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CLINICAL STUDY

Changing trends in pediatric renal biopsies: analysis of pediatric renal biopsies in national nephrology registry data

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ABSTRACT

Renal biopsy is the gold standard method for determining the diagnosis, treatment, and prognosis in children with renal disease. This study aims to evaluate the histopathological features of pediatric renal biopsies obtained from the national nephrology registry in the last two decades. Data recorded in the Turkish Society of Nephrology Registry System (TSNRS) in 1991 as well as in between 2001 and 2010 were analyzed. A total of 3892 biopsies were recorded; with the least number in 1991 (total 103 biopsies from 17 centers) and the highest number in 2008 (total 654 biopsies from 23 centers). Glomerular diseases constituted the main group in the registry (62.64%), followed by systemic diseases (20.06%). Focal and segmental glomerulosclerosis (FSGS) and Henoch–Schönlein purpura (HSP) nephritis (IgA vasculitis) were the most common glomerular and systemic diseases, respectively. Overall prevalence of renal amyloidosis and membranous nephropathy (MN) was quite low (1.87% and 1.56%, respectively) in all periods. Compared to 1991, there was an increasing trend in the frequencies of certain disorders including hemolytic uremic syndrome (HUS), IgA nephropathy, and HSP nephritis; and there was a decrease in acute proliferative glomerulonephritis (GN) in 2008. As well as demonstrating the etiologies of renal diseases which can only be identified by renal biopsies, this study provides important information regarding the changing patterns of histopathological findings due to better management of pediatric renal diseases over the years in Turkey.

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Children; glomerular diseases; histopathology; registry; renal biopsy

Introduction

Despite advances in laboratory and radiologic techniques, renal biopsy still carries major importance in the management of renal disease in children.[1–3] Renal biopsy is an essential diagnostic tool used to obtain renal cortical tissues for histological evaluation. As it enables diagnosis, evaluating the acuteness and severity of the disease, monitoring disease progression as well as categorizing the prognosis and assessing the response to therapy, renal biopsy has been recognized as the most valuable examination for patients with kidney disorders.[4,5] The main indications for a renal biopsy in children include persistent microscopic hematuria with or without hematuria, recurrent gross hematuria, steroid-dependent and steroid resistant nephrotic syndrome (NS), differentiation of nephrotic syndrome/nephritic syndrome, persistent low c3 in acute post-streptococcal GN, acute renal failure of unknown etiology, cyclosporine protocol biopsy, renal involvement in systemic lupus erythematosus (SLE), and staging of HSP nephritis.[4,6]

In this study, we evaluated the histopathological results of pediatric renal biopsies obtained from the national nephrology registry data in 1991 as well as in between 2001 and 2010 and tried to identify the changing patterns in the biopsy findings in these time periods.

Materials and methods

Pediatric percutaneous renal biopsies have been recorded in TSNRS since 1991. Data of pediatric nephrology centers from all around Turkey in 1991 and the period in between 2001 and 2010 were included in this study. The data were collected via mails until 2007 and starting from that year the data were collected via web based system every year.

The system contained the following parameters: patients' age and gender, the number of the participating centers, and renal biopsy results of each center. However, the indications for performing the renal biopsies were not available. Using the above data, a

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retrospective review of the main histopathological findings of renal biopsies (obtained by light microscopy and immunofluorescence) throughout the consecutive years was carried out and distribution patterns of the diagnoses among these time periods were determined. This study was performed in accordance with the Declaration of Helsinki after obtaining required permissions by Turkish Society of Nephrology.

Data were stored on a database file (Excel) and processed for descriptive analysis using the SPSS statistical software package (version 10; SPSS, Inc., Chicago, IL).

Results

Patient characteristics

A total of 3892 pediatric renal biopsies were recorded in the TSNRS for the year 1991 and for the period in between 2001 and 2010. Male/female ratio was 1.1. The least number of biopsies was recorded in 1991 (total 103 biopsies from 17 centers) whereas the highest number was in 2008 (total 654 biopsies from 23 centers). The number of patients with renal biopsies according to the years is given in Figure 1. The number of the participating centers was highest in 2003 (27 centers) and lowest in 2007 (nine centers).

