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Original Article

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Indications and Outcomes of Renal Biopsies in Children: A Single-Center 12-Year Experience

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Abstract

Objective: Renal biopsy plays a crucial role in the diagnosis and treatment of renal diseases. The aim of the present study was to review the reasons leading to biopsy and the pathological diagnoses and to investigate the effectiveness and safety of ultrasound-guided percutaneous renal biopsy in children.

Materials and methods: A total of 410 renal biopsies performed in 362 patients between January 2007 and January 2018 at Dr. Sami Ulus Maternity and Child Health and Diseases Training and Research Hospital, Department of Pediatric Nephrology and Rheumatology were retrospectively reviewed. Pathology specimens were evaluated by light and immunofluorescence microscopy. Electron microscopy was performed only on specific occasions.

Results: The mean age of the patients was 10.1±4.4 years, and 55.2% were males. Nephrotic syndrome (44.5%) was the most common indication for renal biopsy. Hematuria±proteinuria (19.9%), acute renal injury (15.7%), chronic renal disease (3.2%), and complex renal manifestations (16.6%) were the following indications. The overall complication rate was 8%, and the most common of which was perirenal hematoma (7.5%). The most common histopathological diagnosis was primary glomerulopathy (56.6%). Among primary glomerulopathies, focal segmental glomerulosclerosis was the leading diagnosis (16.5%), followed by mesangioproliferative glomerulonephritis (7.7%) and IgA nephropathy (7.7%). The second most common histological diagnosis was manifestations secondary to systemic diseases (30.9%), among which Henoch-Schönlein purpura (12.4%) and lupus (9.1%) were the leading causes.

Conclusion: Renal biopsy is a safe and effective procedure in the diagnosis and treatment of childhood kidney diseases.

Keywords: Renal biopsy, glomerular disease, children, histopathological diagnosis

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INTRODUCTION

Although renal parenchymal diseases are relatively rare in childhood, they are the second most important cause of chronic kidney disease after congenital anomalies of the kidney and urinary tract (1). The epidemiology of patients with renal parenchymal is of great importance with respect to providing information on clinical and histopathological features and useful data in clinical practice. Despite many studies, there are no early diagnostic markers for chronic kidney disease, and renal biopsy still plays a key role (2). Renal biopsy is an indispensable method not only to diagnose the patient but also to determine the etiology, treatment, and prognosis (3, 4). Kidney biopsy has been reported to change the initial diagnosis in half of the patients and one-third change in treatment approach (5). Ultrasonography (USG) guiding of the most commonly preferred percutaneous technique makes the procedure safer and more effective.

The aim of the present study was to evaluate the results of all renal biopsies performed in the 12-year period between 2007 and 2018, to determine the frequency of renal diseases that can be diagnosed by biopsy in childhood, to determine whether there is a correlation between the clinical and laboratory findings and histological findings of the patients, to predict the prognosis in

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light of these data, and to evaluate the safety of percutaneous renal biopsy in children by identifying complications.

MATERIALS AND METHODS

In the present study, the records of 362 patients who underwent percutaneous native renal biopsy between January 2007 and September 2018 in the Pediatric Nephrology Department of Dr. Sami Ulus Maternity and Child Health and Diseases Training and Research Hospital were retrospectively reviewed. Data on age, sex, indications for renal biopsy, histopathological diagnoses, and biopsy complications were obtained from medical records. Ethics committee approval was received for this study from the Ethics Committee of Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital, on November 12, 2018 (2018-169).

Written informed consent was obtained from the parents of the patients to perform renal biopsies in our clinic. Before biopsy, all patients underwent complete blood count, prothrombin time, partial thromboplastin time, blood biochemistry, complete urine analysis, 24-hour urine protein excretion, and renal USG after physical examination. Biopsy was performed under sedation with midazolam and ketamine by pediatric nephrologist, accompanied with USG (Toshiba-Aplio 500, 3.5 MHz probe), and was performed with percutaneous technique using tru-cut percutaneous renal biopsy needle with varying numbers according to the size of the child. Biopsy site was determined by marking the renal lower pole center using USG, and local anesthesia was applied to the marked entry point with lidocaine. After observing the presence of the biopsy needle in the kidney via USG, at least two biopsy specimens were obtained from each patient.

