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Frequency and clinicopathological correlations of histopathological variants of idiopathic focal segmental glomerulosclerosis in nephrotic adolescents

Shaheera Shakeel, Muhammed Mubarak, Javed Iqbal Kazi

Abstract

Objective: To determine the frequency and clinicopathological correlations of focal segmental glomerulosclerosis variants in adolescents with idiopathic nephrotic syndrome.

Methods: All consecutive adolescents (12 to 18 years) who presented with idiopathic nephrotic syndrome in the period, January 2009 to December 2012, and in whom the histological diagnosis of focal segmental glomerulosclerosis was made on renal biopsies, were included in this prospective study. Their clinical, laboratory and histopathological features at the time of presentation or biopsy were noted from the case files and the biopsy reports.

Results: Among 50 adolescents, 34 (68%) were males and 16 (32%) females. The mean age was 15.14±2.3 years. The mean duration of disease was 6.3±11.2 months. The mean serum creatinine was 0.96±0.82 mg/dl. The mean 24-hour urinary protein excretion was 3.8±0.68 grams. Biopsy indications were steroid-resistant nephritic syndrome in 15 (30%), steroid-dependant nephritic syndrome in 19 (38%) and adolescent nephritic syndrome in 16 (32%) cases. Among the focal segmental glomerulosclerosis variants, 40 (80%) were "not otherwise specified" , followed by the collapsing variant, which accounted for 8 (16%) cases. The tip and cellular variants, both were found in one (2%) case each. Among the histological features, global glomerulosclerosis was found in 23 (46%) cases, and segmental scarring/collapse in all (100%). A variable degree of tubular atrophy and interstitial fibrosis was noted in 44 (88%) cases.

Conclusion: The results from this study indicate that the pattern of focal segmental glomerulosclerosis variants differs markedly in adolescents compared with younger children.

Keywords: Adolescents, Focal segmental glomerulosclerosis, Nephrotic syndrome, Pakistan, Variants. (JPMA 64: 322; 2014)

Introduction

Primary or idiopathic focal and segmental glomerulosclerosis (FSGS) is increasingly being recognized as the leading cause of idiopathic nephrotic syndrome (INS) in both children and adults in many parts of the world.[1-6] Partly this increase is attributable to a real increase in the incidence of the disorder and partly due to heightened awareness of the lesion among the nephropathologists and the nephrologists. This quest for FSGS diagnosis is, in part, fuelled by the guarded prognosis of the condition in a significant number of affected patients. The rate of end-stage renal disease (ESRD) development approaches 78% over 20 years of follow up in children in some studies.[7,8]

On the morphological front, FSGS is not a single disease entity. Rather, it represents a heterogeneous group of morphological lesions caused by a bewildering variety of etiologic agents and unified only by the focal and segmental distribution of the pathology in the glomeruli.[9-14] The clinical course and prognosis of the lesion is equally heterogeneous and affected largely by the underlying etiology and to some extent by the histological features. Numerous clinicopathological studies of the condition in both children and adults have helped understand the clinicopathological correlations of the disease and identify histological variants with different prognostic implications. The lesions are also heterogeneous even in a single biopsy, necessitating a hierarchical approach to the classification of the variants, popularly known as Columbia classification.[9] For example, if the collapsing lesions are present on a renal biopsy, the variant is classified as collapsing type, even if other lesions are present.

Many studies have been conducted on the clinicopathological correlations, clinical course and prognosis of the Columbia variants of primary FSGS in adults.[10-14] A few studies have been reported in children also, including one by our group.[15-19] But there is no such study specifically addressing the issue of FSGS variants in adolescents. We and others have already reported significant differences in the pattern of glomerulopathies

Department of Histopathology, Sindh Institute of Urology and Transplantation (SIUT), Karachi, Pakistan.