Although the rate of hospitalization due to renal diseases were close in patients aged 0–2 years, 2–6 years, 6–10 years, and 10–15 years (24.5%, 20.4%, 19.8%, and 22.5%, respectively), it was the least in patients over 15 years of age (12.7%). An average 10% of the patients with a given renal disease were undergone renal biopsy procedure in all periods (12.97% in 1991 and 10.5% in 2009). This percentage was unchanged despite the increase in the total population of patients with renal disease.

Renal biopsy results

In general, the biopsy results were grouped as glomerular diseases, systemic diseases, tubulointerstitial diseases, and miscellaneous pathologies (including metabolic and familial disorders such as oxalosis and nephrocalcinosis, normal or suspicious biopsy results, toxic nephropathy, and chronic pyelonephritis). Glomerular diseases constituted the main group in the registry (62.64%) with FSGS as the main glomerular disease. Most common systemic disease was HSP nephritis (9.17%). The renal biopsy results are given in Table 1.

Table 1. Renal biopsy results.

Diseases	*n* (%)
Glomerular diseases	**2438 (62.64)**
FSGS	641 (16.46)
Mesangioproliferative GN	400 (10.27)
Minimal change disease	396 (10.17)
MPGN	317 (8.14)
IgA nephropathy	237 (6.08)
Idiopathic crescentic GN[a]	198 (5.08)
Acute proliferative GN	188 (4.80)
MN	61 (1.56)
Systemic diseases	**781 (20.06)**
HSP nephritis	357 (9.17)
SLE nephritis	211 (5.42)
Amyloidosis	73 (1.87)
HUS	70 (1.79)
Others (PAN, WG)	70 (1.79)
Miscellaneous pathologies	**501 (12.87)**
Tubular/tubulointerstitial diseases	**172 (4.41)**
Other tubular diseases	127 (3.26)
Acute TIN	45 (1.15)
Total	**3892 (100)**

MPGN: membranoproliferative GN; MN: membranous nephropathy; HUS: hemolytic uremic syndrome; PAN: poliarteritis nodosa; WG: Wegener granulomatosis; TIN: tubulointerstitial nephritis.
[a]Patients with secondary crescentic GN were classified in their primary pathologies including HSP nephritis, MPGN, SLE nephritis, IgA nephropathy, and acute proliferative GN.

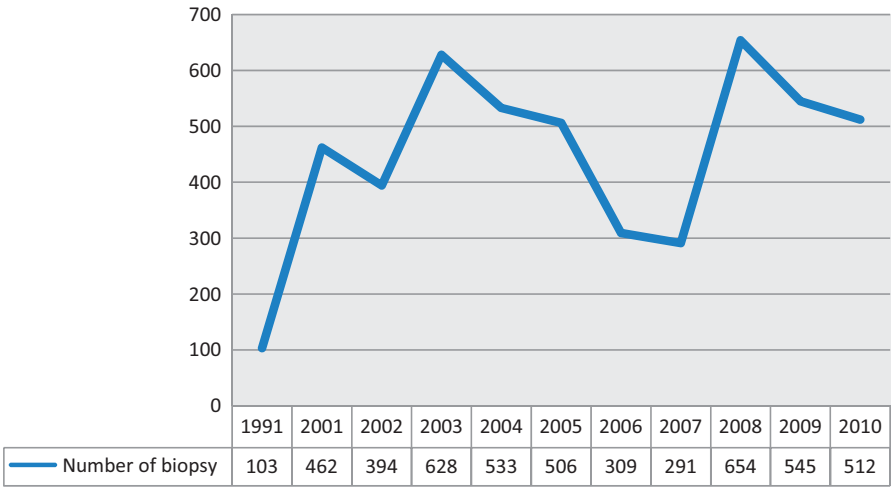


Figure 1. Number of renal biopsies according to the years.