After biopsy, the patients were followed up according to a specific protocol. The patient was placed in the supine position for 24 h, and bleeding control was tried to be performed with sandbag in the biopsy area. The vital signs of the patients were measured every 15 min in the first 2 h and then hourly in 1 day. The hemoglobin levels were measured at 2-4 and 6-12 h. The presence of abdominal and low back pain, severe pain or swelling at the biopsy site, and macroscopic hematuria were questioned, and the patients were kept under observation for at least 1 day and clinical follow-up for 1 week. Routine USG was performed at 24 h after biopsy in all cases, and the patients were discharged 24 h later if there were no complications. Patients who developed macroscopic hematuria were followed up until the bleeding stopped. Patients with perirenal hematoma were discharged within a few days under the conditions as to showing that the size of the hematoma did not increase, until the hematoma resolved, and USG was repeated every 2 weeks after discharge.

Biopsy specimens soaked in gauze with saline were examined by light microscopy and immunofluorescence methods at the pathology laboratory where they were examined within 1 h at the latest. Hematoxylin-eosin, periodic acid Schiff, Masson's trichrome, methenamine silver, and Congo Red staining were performed under light microscopy. In the immunofluorescence method, IgA, IgM, IgG, C3, kappa and lambda light chains, fibrinogen, and fluorescein bound antibodies for C1q were studied. If <10 glomeruli were detected, the biopsy was repeated. The biopsies were also re-performed to evaluate the stage of the disease and to determine the treatment approach. Electron microscopic evaluation was performed in 56 patients who could not be diagnosed by light microscopy, and glomerular basement membrane defects in particular were suspected.

Renal biopsy indications were determined as nephrotic syndrome (NS), proteinuria with an unknown cause, renal manifestations of systemic diseases, chronic renal disease, acute renal failure of unknown origin, hematuria (recurrent macroscopic and/or persistent microscopic), and rapidly progressive glomerulonephritis (>50% reduction in glomerular filtration rate). Indications for biopsy in idiopathic NS were atypical age at admission (<12 months or >10 years), atypical clinical presentation, steroid-resistant NS, steroid-dependent NS, and/or frequently recurrent NS before using cytotoxic therapy. No transplant biopsy was included in the study.

Nephrotic syndrome was defined as the presence of a protein/creatinine ratio >40 mg/m^2/h in 24-hour urine or spot urine, edema, and hypoalbuminemia. The disease was defined as steroid-resistant if there is >40 mg/m^2/h proteinuria after 4 weeks of prednisolone treatment, steroid-dependent if two relapses during steroid therapy or within 2 weeks after completion of the therapy, and frequently repetitive NS if two or more relapses in 6 months or four or more relapses within 12 months.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) version 20.0 for Windows (IBM Corp.; Armonk, NY, USA) was used for statistical evaluations. Descriptive statistics were used as the statistical method and are expressed as number, percentage, and mean±SD. A p value <0.05 was considered statistically significant.

RESULTS

Of the 362 patients who underwent renal biopsy between January 2007 and September 2018, 200 (55.2%) were male, and 162 (44.8%) were female. The average age of the patients was 10.1±4.4 years. The age distribution ranged from 1 month to 18 years. During the procedure, 172 patients had edema, 83 patients had hypertension, and 80 patients had rash. The laboratory examinations revealed proteinuria in 273 patients, hematuria in 205 patients, impaired renal function in 138 patients, and anemia in 69 patients (Table 1). The serum creatinine levels ranged from 0.1 to 20 (mean 1.42) mg/dL and albumin from 0.7 to 5.3 (mean 2.86) g/dL.

The most common indication for percutaneous renal biopsy was NS with 161 (44.5%) patients, whereas other causes were hematuria and/or proteinuria in 72 (19.9%) patients, acute renal injury in 57 (15.7%) patients, chronic renal disease in 12 (3.2%) patients, and complex renal involvement in 60 (16.6%) patients (Table 2).

