Changing trends of histopathology in childhood nephrotic syndrome in western Saudi Arabia

Jameela A. Kari, MD, FRCPCH.

ABSTRACT

Objectives: It is widely accepted that minimal change nephrotic syndrome is the most common cause of nephrosis in children. Recent studies have demonstrated an increasing incidence of focal segmental glomerulosclerosis in adults and children. This study was conducted to analyze the trend of histopathologic subtypes in idiopathic nephrotic syndrome in the western area of the Kingdom of Saudi Arabia.

Methods: To determine the possible changes in the etiology of childhood nephrosis, the clinical charts of 46 pediatric patients diagnosed with idiopathic nephrotic syndrome between 1997 and 2001, group A, were reviewed. Results were compared with our initial published data of 132 patients with idiopathic nephrotic syndrome diagnosed between 1983 and 1992, group B.

Results: There was no difference in the percentage of biopsies between group A (43%) and group B (31.8%), P= 0.9. There was a decline in the incidence of minimal change nephrotic syndrome in recent years. Even if we assume that all patients without a histological diagnosis had minimal change nephrotic syndrome, presumptive minimal change nephrotic syndrome, the total incidence of minimal change nephrotic syndrome (biopsy proven + presumptive) in group A, was only 65% compared to 79.5% in group B, P=0.02. The incidence of focal segmental glomerulosclerosis was significantly greater in biopsies performed in the recent period, group A, 35% versus group B, 16.7%, P=0.05, and in the total number when we included the presumptive minimal change nephrotic syndrome, group A, 15.2% and group B, 5.3%, P<0.0001. Similarly we found an increased incidence of membranoprolifrative glomerulonephritis in total patients when we included the presumptive minimal change nephrotic syndrome, group A, 13.0% and group B, 5.3%, P=0.02.

Conclusion: There is a shift toward an increasing prevalence of focal segmental glomerulosclerosis and membranoprolifrative glomerulonephritis over the years in the western area of the Kingdom of Saudi Arabia. These findings may have significant implications in the management of childhood nephrotic syndrome

Keywords: Nephrotic syndrome, children, focal segmental glomerulosclerosis, membranoprolifrative glomerulonephritis.

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Nephrotic syndrome (NS) is a clinical manifestation of different histopathologic subtypes. Based on histopathological findings on renal biopsy, primary NS is further classified into minimal change nephrotic syndrome (MCNS), focal segmental glomerulosclerosis (FSGS), mesengioprolifrative glomerulonephritis (MePGN), membranoprolifrative glomerulonephritis (MPGN), membranous glomerulonephritis (MGN) and focal and global glomerulosclerosis.[1] The International

From the Department of Pediatrics, King AbdulAziz University Hospital, Jeddah, Kingdom of Saudi Arabia.

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Address correspondence and reprint request to: Dr. Jameela Kari, Associate Professor, Department of Pediatrics, King AbdulAziz University Hospital, PO Box 80215, Jeddah 21589, Kingdom of Saudi Arabia. Tel. +996 (2) 55677904. Fax. +996 (2) 6743781. E-mail: jkari@doctors.org.uk

Study of Kidney Disease in Children (ISKDC) reported in the 1970s that MCNS was the most common histological lesion in renal biopsies from children with idiopathic nephrotic syndrome (INS).[2,3] A similar study was carried out by White et[4] al in the United Kingdom at the same time reporting an incidence of 76.5% and 8.3% of MCNS and FSGS. We have reported the same observation in our previous study of histopathological lesions in children with NS presented between 1983 and 1992.[5] We have reported MCNS in 79.5% of nephrotic cases and showed like others[2-4,6] that FSGS was a rare cause of nephrosis in children, observed in only 5.3% of the total patients and in 16.7% of the biopsies. More recent studies in adults and children showed changing trends of histopathology in adulthood[7,8] and childhood NS[9-11] with increasing incidence of FSGS during the last 20 years, accompanied by significant decline in the incidence of MCNS. We report the changing trend in the histopathological lesions in INS syndrome in the Western area of Kingdom of Saudi Arabia (KSA). We have retrospectively reviewed all the children presented with INS to King AbdulAziz University Hospital (KAUH) between 1997 and 2001 and compared the results with our previously published data. King AbdulAziz University Hospital is located in a racially mixed population of a major urban area in the Western area of KSA. The demographic data and the histopathological findings were reviewed.