Correspondence: Muhammed Mubarak. Email: drmubaraksiut@yahoo.com

in adolescents as compared with young children but the studies on FSGS variants in adolescents are entirely lacking.[20-25]

We undertook this study primarily to determine the relative frequencies of different histologic variants of FSGS in adolescent age group presenting with idiopathic nephritic syndrome (INS) at our center and to compare these with young children. We also aimed to seek the clinicopathological correlations of these variants in adolescents. Moreover, we have also compared our findings with those already reported from different parts of the world.

Material and Methods

This study was conducted from January 2009 to December 2012 at the department of Histopathology, Sindh Institute of Urology and Transplantation (SIUT). All consecutive adolescent age group children (12 to 18 years) who presented with INS at paediatric nephrology outpatients department of SIUT and in whom the histological diagnosis of FSGS was made on percutaneous ultrasound guided native renal biopsies, were included in the study. The biopsies were studied in a standardized approach using light microscopy (LM), immunoflourescence (IF) and electron microscopy (EM) as described in detail in our preceding papers.[6] Cases with known etiology of segmental glomerulosclerosis, like lupus nephritis or IgA nephropathy (IgAN) were excluded. The clinical and laboratory parameters of the cohort at the time of presentation were recorded from the case records. The histopathological features, IF observations and final diagnosis were recorded from the original renal biopsy request forms. The standardized definitions of NS, steroid response, renal failure at the time of presentation and last follow-up and remission were used as in our previous studies.[6,20] The histopathological diagnosis and features were also noted using standardized definitions and approaches.[14] Renal biopsy diagnosis was made by two experienced nephropathologists (MM, JIK), first independently and then jointly to arrive at a consensus diagnosis. The frequency of histopathological variants of FSGS in this age group was also compared with 104 young children (1 to 11 years) with FSGS who presented at our center during the same study period.[19] The research was conducted according to the tenets of Declaration of Helsinki. Written informed consent was taken from the patients or parents for the biopsy procedure and for inclusion in the study.

Statistical Analysis

Data were analyzed using the IBM compatible SPSS for Windows version 19.00 (SPSS, Chicago, IL, USA). Descriptive statistics such as mean ± standard deviation (SD) or median and range were used for continuous variables such as age and laboratory data. Numbers (percentages) were used to describe the proportion of categorical variables such as sex and the frequency of histological variants. The statistical analysis was carried out using x^2 or Fisher's exact test, as appropriate, to determine the association of various clinical and pathological parameters with the morphological variants of FSGS. A p-value of ≤ 0.05 was considered significant.

Results

The main demographic, clinical and laboratory data are shown in Table 1. A total of 50 adolescent patients were included in this study. There were 34 (68%) males and 16 (32%) females. The indication of biopsy was steroid-resistant nephrotic syndrome (SRNS) in 15 (30%), steroid-dependant nephrotic syndrome (SDNS) in 19 (38%) and adolescent NS in 16 (32%) cases. It is to be noted that the majority of adolescents who were given steroids belonged to the younger age group (12-15 years) and were treated for variable periods of time before performing a renal biopsy. The mean age of the patients

Table-1: The main demographic, clinical and laboratory characteristics of 50 adolescents with different FSGS variants at the time of presentation or biopsy.

	NOS (n=40)	Collapsing (n=8)	Tip (n=1)	Cellular (n=1)	Total (n=50)
Mean age (years) at time of biopsy	15.4±2.3	16.6±2.2	15	14	5.14±2.3
Range in years	(12-18)	(12-18)	15	14	(12-18)
24-hr urinary proteins	3.59±0.6	4.56±0.4	3.57	4.13	3.76±0.68
Haematuria, %	25	62.5	0	0	30
Family history of renal disease, %	22.5	25	0	0	22
Disease duration (mon)	6.8±12.1	2.75±4.7	17.2	0.67	6.3±11
Mean Systolic BP (mmHg)	117±10	121±11	100	110	117±11
Mean Diastolic BP(mmHg)	77.5±9.5	80.6±8.1	70	80	77.9±9.7
Mean Serum creatinine (mg/dl)	0.9±0.6	1.2±1.4	0.6	0.4	0.9±0.8

NOS = not otherwise specified.

