membranoproliferative GN, respectively. No complications were observed.

The number of USG-guided biopsies performed was 79 (46.20%), and the number of PRNBs was 92 (53.80%). The total complication rate was 5.26% (9/171). One patient developed an arteriovenous fistula (0.58%), 2 patients (1.17%) had gross hematuria and required packed red cell transfusion, 4 patients (2.34%) developed gross hematuria, and 2 patients (1.17%) had a perirenal collection. No statistically significant difference was found in terms of complications between USG-guided biopsy and PRNB (p=0.50). The median number of glomeruli taken with USG-guided biopsy and PRNB was 13 (1-57) and 22 (0-100), respectively. The number of glomeruli taken with PRNB was greater than those taken with USG-guided renal biopsy (p=0.003). No statistically significant difference was found in terms of an inadequate number of glomeruli between USG-guided biopsy and PRNB (USG guided, 9/79; without USG, 9/92) (p=0.273).

DISCUSSION

The present study found that the most common pediatric renal pathology in the city was MPGN. The MPGN remains one of the most common causes of nephrotic syndrome and accounts for 30%-40% of all cases in the Middle East (Saudi Arabia), South America (Peru), and Africa (Nigeria) (10). It was reported that the proportion of pediatric patients with primary MPGN in Turkey did not change significantly (11). Although recent reports revealed a decrease in the number of pediatric patients with MPGN in industrialized countries (Spain and Japan) (12, 13), the decrease in MPGN has never been confirmed in developing countries. The reason for this difference between developing countries and industrialized countries is unknown. It might be related to the high incidence of infections in developing countries. A previous study showed that the overall hygiene and socioeconomic status of a country might predispose its citizens to either Th1- or Th2-dominant glomerular diseases (14).

Table 2. Histopathological Diagnosis

Histopathological Diagnosis	Number of Patients (%)	Histopathological Diagnosis	Number of Patients (%)
Glomerular diseases	81 (47.37)	Tubulointerstitial diseases	15 (8.77)
MPGN	33 (19.30)	Chronic TIN	11 (6.43)
MCNS	8 (4.70)	Acute TIN	2 (1.17)
FSGS	9 (5.27)	Acute tubular necrosis	2 (1.17)
IgA nephropathy	10 (5.84)	Hereditary and congenital diseases	9 (5.26)
Diffuse proliferative GN	7 (4.09)	Alport's syndrome	6 (3.51)
Crescentic GN	6 (3.50)	Thin membrane disease	1 (0.58)
Mesangial proliferative GN	5 (2.92)	Congenital nephrotic syndrome	1 (0.58)
C3GN	2 (1.17)	Anti-GBM disease	1 (0.58)
Diffuse mesangial sclerosis	1 (0.58)		
Systemic diseases	35 (20.47)	Chronic pyelonephritis	9 (5.26)
SLE	21 (12.28)	Malignancy	1 (0.58)
HSP	12 (7.02)	Inadequate number of glomeruli	21 (12.28)
HUS	2 (1.17)		

MPGN: Membranoproliferative glomerulonephritis; MCNS: Minimal change nephrotic syndrome; FSGS: Focal segmental glomerulosclerosis; GN: Glomerulonephritis; C3GN: C3 Glomerulonephritis; SLE: Systemic lupus erythematosus; TIN: Tubulointerstitial nephritis; GBM: Glomerular basement membrane