Methods. A retrospective study was performed from January 1997 to June 2001 at KAUH, involving 46 patients aged up to 14 years with childhood NS. The results were compared with our published data of 132 nephrotics presented to the same institution between 1983 and 1992.[5] These patients comprised a racially mixed population of a major urban city in KSA located near to the holy city of Makkah where expatriates are common. Most had been treated earlier with other physicians and referred to our unit for management. Patients with congenital nephrotic syndrome (CNS) or with systemic illness such as systemic lupus erythematosus, Henoch-Schönlein purpura, sickle cell anemia, malignancies, metabolic disorders or hepatitis were excluded. Indications for biopsy included steroid resistance, an age older than 8 years, unusual presentation such as significant elevation of serum creatinine or gross hematuria and prior cyclosporin therapy in frequent relapsers and steroid dependent nephrotics. The biopsy specimens were evaluated histopathologically by light, immunofluorescent and electron microscopy (EM). Histopathologic findings were interpreted by the same pathologists in accordance with similar criteria as applied in our previous study. Adequacy of biopsy was defined as the presence of at least 5 glomeruli in the specimen on light microscopy.[12] Minimal change disease (MCD) was characterized by the absence of any conspicuous abnormality on light microscopy. Mesengioprolifrative glomerulonephritis was labeled in the presence of diffuse mesangial hypercellularity lacking immune deposits. Focal segmental glomerulosclerosis was characterized by the presence of at least one glomerulus showing a segmental area of sclerosis with or without accompanying tubular atrophy and interstitial fibrosis. Membranoprolifrative glomerulonephritis was labeled in the presence of intense cellular proliferation on light microscopy and immune deposition on EM. In the absence of atypical presentation of childhood NS, our practice is to treat patients with corticosteroids. The group of patients who readily respond to prednisolone (56.5%) is presumed to have MCNS. Renal biopsy in such patients was not performed. All patients were treated initially with corticosteroids, prednisolone, at a dose of 60 mg/m^2/day (maximum 80 mg/day) for 4 weeks. Nine patients received levamisole and 11 patients were treated with cyclophosphamide. Cyclosporin was used in 4 patients with FSGS, 2 steroid dependent and 2 steroid resistant.

Definitions. Nephrotic syndrome was defined as the association of heavy proteinuria and hypoalbuminemia. The response to therapy was classified according to the definition from the British Pediatric Nephrology Association:[13] a. steroid sensitive - complete resolution of proteinuria within 4 weeks of predisolone therapy, b. steroid resistant - failure to respond after 4 weeks of prednisolone 60 mg/m^2/day, c. steroid dependence - recurrence of nephrosis when the dose of corticosteroids is reduced or within 2 weeks after discontinuation of therapy, d. frequent relapses - 2 or more episodes of nephrosis within 6 months of the initial response or 4 or more within any 12-month period. Congenital NS was defined as NS presented at less than 3 months of age.

Statistical analysis. Data from groups of patients are reported as mean ± standard deviation (SD) or as percentage (frequency of observation in a particular group). The statistical analysis was performed by Z test and t-test assuming equal variance was used to compare between the ages of different groups. Statistical significance was defined as a $P \leq 0.05$.

Results. Our populations were presented by one major ethnic group; Arabs [N=37 (80%), 20 of them were Saudis (43%)] and 3 minor ethnic groups; Asians (Indians and Pakistanis, N=5); Africans (N=2) and 2 patients were from the Far East (Indonesian and Filipino). The mean ± SD age of our population (group A) at first presentation of NS was 3.8 ± 2.8 (range 0.7 to 14 years old) compared to 6.2 ± 3.7 in group B. Three patients with CNS were excluded

from the study in group A and 10 patients in group B. All patients of the study were seronegative for hepatitis surface antigen (HbsAg) and antinuclear antibodies (ANA). The fraction of patients who underwent biopsy in the 2 groups was similar, group A 20 of 46 (43%) versus group B, 42 of 132 (31.8%), P=0.09. In group A, children with INS who under went biopsies, FSGS was the most common histopathological subtype, occurring in 7 children (35%), followed by MPGN in 6 children (30%). Other subtypes included MesPGN in 4 patients (20%) and MCD in 3 patients (15%), **Table 1**. If we assumed that all children that were not biopsed had MCD (presumptive MCD), the total incidence of MCNS (presumptive + biopsy proven) was 65%, which is lower than that of group B (79.5%), Z= 2.02, P=0.02, **Table 2**. The prevalence of FSGS was significantly higher in-group A (35% of the biopsies versus 16.7% in group B; P=0.05), **Table 3.** The increase in fraction of patients with FSGS was significant in group A, even if all patients including those who did not undergo biopsies were considered, group A, 7 of 46 (15.2%) versus group B, 7 of 132 (5.3%), P=<0.0001, **Table 2.** There was a non-significant increase in the MPGN in biopsied patients, group A 6 of 20 (30%) versus 7 of 42 (16.7%), P=1.2, **Table 3**. However, when we included patients who did not have renal biopsies as presumptive diagnosis of MCD, the increase in MPGN was significant, group A 6 of 46 (13%) versus group B 7 of 132 (5.3%), P=0.02, **Table 2.** We thought of the effect of the racial origin, however, when we studied patients from Arabic origin only 37 patients, after excluding Asian and African patients, we found similar results. Fifteen patients (40.5%) had a renal biopsy. Of those 6 patients (40%) had FSGS, 6 (40%) had MPGN and 3 (20%) had MesPGN. The Saudi patients, 20 children, as a sub-group had the same distribution of the whole group or the Arab group. Seven had a renal biopsy, 3 (42.8%) had FSGS, 3 (42.8%) had MPGN and 1 (14.2%) had MesPGN, **Table 4.** We do not have the racial fractions of our previous study but they were from the same population. Familial steroid resistant nephrotic syndrome (SRNS) was observed in 3 Arabs siblings from Yemeni origin with MPGN. Another patient with SRNS due to MPGN had a family history of a sibling who died from chronic renal failure that complicated SRNS. The mean ± SD of total (presumptive and biopsy proven) MCD was 3.6 ± 2.2, range 0.9-11, years. There was no difference between the presenting age (mean ± SD) of MPGN patients; 2.8 ± 3.1, range 0.8-5 years and MCNS patients, P=0.6. However, FSGS patients had an older age at presentation 6.14 ± 4.7, range 2-14, years, P=0.03. Ten patients were steroid resistant, 8 never responded to steroids and 2 were initially steroid dependant, frequent relapses and changed to resistant after 6 months and 3 years from the time of