Histopathologic analysis of renal diseases

Year 1991

As mentioned above, TSNRS was initiated in 1991. In that year a total of 103 biopsies were recorded and the most common diagnosis was glomerular diseases ($n = 58$, 56.31%); mostly FSGS ($n = 17$, 16.50%) and acute proliferative GN ($n = 13$, 12.62%). However, IgA nephropathy was infrequent ($n = 1$, 0.97%). Miscellaneous pathologies were second most common group ($n = 27$, 26.21%). Systemic diseases were recorded in low ratios ($n = 14$, 13.59%) including HSP nephritis ($n = 6$, 5.82%) and SLE nephritis ($n = 3$, 2.91%). In this group, histopathologic diagnoses of amyloidosis and HUS were also remarkably low ($n = 1$, 0.97%, for both). Tubular/tubulointerstitial disorders were rarely detected on biopsies ($n = 4$, 3.88%).

Year 2001

In this year, the most common renal biopsy diagnosis was glomerular diseases ($n = 360$, 77.92%); mostly FSGS ($n = 95$, 20.56%) and idiopathic crescentic GN ($n = 92$, 19.91%). The prevalence of IgA nephropathy increased ($n = 29$, 6.27%) whereas acute proliferative GN constituted the 2.38% of all biopsies ($n = 11$), demonstrating a prominent decrease compared to 1991. Systemic diseases were less prevalent ($n = 51$, 11.03%); mostly SLE nephritis ($n = 25$, 5.41) and HSP nephritis ($n = 16$, 3.46%), and with low frequencies of HUS and amyloidosis ($n = 2$, 0.43% and $n = 6$, 1.29%, respectively).

Year 2008

This year corresponds to nearly the end of the study and the year with the highest number of renal biopsies. In this period, the most common histopathology was again glomerular diseases ($n = 381$, 58.25%); mostly FSGS ($n = 101$, 15.44%), followed by systemic diseases ($n = 147$, 22.47%), especially HSP nephritis ($n = 76$, 11.6%). There was a slight increase in the percentage of acute proliferative GN compared to 2001 ($n = 27$, 4.12%), whereas SLE nephritis were recorded as nearly unchanged ($n = 38$, 5.81%). Frequencies of IgA nephropathy ($n = 48$, 7.33%) and HUS ($n = 14$, 2.14%) were also increased compared to 1991 and 2001, whereas the percentage of amyloidosis remained almost constant ($n = 8$, 1.22%).

Distribution of frequencies of specific diseases

Hemolytic uremic syndrome

In the whole study period 70 patients were recorded as HUS (1.79% of all biopsies). In 1991 and 2001, the numbers of patients with renal biopsy revealing HUS were quite low ($n = 1$ and $n = 2$, respectively), whereas it was highest in 2008 ($n = 14$, corresponding for 20% of all HUS patients at all time periods, Figure 2). Moreover, among all biopsy results, the frequency of HUS was highest in this year (2.15%) compared to 1991 and 2001.

Membranous nephropathy

Overall 61 patients were identified as MN throughout the study (1.56% of all biopsies). None of the patients had MN diagnosis in 1991 and this number was still low in 2001 ($n = 4$, corresponding to 0.86% of the biopsies performed at that year and 6.56% of all biopsies with MN). The number of patients with MN was highest in 2008 ($n = 13$, corresponding to 21.35% of all patients