Table 1. The clinical and laboratory features of the patients

Clinical and laboratory features	No. of patients (n, %)
Age (ave±SD)	10.1±4.4
Gender	
Male	200 (55.2)
Female	162 (44.8)
Edema	172 (47.5)
Hypertension	83 (22.9)
Rash	80 (22.1)
Hematuria	205 (56.6)
Macroscopic	68 (18.7)
Microscopic	137 (37.9)
Proteinuria	273 (75.4)
Non-nephrotic	106 (29.2)
Nephrotic	167 (46.1)
Hypoalbuminemia	185 (51.1)
Impaired renal function	138 (38.1)
Anemia	69 (19.1)
Duration of hospital stay (days) (average, minimum–maximum)	2 (2-7)

Table 2. Indications for renal biopsy

Indications	No. of patients (n, %)
Nephrotic syndrome	161 (44.5)
Hematuria and/or proteinuria	72 (19.9)
Acute kidney injury	57 (15.7)
Chronic kidney disease	12 (3.3)
Complex kidney findings	60 (16.6)

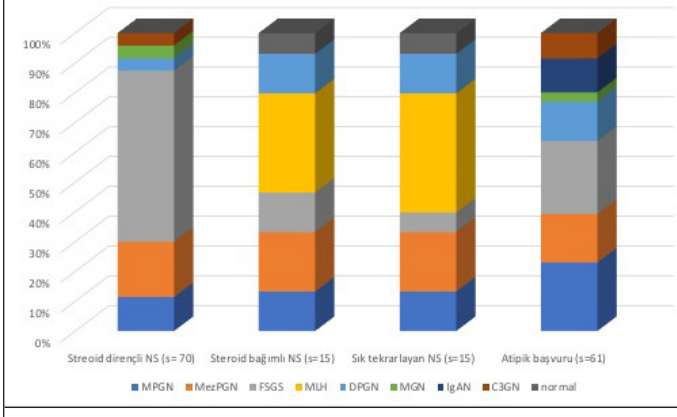

Figure 1. Indications for renal biopsy in patients with nephrotic syndrome.

Of the 161 patients with NS, 70 (43.7%) were steroid-resistant NS, 15 (9.3%) were steroid-dependent NS, and 15 (9.3%) were recurrent NS. The remaining 61 (37.8%) patients presented with atypical age or clinical findings (Figure 1).

Table 3 shows the relative distribution of histopathological diagnoses detected in renal biopsy. Idiopathic glomerular diseases were more common in 205 (59.6%) patients than secondary glomerular diseases (n=112, 30.9%). Hereditary glomerulopathy and tubulointerstitial nephropathy were found in 20 (5.5%) cases and 11 (3%) cases, respectively, whereas normal renal tissue was detected in 5 (1.3%) cases. The most common idiopathic glomerular disease detected by renal biopsy was focal segmental glomerulosclerosis (FSGS) in 60 (16.5%) patients. This was followed by mesangioproliferative glomerulonephritis (MesPGN) (7.7%), IgA nephropathy (IgAN) (7.7%), diffuse proliferative glomerulonephritis (DPGN) (6.9%), and membranoproliferative glomerulonephritis (MPGN) (6.3%). Henoch-Schönlein purpura nephritis (HSPN) (12.4%) and systemic lupus erythematosus (SLE) (9.1%) accounted for the majority of glomerulopathies secondary to systemic diseases. There were 14 hemolytic uremic syndrome, 9 amyloidosis secondary to familial Mediterranean fever (FMF), 8 polyarteritis nodosa, and 3 Wegener's granulomatosis.

The distribution of primary glomerulonephritis according to age is evaluated in Figure 2. The most common idiopathic glomerular diseases are FSGS (38.4%) and minimal change disease (MCD) (15.3%) in the 0-4 age group, FSGS (25.9%) and DPGN (16.6%) in the 5-9 age group, and FSGS (34.2%) and DPGN (13.6%) in the 10-13 age group. The most common diagnoses were IgAN (21.1%) and MesPGN (17.3%) in the >13 age group.

