Renal histopathology spectrum in children with kidney diseases in Saudi Arabia, 1998-2017

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ABSTRACT

هناك تغييرات كبيرة في انواع الأمراض الكبيبيه لدى الأطفال خلال العقود الماضية و هذه الدراسة تهدف إلى تحديد الاتجاهات في تواتر تشخيص مرض الكبيبي عن طريق خزعة الكلى لدى الأطفال في المملكة العربية السعودية على مدى السنوات ال 20 الماضية.

أساليب: في هذه الدراسة الرصدية بأثر رجعي ، حددنا جميع المرضى السعوديين الذين تقل أعمارهم عن 18> عامًا والذين تم إجراء خزعة الكلى لديهم من يناير 1998 إلى ديسمبر 2017 وتم تجزئتها الى الفترات التاية: (1998–2004 و 2005–2011 و 2012–2017) وتم فحص البيانات الديمغرافية وارتباطها بانتشار الأمراض الكبيبية المختلفة.

النتائج: تم دراسة 326 حالة مرضية مع خزعة الكلى بمتوسط عمر 11 سنة و 45.4% منهم من الاناث. شكلت التهاب كبيبات الكلى الثانوية 42.3% من الحالات ، وكانت الذئبة الحمراء السبب الأكثر شيوعا (20.7%) من الحالات. كان التغيير البسيط والتصلب الكبيبي القطاعي أهم الخصائص الرئيسية لتشخيص التهاب كبيبات الكلى في 59% من الحالات. انخفض تواتر التهاب كبيبات الكبيبات التكاثرية الغشائية والتهاب كبيبات الكبيبات التكاثرية المتوسطة بشكل كبير من 15% و 17% في الفترة السابقة لعام 2004 إلى 3.3% و 17% في 2012–2012 ، على التوالي.

الاستنتاجات: هناك تحولًا كبيرًا في تواتر العديد من الأنواع الفرعية لأمراض الكبيبات في الفترة 1998–2017. والجدير بالذكر أن الانخفاض الكبير في وتيرة التهاب كبيبات الكلى التكاثرية الغشائية والتهاب كبيبات الكلى المتوسطة التكاثر على مدى العقدين الماضيين. التهاب الكلية الذئبة هو السبب الأكثر شيوعا لالتهاب الكلية الكبيبي الثانوي.

Objectives: To identify the trends in the diagnostic frequency of glomerular disease subtypes by renal biopsy in children in Saudi Arabia over the last 20 years.

Methods: In this retrospective observational study, we identified all patients aged <18 years for whom native kidney biopsy was performed between 1998 and 2017. The period during which biopsy was performed (1998-2004, 2005-2011, and 2012-2017) and the demographic information and their association with the prevalence of various glomerular disease subtypes were our primary outcomes.

Results: A total of 326 cases with renal biopsy were analyzed; the mean age of participants being 11 years and 45.4% of them were girls. Unexpectedly, secondary glomerulonephritis accounted for 42.3% of the cases, and lupus nephritis was the most common cause noted in 20.7% of the cases. The minimal change and focal segmental glomerulosclerosis were the most common glomerulonephritis in 59% of the cases. The frequency of membranoproliferative glomerulonephritis and mesangioproliferative glomerulonephritis significantly decreased from 15% and 17% in the period prior to 2004 to 3.3% (p=0.003) and 1.7% in 2012-2017 (p<0.001).

Conclusions: We found a considerable shift in the frequency of many glomerular disease subtypes in 1998-2017, which make clinical predication of the underlying etiology challenging for clinician. Renal biopsy still remains a critical diagnostic procedure for managing a considerable proportion of renal diseases.

Keywords: glomerulonephritis, biopsy, nephrotic syndrome, focal segmental glomerulosclerosis

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Renal disease has been recognized as an important cause of morbidity and mortality for the last decades in Saudi Arabia.[1,2] The main consequences of kidney disease include disease progression and, subsequently, increased risk of cardiovascular disease. Although advances in technology and medical treatment have been reported during the past decades,[3,4] data on the incidence and prevalence of various types of glomerular diseases in the kingdom have been limited. Additionally, most of the reports are outdated and do not reflect the spectrum of glomerular diseases among Saudi children in the last 10-20 years. In a previous study conducted at King Faisal Specialist Hospital and Research Centre, Riyadh, researchers identified a high proportion of focal segmental glomerulosclerosis (FSGS) and a low proportion of membranous nephropathy (MN) cases among 147 renal biopsy samples.[5] In another multicenter study conducted in Saudi Arabia,[2] investigators found that the most common renal diseases were FSGS (34.9%), mesangioproliferative glomerulonephritis (MesPGN) (29.1%), and membranoproliferative glomerulonephritis (MPGN) (10.5%). The least frequent were MN (6.5%), minimal change disease (MCD) (5.8%), and immunoglobulin A (IgA) nephropathy (5.8%). However, both studies included both adult and pediatric cases.