Th1-dominant glomerular diseases, such as MPGN and non-immunoglobulin A (IgA) mesangial proliferative GN, are seen widely in developing countries where early and frequent exposure to bacterial and other antigens is common. In contrast, IgA nephropathy and minimal change nephrotic syndrome, which are Th2-dominant glomerular diseases, are more common in developed countries. A Japanese study demonstrated that the rate of occurrence of primary MPGN in Japan decreased by taking measures to decrease infections, such as immunization, improving school health, environmental pollution control, deployment of water supply, and proper sewage systems (15). A Turkish single-center study revealed that primary glomerular diseases accounted for 61.2% of all pediatric biopsies, and MPGN was the most common pathology consistent with the findings of the present study (9). However, Fidan et al. (5) analyzed pediatric renal biopsies in national nephrology registry data and demonstrated that the FSGS was the most common glomerular disease in Turkey. In another study reporting the pediatric renal biopsy results in the Thrace region of Turkey, the most common pediatric glomerular pathology was IgA nephropathy (24%) (16). It indicated that the epidemiologic patterns of glomerular disease might vary even in different regions in Turkey. Therefore, local reports such as the present study are needed to understand these differences among different geographical regions of a country. Centers should publish their pediatric renal biopsy results to show this difference. In the aforementioned study, systemic lupus erythematosus was the most frequently observed secondary glomerulonephritis, consistent with the present study.

Although it is considered that minimal change nephrotic syndrome (MCNS) is the most common glomerular disease in childhood, its frequency in the present study was 4.70%. When MCNS is clinically diagnosed, steroid treatment is initiated without performing a renal biopsy. If steroid response is observed, the therapy is continued, and the dose is gradually tapered. Therefore, the MCNS was considered the most common glomerular disease in pediatric patients at the center.

In Demircin's study (9), hereditary and congenital diseases accounted for 2.3% of all biopsies, but in the present study, the rate was 5.26%. It is believed that this difference might be attributed to a high frequency of consanguineous marriages in the region. In addition, since the hospital was a tertiary referral center in the region, the patients who were considered to have congenital diseases were referred to the center from other cities. This might have contributed to the increment in the ratio. In a Japanese study, the rate of Alport's syndrome was 3%, consistent with the present study (3.51%) (2).

Nephrotic syndrome has been reported as the most common renal biopsy indication in both adults and children in the literature (17, 18), which is consistent with present study findings.

A large number of studies in the literature revealed that the USG-guided biopsy was a safe and efficient diagnostic method (1-3). However, this novel study compared the USG-guided biopsy with PRNB in terms of safety. In Demircin's study (9), the complication rate with PRNB was 15.2%, and the most common complications were perirenal hematoma and macroscopic hematuria. Another study reported no major complications with PRNB (19). Further, the present study showed no statistically significant difference in terms of complications between the USG-guided biopsy and PRNB. In addition, the median number of glomeruli obtained with PRNB was greater than that obtained with the USG-guided biopsy. It is known that the USG-guided biopsy is a gold standard method for assessing renal diseases. However, experienced nephrologists or radiologists are required to perform both the modalities. PRNBs have been performed by one experienced nephrologist for 13 years at the center. However, USG-guided renal biopsies have been performed by different radiologists, mostly by radiology trainees. The present study revealed that the safety and success of the diagnostic renal biopsy procedure depended on the experience of the physician performing the biopsy. It was reported that the PRNB has remained a relatively safe procedure, whether performed by radiologists or nephrologists, with a low complication rate consistent with the findings of the present study (20).

The limitations of this study are its retrospective design and limited number of patients due to it being single centered.

CONCLUSION

This study revealed epidemiological data regarding the pediatric renal disease pattern in the south of Turkey. It found that the most common pediatric renal pathology among glomerular diseases was the MPGN in the region. This might be due to a high incidence of infections and low socioeconomic status in the region. Therefore, it is believed that the efforts to prevent infections and improve the socioeconomic status of people might decrease the frequency of these diseases. In addition, the results suggested that the PRNB was as safe as the USG-guided biopsy when performed by experienced nephrologists.

Ethics Committee Approval: Ethics Committee approval was received for this study from the Ethics Committee of Mersin University (2017/144).

Informed Consent: Written informed consent was obtained from the patients' parents who participated in this study.

Peer-review: Externally peer-reviewed.

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Conflict of Interest: The authors have no conflict of interest to declare.

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