Of the 362 patients, 48 (13.3%) required biopsy repetition; 39 (10.7%) of them had two biopsies and 9 (2.6%) had three biopsies (Table 4). Of the 48 repeated biopsies, 21 (43.7%) were unresponsive to treatment, 15 (31.2%) were performed to determine prognosis and follow-up, and 12 (25%) were repeated due to insufficient material (Table 4). Of the 36 biopsies, 25 were followed with NS, 10 with systemic diseases, and 1 with recurrent macroscopic hematuria. After repeated biopsies, in 36% of the patients diagnosis and in 58% treatments were changed. The overall complication rate was 8%. The most common complication was perirenal hematoma which was detected in 31 (7.5%) patients, and all resolved spontaneously within 2-8 weeks. Only 2 (0.5%) patients had macroscopic hematuria requiring blood transfusion. Eight (1.95%) patients had delayed discharge due to perirenal hematoma and bleeding follow-up. In addition, no clinically significant complications were observed. The standards used to evaluate the efficacy and safety of renal biopsies performed in our clinic are given in Table 5.

DISCUSSION

Percutaneous renal biopsy has been a widely used technique for the evaluation of various nephropathies since its intro-

Table 3. Kidney biopsy results

Histopathological findings	No. of patients (n, %)
Glomerulonephritis	205 (56.6)
Focal segmental glomerulosclerosis	60 (16.5)
Mesangioproliferative glomerulonephritis	28 (7.7)
IgA nephropathy	28 (7.7)
Diffuse proliferative glomerulonephritis	25 (6.9)
Membranoproliferative glomerulonephritis	23 (6.3)
Minimal change disease*	11 (3.0)
Crescentic glomerulonephritis	10 (2.7)
C3 glomerulopathy	10 (2.7)
Membranous glomerulonephritis	5 (1.4)
Diffuse mesangial sclerosis	4 (1.1)
C1q nephropathy	1 (0.3)
Systemic diseases	112 (30.9)
Henoch-Schönlein purpura	45 (12.4)
Systemic lupus erythematosus	33 (9.1)
Hemolytic uremic syndrome	14 (3.8)
Amyloidosis	9 (2.5)
Polyarteritis nodosa	8 (2.2)
Wegener's granulomatosis	3 (0.8)
Hereditary and congenital diseases	20 (5.5)
Alport syndrome*	13 (3.6)
Cystic kidney diseases	6 (1.6)
Thin basal membrane disease	1 (0.3)
Tubulointerstitial nephritis	11 (3.0)
Other	9 (2.5)
Chronic pyelonephritis	6 (1.6)
Oxalosis	3 (0.8)
Normal*	5 (1.4)

*Electron microscopy was performed in patients with minimal change disease, Alport syndrome, and normal renal tissue.

Table 4. Number of repeated biopsies and number of patients whose biopsy was repeated

	Patients to whom biopsy was performed twice	Patients to whom biopsy was performed three times
Non-response to treatment	17	4
Determining the prognosis	10	5
Insufficient glomeruli	12	–

Table 5. Kidney biopsy standards (31)

Kidney biopsy standards	Patient (%)
In 80% of the patients, the number of punctures performed to obtain sufficient biopsy material from native kidneys should be ≤3.	92
In 80% of the patients, the number of punctures performed to obtain sufficient biopsy material from native kidneys should be ≤2.	–
In >95% of biopsies, sufficient tissue for histological diagnosis should be obtained.	96.7
Major complication rates (macroscopic hematuria, blood transfusion and/or surgical requirement, delayed discharge, and re-admission) should be <5% of total biopsies.	2.45