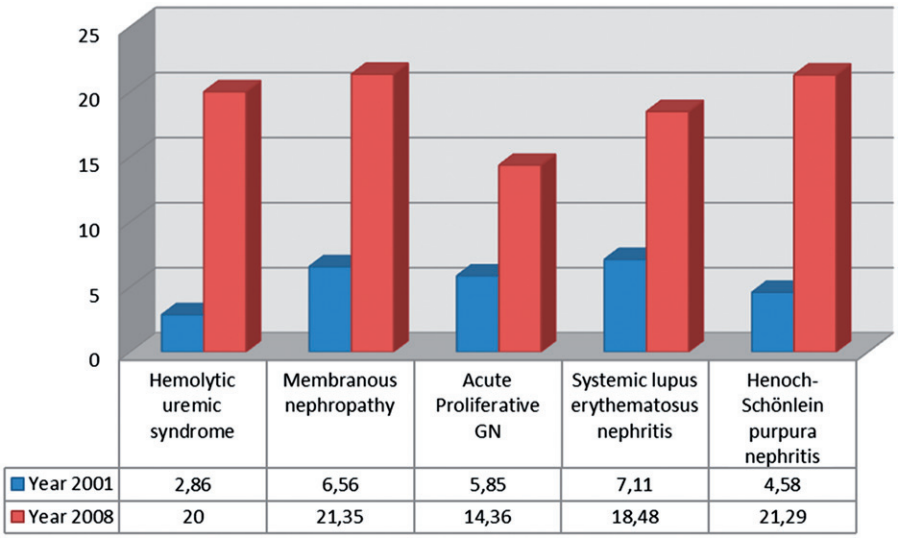


Figure 2. Changing patterns in the diagnosis of certain diseases in 2001 and 2008.

with MN) (Figure 2). Although the number of patients with MN increased, the disease comprised only 1.98% all biopsies in 2008.

Acute proliferative GN

Overall 188 biopsies revealed acute proliferative GN throughout the study period (4.88% of all biopsies). The number of patients with acute proliferative GN was highest in 2008 ($n = 27$) which represented 14.36% of biopsies with this specific histopathological diagnosis (Figure 2). However, the percentage of that disease was only 4.12% among all biopsy results in 2008; which was significantly lower than the percentages (12.62%) in 1991.

SLE nephritis

A total of 211 patients had histopathologic diagnosis of SLE nephritis in the study (5.42% of all biopsies). The number of patients with this diagnosis was highest in 2008 as well ($n = 38$), corresponding to 18.48% of all patients with SLE nephritis (Figure 2). On the other hand, its percentage was only 5.81% among all biopsies that year, which remained only slightly higher than 2001 ($n = 25$, 5.41%).

HSP nephritis

Three hundred and fifty-seven patients had HSP nephritis diagnosis throughout the study period (9.17% of all biopsies). Both the number and the ratio of patients with HSP nephritis increased in 2008 compared to 1991 and 2001. Only six and 16 patients had biopsies revealing HSP nephritis in 1991 and 2001 (1.68% and 4.48% of all patients with HSP nephritis, respectively). On the other hand, this number was 76 in 2008, corresponding to 21.29% of all patients with HSP nephritis (Figure 2) and 11.62% of biopsies performed at that year.

Discussion

Knowledge of the epidemiology of renal disease in children and clinicopathological correlations provides important information in pediatric nephrology. However, there are relatively few studies demonstrating the histopathological findings of renal biopsies in the literature and they usually include all age groups. Moreover, there is variation in the spectrum of renal diseases in the pediatric age group in different geographical regions.[2,4,7]

Primary GN is the most frequent histopathology in all previous studies both in children and adults, and not much change occurred over the decades.[2,4,7,8] As steroid-resistant or frequent-relapsing steroid-dependent NS is the most common indication for renal biopsies in the pediatric age group,[3–6] membranoproliferative GN (MPGN) and FSGS are usually the most common glomerular diseases identified by renal biopsies in children. In a Turkish single-center study by Demircin *et al.* primary glomerular diseases accounted for 61.2% of all pediatric biopsies and MPGN was the most common pathology.[4] Our study included multicenter pediatric biopsies and revealed very similar frequencies for glomerular diseases (62.64%). However, FSGS was the most common glomerulopathy in our study. Steroid sensitive NS is usually managed without performing renal biopsy in our country, and therefore, the frequency of minimal change disease (MCD) in our registry remained relatively lower than FSGS or mesangioproliferative GN at all periods.