Therefore, this study aimed to examine the trend of various pathologies in native kidney biopsies conducted in children between 1998 and 2017, to describe trends in various glomerular disease frequencies over the last 2 decades, and to examine their relationship with age and gender. We also report the clinical presentation of different glomerular diseases.

Methods. This is a cross-sectional multicenter on native kidney biopsy specimens of glomerular disease conducted in children from January 1998 to December 2017, including 4 tertiary referral hospitals in Saudi Arabia: King Saud University Medical City in Riyadh, Security Forces Hospital in Riyadh, King Abdulaziz Medical City in Riyadh, and King Abdulaziz University Hospital in Jeddah. After excluding patients with missing histologic diagnosis or with inadequate biopsy (adequate biopsy was defined as 10 or more glomeruli), a total of 326 biopsies were included in the analysis. Pediatric patients were divided into 2 age strata: young children (aged 0-12 years) and adolescents (aged 13-17 years). The indications for kidney biopsy included nephrotic syndrome with steroid resistant after 6-8 weeks of therapy or frequent relapse, nephritic syndrome, unexplained renal impairment, subnephrotic proteinuria, asymptomatic urine abnormalities. Institutional Review Board (IRB) approval for the study was obtained from King Khalid University Hospital, Riyadh, Saudi Arabia (E12-811), and a waiver of consent was granted.

All renal biopsies had been carried out by either pediatric nephrologist or interventional radiologist under real-time ultrasound guidance. Most of the time, the renal biopsy carried out under general anesthesia specially in children below 12 years of age. All renal biopsy specimens were processed using the standard light, immunofluorescence, and electron microscopy procedures. Diagnoses were made by nephropathologists. Clinical, demographic, and laboratory data and renal histopathological diagnosis were collected from patient's medical records. There were 20 renal pathologists involved in reporting of kidney biopsies.

The histologic findings were classified according to Revised Protocol for the Histological Typing of Glomerulopathy.[6] Histologic diagnoses were classified into one of 4 major categories: (i) primary glomerulopathy, such as MCD, IgA nephropathy, MGN, MPGN, mesangioproliferative, and FSGS; (ii) secondary glomerulopathy associated with primary diseases, including but not limited to lupus, Henoch-Schonlein purpura, and diabetes; (iii) hereditary glomerulopathy, such as Alport syndrome; (iv) and unclassified glomerulopathy, such as end-stage kidney disease of undetermined origin.

Timing of biopsy period was our primary exposure, categorized in to 3 consecutive 7-year time intervals (1998-2004, 2005-2011, and 2012-2017) for data analysis. Glomerular disease subtype frequency was our primary outcome. As secondary outcomes, the clinical presentation and trends in glomerular disease frequency within demographic subgroups were examined. Ethical approval was obtained from Ethics Committee of College of Medicine Research Center at King Saud University according to principles of Helsinki Declaration.

Statistical analysis. Statistical analyses were performed using SAS software (SAS Institute, Cary, US). Categorical variables are reported as absolute number and percentage, and the continuous variables are presented as the mean ± standard deviation. When analyzing different glomerular diseases across the study

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eras, probability for trend values are reported. Differences in the frequency of various glomerular diseases among age groups were compared using the Chi-square test/ Fisher exact test. A $p \leq 0.05$ was considered significant.

Results. Among the 326 cases analyzed, more than half the patients were male. The mean age of the patients at biopsy was 11.0 ± 5.0 years. The mean urine protein, serum albumin, and serum creatinine levels are presented in **Table 1**.

Gender and age characteristics of patients with primary glomerular disease are shown in **Table 2**. In most cases, male was more commonly affected, except for membranous nephropathy (MN), where both sexes were equally affected.

The frequency of MPGN in 2012-2017 significantly decreased to 3.3% and MesPGN to 1.7%, compared to that in the period before 2004; the frequency of MPGN in 1998-2004 were 15% (p=0.003) and MesPGN were 17.5% (p<0.001) (**Figure 1**). Conversely, the frequency of MCD consistently increased across the study periods, from 8.8% in 1998–2004 to 18.3% in 2012–2017 (p=0.1). The frequencies of IgA nephropathy (IgAN) and MN were stable throughout the study periods (p=0.7 and p=0.2), whereas the frequency of FSGS modestly increased in 2005-2011 and then slightly decreased in 2012-2017 (p=0.7).