Table-2: Relative frequency distribution of FSGS variants in 50 adolescents and its comparison with young children at our center.[19]

Variants	Adolescents (n=50)		Young children (n=104)	
	Numbers	%	Numbers	%
NOS	40	80	97	93.2
Collapsing	8	16	5	4.8
Tip	1	2	1	0.96
Cellular	1	2	0	-
Perihilar	-	-	1	0.96

NOS = not otherwise specified.

Table-3: The main histopathological characteristics on renal biopsies in 50 adolescent patients according to FSGS variants.

	NOS (n=40)	Collapsing (n=8)	Tip (n=1)	Cellular (n=1)	Total (n=50)
No. of glomeruli	13.7±5.7	11.7±3.6	9.0	16	13.3±5
GS, (%)	45	50	100	0	46
Mean GS,	1.25±1.88	1.0±1.4	2.0±0	0	1.2±1.7
SS, (%)	100	100	100	100	100
Mean SS	2.9±2.5	2.8±1.3	2.0	1.0	2.8±2.3
Mesangial proliferation (%)	52.5	37.5	100	100	52
Vasculopathy (arteriolar hyalinosis (%)	7.5	0	0	0	6
Tubular atrophy/interstitial fibrosis (%)					
Mild	67.5	0	100	100	58
Moderate	17.5	87.5	0	0	28
Severe	0	12.5	0	0	2

GS, global glomerulosclerosis, NOS, not otherwise specified, SS, segmental glomerulosclerosis.

at the time of biopsy was 15.14±2.3 years. The median duration of symptoms from presentation to biopsy was 1.33 years (range: 0.13 to 50.77). The clinical parameters recorded at the time of presentation and last follow up were serum creatinine, blood pressure, urinary proteins and haematuria. The mean serum creatinine at the time of presentation was 0.96±0.62mg/dl and at last follow up was 1.40±1.64mg/dl. The mean systolic blood pressure at the time of presentation was 117.2±10.05mmHg and at last follow up was 119.8±12.2mmHg. The mean diastolic blood pressure at the time of presentation was 77.5±9.5mmHg and at last follow up was 77.9±7.8 mmHg. The mean 24-h urinary proteins at the time of presentation were 3.59±0.68 grams and at last follow-up, persistent variable degree of proteinuria was found in 40 (80%) cases. Haematuria was detected in 15 (30 %) cases at presentation and was persistent in 8 (16 %) cases at last follow-up. Family history of renal disease and failure was noted in 11 (22%) patients.

The mean duration of follow-up from presentation of disease to the last visit recorded in all adolescents was 27.1±19.9 months, and from the time of biopsy to last visit, 26.2±19.2 months. Only two patients developed ESRD during this follow-up period and both belonged to FSGS, "not otherwise specified" (NOS) group. We did not analyze the prognostic factors because of extremely small number of children reaching ESRD over this period. Notably, all patients with FSGS, collapsing variant, were able to maintain their renal functions within normal range during this period.

Among the histologic variants, majority of cases (40; 80%) fell in the category of FSGS, not otherwise specified (NOS) variant, followed by the collapsing variant, which accounted for 8 (16%) cases. The tip and cellular variants, both were found in one (2%) case each, as shown in Table 2, which also shows the distribution of FSGS in younger children. The mean number of glomeruli included was 13.34±5.4 per biopsy specimen. Among the histologic features, global glomerulosclerosis was found in 23 (46%) cases, segmental scarring was found in all (100%) cases and mesangial proliferation was noted in 26 (52%) cases. Arteriolar hyalinosis was observed in only 3 (6%) cases. In the tubulointerstitial compartment, a variable degree of tubular atrophy and interstitial fibrosis (IF/TA) was noted in 44 (88%) cases. The main histopathological features on the biopsies are shown in Table 3.