IgA nephropathy is notified as a frequent glomerular disease detected by renal biopsy in adults.[7,9] In our study, although IgA nephropathy was the histopathologic diagnosis in only 6.08% of all biopsies, its frequency increased from 0.97% in 1991 to 7.33% in 2008. Prevalence of IgA nephropathy in the renal biopsy specimens differs according to the protocols of each center on the approach to the patients with hematuria. Similar to our study, reports from Italy and south-east Asia indicate a trend of increase in the pathologic diagnosis of IgA nephropathy.[10–12] This gradual increase could be attributed more to the tendency to select more patients with persistent microscopic hematuria with or without associated proteinuria for renal biopsies rather than a true increase in the incidence of IgA nephropathy.

Acute post-streptococcal GN is the most classical form of acute post-infectious GN demonstrated mostly by diffuse proliferative and exudative glomerular histology.[13] In our registry, the frequency of acute proliferative GN was relatively high in 1991. Despite increased number of patients, its frequency significantly declined over two decades. This finding was believed to be due to more proper treatment of streptococcal infections in our country and thus, prevention of progression into acute post-infectious GN.

Membranous nephropathy is rare in pediatric patients.[14] In our registry, despite an increase in the number of cases with MN over the years, the frequency of MN was still low among all biopsies; which concluded to be a reflection of general incidence of the disease.

Second most common group of histopathology was GN secondary to systemic diseases. From these, HSP nephritis was the leading entity in our registry, with an increased trend of detection in the recent years. HSP is

the most common childhood vasculitis, and renal involvement occurs in up to 30–50% of affected cases in variable degrees ranging from only hematuria and/or low-grade proteinuria to nephrotic syndrome or renal function impairment.[15] The increased ratio and number of patients with HSP nephritis is most likely the result of both high frequency of the disease itself and increased awareness toward referral of patients with renal involvement to pediatric nephrology departments.

Despite a slight increase in the last decade compared to 1991, our registry showed prominently low number of biopsies with SLE nephritis throughout the study period. The incidence and severity of SLE in children are variables depending on ethnicity: Asians, Blacks, and Hispanics were more frequently affected than Caucasians.[3] Moreover, renal biopsies are usually reserved for SLE patients with urine abnormalities in order to document the histological type of magnitude of renal injury. It may be speculated that the frequency of SLE nephritis could have been much higher in our country if protocol biopsies are generally performed for those without overt urinary abnormalities.

Amyloidosis is the most devastating complication of Familial Mediterranean fever (FMF); a common disease in our country.[16] Its frequency was low throughout the study (0.97%, 1.29%, and 1.12% in 1991, 2001, and 2008, respectively). In the literature, this percentage does not exceed 0.5–3%.[4] The relatively low ratio consistent with previous reports was suggested to be linked to prompt diagnosis of FMF and appropriate use of colchicine treatment which is known to prevent the development of amyloidosis.

Similar to the recent years of our registry, HUS became to be more commonly notified in renal biopsies.[2] Although the indications for renal biopsies were not determined in this study, this may be the result of the development of a better approach to acute renal failure in pediatric nephrology practice in our country.

Miscellaneous pathologies were the third most common group of disease on our registry. This group also included normal biopsy reports determined by light microscopy or immunofluorescence. A limitation of our study was that the electron microscopy results of these biopsies were not available. Therefore, histopathological diagnoses like thin basal membrane disease or Alport syndrome were not recorded in our registry.

In conclusion, the outcomes of the over 10-year evaluation of pediatric renal biopsies in Turkey showed discrepancies in the histopathologic diagnoses of certain conditions: an increase in certain disorders including HUS, HSP, and IgA nephritis; and a decrease in acute proliferative GN. The TSNRS also provided us an important insight for the differences in the management of renal diseases and tendencies toward performing pediatric renal biopsies over the years in Turkey.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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