Table 1 - Distribution of histopathological lesions in group A.

Histological lesion	All patients N (%) (N=46)	Biopsy specimens N (%) (N=20)
MCD-Bx	3 (6.5%)	3 (15%)
MCD-Pres	27 (58.7%)	0
FSGS	7 (15.2%)	7 (35%)
MesPGN	4 (8.7%)	4 (20%)
MPGN	6 (13.0%)	6 (30%)

N - number, MCD-Bx - biopsy proven minimal change disease, MCD-Pres - presumptive minimal change disease, FSGS - focal segmental glomerulosclerosis, MesPGN - mesangial prolifrative glomerulonephritis, MPGN - membranoprolifrative glomerulonephritis

Table 2 - Changes in histopathology in all patients, biopsies and presumptive diagnosis, between the period of 1983-1992 (132 patients) and 1997-2001 (46 patients).

Histological lesion	Years	Incidence N (%)	Z Value	P value
FSGS	1983-1992 1997-2001	7 (5.3) 7 (15.2)	16.00	<0.0001
MPGN	1983-1992 1997-2001	7 (5.3) 6 (13.0)	2.05	0.02
MesPGN	1983-2001 1997-2001	8 (6.0) 4 (8.7)		
MCD	1983-1992 1997-2001	105 (79.5) 30 (65.0)	2.02	0.02

N - number, MCD - minimal change disease (biopsy proven and presumptive), FSGS - focal segmental glomerulosclerosis, MPGN - membranoprolifrative glomerulonephritis, MesPGN - mesangial prolifrative glomerulonephritis

Table 3 - Changes in histopathology in biopsies performed between the period of 1983-1992 (42 biopsies) and 1997-2001 (20 biopsies).

Histological lesion	Years	Incidence N (%)	Z -value	P-value
FSGS	1983-1992 1997-2001	7 (16.7) 7 (35.0)	1.63	0.05
MPGN	1983-1992 1997-1992	7 (16.7) 6 (30.0)	1.18	1.2
MCD-Bx	1983-1992 1997-2001	15 (35.7) 3 (15.0)	15.00	<0.0001

N - number, FSGS - focal segmental glomerulosclerosis, MPGN - membranoprolifrative glomerulonephritis, MCD-Bx - biopsy proven minimal change disease.

Table 4 - Distribution of histopathology by ethnicity.

Histological lesion	All patients N (%) N=20	Arab N (%) N=15	Saudi N (%) N=7
FSGS	7 (35)	6 (40)	3 (42.5)
MPGN	6 (30)	6 (40)	3 (42.5)
MesPGN	4 (20)	3 (20)	1 (15.0)

N - number, FSGS - focal segmental glomerulosclerosis, MPGN - membranoprolifrative glomerulonephritis, MesPGN - mesangial prolifrative glomerulonephritis

first presentation. Twenty-two were frequent relapsers (61% of steroid sensitive patients) and 14 patients were infrequent relapsers. There was no difference in the percentage of initial steroid resistance between group A (17%) and group B (11%), Z value=1 and P=0.15. Cyclophosphamide was used in 11 children, 3 steroid resistant and 8 steroid dependent. All patients with SRNS had a renal biopsy before the cyclophosphamide and 6 of the steroid dependent patients (75%). All except one were found to have a non-minimal change histopathology.