Table 1 - Demographic and indication for kidney biopsy of 326 Saudi children who underwent kidney biopsy in from 1998 to 2017.

Demographic and indication	n (%)
Gender	
Male	178 (54.6)
Female	148 (45.4)
Urine protein (g/day)	4.0
Median	2.5
Serum albumin	24.3
Age at biopsy, mean in years (SD)	11.0 (5.0)
Serum creatinine (µmol/L)	91
Median (µmol/L)	52
Indication for kidney biopsy	
Nephrotic syndrome	171 (52.5)
Nephritic syndrome	118 (36.2)
Unexplained renal impairment	9 (2.8)
Asymptomatic urinary abnormalities	20 (6.1)
Subnephrotic proteinuria	8 (2.4)
Histological diagnosis	
Primary glomerular disease	182 (55.8)
Secondary glomerular disease	138 (42.3)
Others	6 (1.8)

Table 2 - Gender and age characteristics of 326 children patients with primary glomerular disease underwent kidney biopsy in Saudi Arabia from 1998 to 2017.

Glomerular pattern	n (%)	Gender M:F (*P*-value)	Age (years) mean
FSGS	56 (30.8)	2:1 (0.05)	10.5 ± 5.6
MCD	52 (28.6)	1.6:1 (0.2)	9.5 ± 5.0
MN	13 (7.2)	1:1 (0.5)	14.5 ± 3.3
IgAN	17 (9.3)	1.8:1 (0.3)	11.7 ± 4.6
MPGN	23 (12.6)	2.3:1 (0.1)	9.7 ± 5.0
MesPGN	21 (11.5)	2.5:1 (0.1)	10.4 ± 5.5
Total	**182**		

FSGS: focal segmental glomerulosclerosis, MCD: minimal change disease, MN: membranous nephropathy, IgAN: immunoglobulin A nephropathy, MPGN: membranoproliferative glomerulonephritis, MesPGN: mesangioproliferative glomerulonephritis

Secondary glomerulonephritis accounted for 42.3% of cases (**Table 1**) and lupus nephritis (LN) was the most common cause, noted in 20.7% of cases (**Figure 2**). Minimal change disease and FSGS were the leading primary glomerulonephritis diagnoses, observed in 59% of cases.

The indications for kidney biopsy varied, with nephrotic syndrome as the most common, followed by unexplained renal impairment (**Table 3**). As FSGS was the most frequent histological pattern in patients who had renal biopsy for nephrotic syndrome, MPGN was more common among those who had unexplained renal impairment.

When stratified by age group, FSGS was more prevalent among children aged 0-12 years (**Table 4**). Similarly, MCD was more common in this age group. Conversely, MN was more common in those aged 13-17 years.

Discussion. Insights into the epidemiology of kidney disease in the pediatric age group provides critical information for pediatric nephrology. Unfortunately, studies investigating the histopathological spectrum of renal biopsies in children are limited, because the most recent available data include all age groups.[7,8] Additionally, the spectrum of kidney diseases varies in children based on the geographic location.[7-11] In the

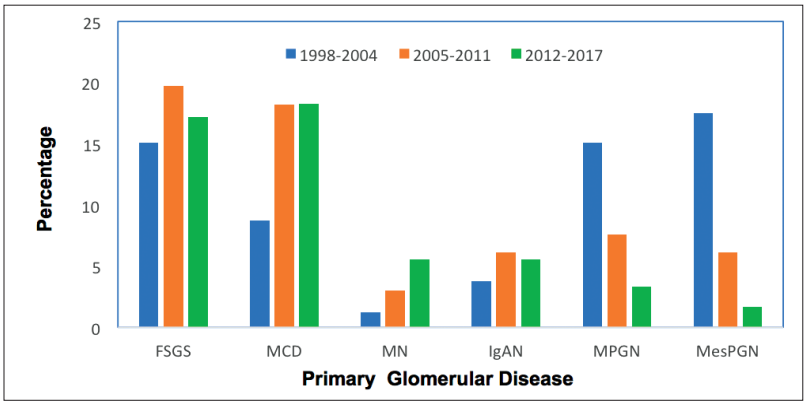

Figure 1 - Temporal trends in primary glomerular disease among 326 children who underwent kidney biopsy in Saudi Arabia from 1998 to 2017. Frequencies of the different subtypes shown as a proportion of the primary glomerular disease cohort. MesPGN: mesangioproliferative glomerulonephritis, MPGN: membranoproliferative glomerulonephritis, IgAN: immunoglobulin A nephropathy, MN: membranous nephropathy, MCD: minimal change disease, FSGS: focal segmental glomerulosclerosis