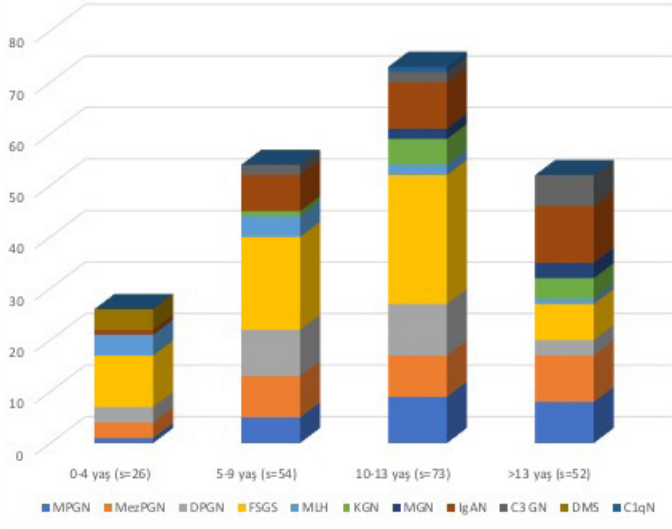

Figure 2. Distribution of histopathological diagnoses according to age.

duction in 1934 (6). It is one of the most important tools in diagnosing, monitoring, and guiding treatment. However, there are various risks of complications, such as gross hematuria, perirenal hematoma, arteriovenous fistulas, infection, damage to adjacent organs, or loss of kidney (7-9). The application of percutaneous renal biopsy, together with imaging techniques, such as fluoroscopy, computed tomography, and USG, increases the effectiveness and reliability of the biopsy. Among these, USG is the preferred technique in children due to the absence of radiation danger, easy application, and cheap use. In the present study, we investigated the incidence of complications in children who underwent USG-guided percutaneous renal biopsy and examined the indications and histopathological results to determine the range of diseases requiring renal biopsy.

A total of 410 biopsies were performed in 362 children under ultrasound-guided percutaneous technique in our clinic in the last 12 years with a success rate of 96.7% and a general complication rate of 8%. Only two patients developed hematuria requiring transfusion, and all other complications were transient and spontaneous, including perirenal hematoma and macroscopic hematuria. The rate of obtaining sufficient tissue by percutaneous renal biopsy in children generally ranges from 92% to 98.7% (3, 10-12). Although the overall complication rates range from 11.4% to 22% in different series, rates as low as 2.6% and as high as 43% have been reported (3, 10-16). In our series, the frequency and success rate of complications were similar to most studies in children. The most common complication in our study was perirenal hematoma (7.5%), and although most of the patients were asymptomatic, the diagnosis was made by routine ultrasonographic examinations on the next day of renal biopsy. Although our overall complication rate is low, we think that our relatively high perirenal hematoma rate may be due to the fact that this routine screening is not used in most of the studies reported in the literature.

In our patient group, NS in 161 (44.5%) cases was the most common biopsy indication as reported in other childhood series (17-19). Other common indications include urinary abnormalities, such as hematuria and/or proteinuria (19.9%) and acute renal failure (14.6%). In addition, renal biopsy was the indication for complex renal findings with a rate of 16.6%. This high rate may be associated with renal biopsy for classification in almost one-third of patients with SLE, as this is the protocol of our clinic for patients with SLE, although they do not have renal findings.

The most common diagnosis in studies evaluating histopathological diagnoses in both children and adult patients is primary glomerulonephritis (20-22). In addition to studies reporting MCD as the most common glomerulopathy, there are also reports stating FSGS, MPGN, and IgAN as the most common (21-24). These differences in biopsy diagnoses are thought to be due to differences in biopsy indications due to age, geographical location, and ethnicity. Yavaşcan et al. (25) reported the results of 458 percutaneous renal biopsies performed over an 11-year period. In their study, the most common diagnoses were FSGS with 74 (19.8%) cases and MCD with 54 (14.4%) cases. These were followed by MPGN (11.8%) and IgAN (11.2%). In our study, the most common histopathological diagnosis was FSGS with 60 (16.5%) cases, and the second were MesPGN (7.7%) and IgAN (7.7%) with 28 cases. In the study in which renal biopsies performed between 1990 and 2006 in our clinic were evaluated, MPGN (11.1%) and mesangial proliferation (10.7%) were in the first place, and FSGS rate was found to be 7.3% (26). This difference in the prevalence of glomerulonephritis may be an indication of a more aggressive biopsy approach in patients with NS due to increasing steroid responsiveness in our center after 2006. We also think that new immunosuppressive drugs that provide more effective treatment options in patients with steroid-resistant, steroid-dependent, and frequently recurrent NS also contribute to these results. The second most common histopathological diagnosis was renal pathologies due to systemic diseases represented with 112 patients. HSPN and SLE compose the majorities of this group. One of the most striking features of our study is that amyloidosis secondary to FMF which constitutes 11.4% of the whole study group between 1990 and 2006 decreased to 2.5% in our study.