Discussion. We have found an increasing incidence of FSGS in Arab children presented with INS over the last decade. Our results showed that FSGS was the most common histopathologic subtype in our patients who underwent renal biopsy in the recent years, compared to MCD in those who were biopsied between 1983 and 1992. This observation is similar to the previous reports from different parts of the world. Bonilla-Felix et al reported an increased incidence of FSGS in American children (23% before 1990 versus 47% after 1990), particularly in those from the African origin in whom FSGS was found to be the most common cause of NS.[9] Similarly, Srivastava et al found a higher incidence of FSGS in American children with reciprocal decline in the incidence of MCD in recent years.[14] Gulati et al reported an increased incidence of FSGS in Northern and Eastern Indian populations from 20% between 1990 and 1992 to 47% between 1992 and 1996.[10] Similar to the authors in the above series, we were careful to exclude any known secondary etiology of FSGS and believe that there is a true universal increase in the incidence. The increased incidence of FSGS in our study is in agreement with that reported in adult and pediatric populations from other countries.[7-14] There is no similar reported study in adult or pediatric populations from the Arab world.

In the 1980's AbdulRahman et al reported MesPGN as a frequent cause of non-minimal change NS in children from the central area of KSA and they reported FSGS as a rare cause.[15-16] In 1990 Mattoo et al reported the same observation on the same population.[17] However, they reported a high prevalence of FSGS (39%) in biopsies in children with NS. Al-Raheed et al reported FSGS to be the cause of childhood INS in 24% of the biopsies performed between 1982 and 1994 but they did not study the increased incidence of FSGS over the years.[18] Mitwalli et al found that FSGS was the most common glomerular disease in 186 biopsies in adult patients between 1989 and 1994.[19] Ethnicity seems to play a critical role in the epidemiology of NS. Minimal change nephrotic syndrome which is usually steroid responsive nephrotic syndrome (SSNS) is more common in Asian children with an annual incidence of 16 per 100,000 children,[20] compared to 2-7 per 100,000 European children per year.[21] While FSGS is more common in black children and the most common cause of NS in Africans and Americans,[9] the reported incidence in Arab children is variable between 6 and 11.6 per 100,000 population.[22-23] We have considered the effect of the mixed racial composition of our population in the increasing incidence of FSGS, however we have found a similar increasing incidence of FSGS in Arab patients and in Saudi patients when they were studied separately. The observed trend is unlikely to be caused by a change in the referral patterns, as there was no difference in the proportion of steroid resistance children in our patient populations over the 2 periods. Furthermore, the mean age of presentation over the recent years was smaller than those in group B, while FSGS patients had an older age at presentation. Our findings support the notion that there is a global trend of increasing FSGS incidence in childhood NS.[9-11] Unfortunately, as the etiology of FSGS is unknown, it is difficult to postulate a potential mechanism for this increasing incidence. Previous studies suggested that it could be secondary to environmental factors including infectious factors related to viruses, chemical exposure or many factors together.[9-11] We have found also an increasing incidence of MPGN in recent years. This observation is different from previous studies.[9-11,14] Membranoprolifrative glomerulonephritis is a rare cause of childhood INS,[24,3-4] we have found that 16.7% of the performed biopsy in group B and 30% in group A were MPGN.[5] This is in contrast to the paucity of MPGN as a cause of INS in other Saudis[16-18] and in international studies.[9-10] Furthermore the increasing incidence has not been reported before. Membranoprolifrative glomerulonephritis was reported as the predominant histological lesion seen in childhood nephrotic syndrome in Ibadan, Nigeria, where MCN remains a rare cause of NS.[25] Membranoprolifrative glomerulonephritis was found to be more prevalent (23%) than FSGS (19%) in the children with nephrotic syndrome in Auckland, New

Zealand.[26] The observed increase in MPGN in recent years could be explained by environmental factors such as antigen-driven mechanism: infective antigen as well as food or other allergens. Alternatively, genetic background could play a role, as all the MPGN patients in our study were Arabs in origin and familial MPGN was noticed in 2 families. Membranoprolifrative glomerulonephritis was most likely the cause of NS in the dead sibling as histopathological findings in siblings with familial NS show close to a 100% concordance rate.[27] Familial MPGN has been reported previously and genetic cause is the most likely predisposing factor in those families.[28-29] We have also observed that the age of presentation of MPGN was younger in our population compared to previous studies.[30,31]

In conclusion, there is an increasing incidence of FSGS and to a lesser extent, the MPGN in children presenting with INS in the western province of KSA. This changing trend of histopathologic patterns has profound prognostic significance. Our finding is in agreement with the recommendation of performing renal biopsies on children with INS who are steroid dependent,[9,11] in addition to those who are steroid resistant particularly before starting cytotoxic medications. This approach will be beneficial in the management of those patients and it will help to solve the mysteries of the disease processes involved.

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