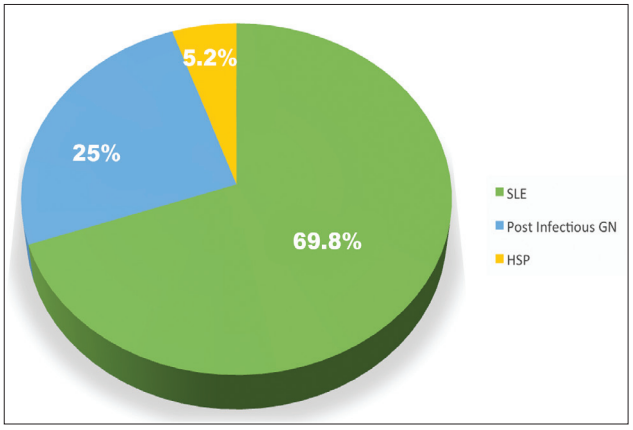

Figure 2 - Frequency of secondary glomerulonephritis among 326 children who underwent kidney biopsy in Saudi Arabia from 1998 to 2017. SLE: systemic lupus erythematosus, GN: glomerulonephritis, HSP: Henoch–Schonlein purpura

study analysis, we examined biopsy results of Saudi children and compared the prevalence of different histopathological subtypes for 3 in 7-year periods. Our analyses indicate a substantial shift in the prevalence of many renal disease subtypes between 1998 and 2017, with an appreciable decline in the prevalence of MPGN and MesPGN between 1998-2004 and 2012-2017. This decline may be due to marked improved socioeconomic conditions and decreased incidence of regional endemic diseases and health care facilities.[12,13] This finding also in consistent with other studies.[14-16] However, we cannot exclude the impact of clinician on avoiding doing biopsy in mild cases or those responding to steroid treatment.

In our cohort, the Alport syndrome confirmed by renal biopsy only in 8 patients (2.5%). Similar findings have also been reported from other Arab country. More detailed genetic testing is mandated to have the true estimate of secondary cases related to genetic mutations.

As no national data are available on the patterns of diagnosing biopsy-proven renal diseases, findings from international cohorts have shown temporal shifts in the frequency of renal disease subtypes during the past 3 decades.[7,8] In one report,[8] investigators found a steady increase in the frequency of diabetic glomerulosclerosis in adolescents over the 3 study decades. Furthermore, they described an initial increase in the frequency of FSGS, which then plateaued and ultimately declined. The frequency of other glomerular subtypes, such as MN and MCD, considerably increased in all study intervals. In contrast, they observed a relatively moderate decline in the frequency of LN and MPGN, while the frequency of IgA nephropathy and anti-neutrophil cytoplasmic antibodies (ANCA)/pauci-immune glomerulonephritis (GN) remained stable.[8] Although these data included all age groups, the researchers did not observe striking variations in the frequency of renal disease subtypes among the different age groups. The mean age for patients with MCD was higher than would be anticipated, likely reflecting the clinical practice on doing kidney biopsy in children with nephrotic syndrome.

A more surprising finding was the decreasing

Table 3 - Indications for kidney biopsy in patients with primary glomerular disease stratified by histological pattern.

Clinical presentation	Histological pattern					
	FSGS	MPGN	MCD	MN	IgAN	MesPGN
Nephrotic syndrome	45 (80.4)	10 (43.5)	39 (83.0)	11 (78.6)	7 (41.2)	13 (61.9)
Unexplained renal impairment	8 (14.3)	6 (26.1)	3 (6.4)	0	3 (17.6)	2 (9.5)
Asymptomatic urinary abnormalities	0	0	0	0	2 (11.8)	1 (4.8)
Nephritic syndrome	2 (3.6)	6 (26.1)	0	1 (7.1)	4 (23.5)	5 (23.8)
Subnephrotic range proteinuria	1 (1.8)	1 (4.3)	5 (10.6)	2 (14.3)	1 (5.9)	0
Total	**56**	**23**	**47**	**14**	**17**	**21**

FSGS: focal segmental glomerulosclerosis, MPGN: membranoproliferative glomerulonephritis, MCD: minimal change disease, MN: membranous nephropathy, IgAN: immunoglobulin A nephropathy, MesPGN: mesangioproliferative glomerulonephritis

incidence of FSGS in a multicenter hospital-based study conducted across 115 hospitals in China.[17] In this report, Nie et al[8] studied the spectrum of biopsy-proven glomerular diseases among children aged more than 11 years and observed a decrease in the frequency of FSGS from 14% to 4%, based on the results of the biopsies. This is in stark contrast to the findings of other investigators who reported an increasing frequency of FSGS in American children. Studies including adult patients have also shown consistent increases in the prevalence of FSGS over time, which have been attributed to the increasing obesity rates.[18] In our report, we observed a modest increase in the rates of FSGS in 2005-2011, followed by a slight decline in 2012-2017. As the rates of obesity among Chinese children are lower than in other regions, this is probably not related to the declining frequency of FSGS,[17] because obesity-related FSGS is very uncommon in children.[9] Of note, because Nie et al[17] reported biopsy numbers as proportions, a true decline in the incidence of FSGS in their cohort may not be reflected.