We also carried out statistical association analysis of the various clinical and laboratory parameters with the morphological variants. Our results showed that there was no significant association among the morphological variants with urinary protein excretion ($p < 0.23$), duration from presentation to biopsy ($p< 0.15$), serum creatinine at the time of presentation ($p <0.99$), age at the time of biopsy ($p < 0.35$), sex ($p < 0.24$) and indication of biopsy ($p < 0.15$). Among the histologic features, no association was found between global glomerulosclerosis and all parameters including age, sex, indication, urinary protein, serum creatinine and disease duration ($p < 0.59$, 0.64, 0.43, 0.71, 0.09 and 0.30 respectively). No association was observed among segmental glomerulosclerosis and all above mentioned parameters except the disease duration ($p < 0.02$). No association was found among mesangial proliferation and all clinical parameters in the previously given order ($p < 0.30$, 0.48, 0.07, 0.47, 0.37 and 0.95 respectively). Vasculopathy and tubular atrophy (TA) also showed no significant association with all clinical parameters (vasculopathy: $p < 0.46$, 0.22, 0.30, 0.73, 0.61 and 0.37 respectively and TA: $p < 0.89$. 0.64, 0.66, 0.16, 0.80, and 0.85 respectively). It is possible that the above lack of association is due to relatively small number of cases, overall, and in some variants, particularly.

Discussion

This study, to the best of our knowledge, is the first in literature to analyze the relative frequencies and clinicopathological correlations in adolescents with INS and a timely contribution to the literature on the histological variants of FSGS from this part of the world. Numerous studies conducted during the past two decades have noted a marked rise in the incidence of FSGS in both children and adults.[1-6] Coupled with this rise, there is also increased interest in identifying and classifying FSGS, into the Columbia types, as these are thought to have prognostic implications.[9] Most of the studies on FSGS variants have been conducted on adult patients.[10-14] Only a few studies are available in literature, which have looked into the prevalence of FSGS variants, specifically in children.[15-19] The later studies have included all the children and none has analyzed the adolescent age group separately from the younger children.

In contrast, this study is focused on the distribution of FSGS variants in adolescent age group children. Previously, we[20] and others[21-25] have shown that the pattern of glomerulopathies in adolescents is significantly different from that observed in their younger counterparts. Other authors have shown that the glomerular lesions in this population resemble more closely the pattern observed in adults rather than in younger children.[25] However, the issue is still far from completely resolved.

It is well known that age, along with other factors constitutes the risk factor for certain glomerulopathies including FSGS and their impact on renal survival.[7,8] This led us to hypothesize that the distribution of FSGS variants may also be different in adolescents compared with younger children. The findings of our current study do support the above hypothesis. The relative frequency of FSGS is markedly higher (16%) in adolescents as compared with younger children.[19] However, the numbers of adolescents or young children with variants of FSGS other then NOS and collapsing are very small. Hence, the conclusions about the significance of differences in other variants may not be entirely valid. Future studies of large size and longer duration with follow up information will help in clarifying the picture.[19]

There was no significant association of the clinical or laboratory parameters with either the pathological parameters or the morphological variants of FSGS in this study cohort. The only significant association was found between the duration of symptoms and the segmental scarring on renal biopsy. This lack of correlation may partly be due to the relatively small number of cases in many variants.

We acknowledge that there are certain limitations in our study, such as its origin from a single center, biopsy indications confined to nephrotic children, and little information on the treatment, clinical outcome, and renal survival, and the relatively short period of follow-up. Despite these shortcomings, this is the first and the largest study on the pathological variants of FSGS in adolescents in literature and we are of the view that this study provides important insights into the presenting clinicopathological features and prevalence of the different variants of FSGS in the adolescent population from Pakistan.

In conclusion, our results show that FSGS, NOS is the most prevalent variant among nephrotic adolescent patients in Pakistan. Collapsing variant is found in a small but significant number of adolescents, while the remaining variants are very rare. The relative frequency of FSGS variants differs markedly in adolescents compared with younger children. Further long-term follow-up studies are needed to determine the impact of these variants on renal survival and clinical outcome in this particular age group.

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