The underlying histopathological features in NS have a great significance in responding to steroid treatment and determining long-term prognosis. In our study, we analyzed the histopathological diagnoses of 161 NS biopsies according to the indications of renal biopsy in childhood NS. Among these, MCD was the most common histopathological diagnosis in steroid-dependent and frequently recurrent NS. However, as expected, FSGS was the most common histopathological diagnosis in steroid-resistant NS. This clinical-pathological relationship reflects the importance of steroid-resistant NS as compared with steroid-dependent and frequent relapse NS, as described elsewhere (27, 28).

When the distribution of biopsy diagnoses was examined according to age groups, the most common histopathological diagnosis in the 0-13 age group was FSGS. This may be related to the initiation of MCD treatment without biopsy under normal conditions. However, there are also reports suggesting that the incidence of FSGS in children may have increased in recent years, as in adults (29, 30). The possible increased frequency in FSGS is of great clinical importance because it tends to be unresponsive to typical steroid therapy and is highly likely to progress to end-stage renal disease, and it is now known that some cases of FSGS are caused by mutations in various genes. Prospective studies are needed to investigate whether this is limited to selected population groups or not. In our study, DPGN was also found to be the second most frequent between aged 5-9 years and 10-13 years. This may be explained by the high prevalence of streptococcal infections in our country and the development of more DPGN. As a result of the high number of DPGN cases, the proportion of atypical patients also increases. These patients were biopsied if hematuria lasted >4 weeks or nephrotic level proteinuria, hypertension, nitrogenemia, oliguria, and decreased C3 or any of them did not improve within the expected time, and 6.9% of all biopsy diagnoses were diagnosed as DPGN.

This is a single-center study that aimed to retrospectively investigate the indications and pathological findings of renal biopsy in our clinic for the last 12 years, comparing with previous 16-year findings. The most important limitations of our study are its retrospective nature, limited number of patients, and use of electron microscopic examination in a small number of cases. However, our single-center cohort has shown that the epidemiology of glomerular diseases is similar to that reported in other national and international publications. In addition, USG-guided percutaneous renal biopsy has been shown to comply with renal biopsy standards in children (31).

CONCLUSION

Renal biopsy is an important procedure for identifying many renal pathologies, especially glomerular and systemic diseases that require immediate and appropriate treatment. It is easy to perform with ultrasound-guided percutaneous technique in experienced hands. The complication rate is low, and it is reliable. Diagnosis rate is high as a result of pathological examinations. It enables interventions to slow down this process with early and appropriate treatment, especially in patients who may progress to end-stage renal failure. It plays an initial role in the diagnosis of rare familial nephropathies, in the examination of related families, and in genetic diagnosis. In cases where it is difficult to diagnose, the patient can be protected from unnecessary treatment and side effects of these treatments.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital, on November 12, 2018 (2018-169).

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - E.K.Ç.; Design - E.K.Ç., F.Y.; Supervision - G.C., E.D.K.Ş., T.G., M.B.; Data Collection and/or Processing - E.Ç., F.K.E., D.K.; Analysis and/or Interpretation -E.K.Ç.; Literature Search - F.Y., Ç.Ü., N.A.; Writing -E.K.Ç.; Critical Reviews - E.K.Ç., M.B.

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

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