Although female represented more than half of the patients in our cohort, the frequency of primary renal disease subtypes was higher in male, except for MN, which was equally reported in both sexes. Contrary to our results, other researchers observed a predominance of kidney disease subtypes in male patients.[10] Similar findings were reported by other authors, who found a higher male-to-female ratio among children with renal disease.[19-22] Our finding that nephrotic syndrome was the most common indication for kidney biopsy is in line with those reported in studies conducted in other developing countries.[10,18] Conversely, the indications for renal biopsy are different from those reported by investigators in developed countries, with isolated microscopic hematuria as the most common indication. Nevertheless, that evolving biopsy practice patterns and expanding indications for biopsy may largely differ between institutions and might considerably affect the frequency of biopsies performed in children with kidney disease. In this cohort, only 3 cases (16.6%) confirmed to have glomerular disease out of cases biopsied because of asymptomatic urine abnormalities

In the Jordanian cohort,[10] investigators reported that the most common primary glomerular disease in nephrotic children was MCD, which accounted for 27% of their cases. As expected, MCD and FSGS were the most common histological subtypes in our study. Although MCD, FSGS, and MPGN are reported as the most frequent histological classifications in children with nephrotic syndrome,[23] differences in biopsy results and the indications for renal biopsy have been reported across studies. Minimal change disease was identified as the most common histopathologic diagnosis for children receiving a biopsy for nephrotic syndrome in our study and in the Chinese cohort[17] as well as in a North American cohort of children receiving a biopsy for proteinuria.[24] Additionally, variations in histopathologic subtypes have been reported across age groups. Also Nasar Yousuf Alwahaibi et al[25] conducted a systematic review and notice same finding.

In this study, FSGS and MCD were more prevalent in children aged 0-12 years. On the other hand, MN was more common in those aged 13-17 years. In the Nephrotic Syndrome Study Network (NEPTUNE),[24] MCD accounted for approximately 65% of children

aged 0-11 years and 35% of children aged 12-18 years. The investigators reported FSGS as the second most frequent histologic subtype in both age groups. In a Chinese cohort,[17] the authors found that FSGS was less common in children aged 13-18 years. Since these biopsies were performed during different periods, the disparities between these studies might be due to varying availability of diagnostic resources or changing indications for kidney biopsy in children. Similarly, epidemiologic studies of glomerular disease in children are always limited by the clinical practice of classifying nephrotic syndrome by sensitivity to steroids. While this obviously decreases the need for an invasive procedure in many children with steroid sensitive nephrotic syndrome, it significantly underestimates the incidence rates of minimal change disease. Early renal biopsy in all children with features of lupus nephritis is critical to diagnosis and early management of lupus nephritis. Our study revealed that lupus nephritis was the most common secondary cause, noted in 20.7% of cases. We are aiming to do more analysis on this data to examine the presentation, histological and clinical outcomes of lupus in children with SLE.

Although this study provides preliminary data for the estimation of trends in the frequency of diagnosing renal biopsy glomerular disease in Saudi children, it has limitations that should be discussed. Since we reported biopsy results as proportions, we could not accurately report the incidence rates of the different histologic subtypes. Additionally, our results may be skewed because we included only cases from 4 major tertiary hospitals across Saudi Arabia. It was not feasible to review the samples in central committee to avoid variation in reporting of various glomerular diseases and data related to biopsy complications were not collected. Similarly, the response to steroid and/or relapses were not captured in our analysis.

In conclusion, primary glomerular disease remains the predominant kidney disease in Saudi children, with MCD and FSGS being the most common pathologies. We found a considerable shift in the frequency of many glomerular disease subtypes in the period 1998-2017. Of note, a considerable decline in the frequency of MPGN and MesPGN over the past 2 decades might reflect improvements in the socioeconomic conditions in the Kingdom. Nevertheless, the underlying reasons for these changing trends should be in future studies to provide new insights into disease pathogenesis or therapeutic options.

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