Original Article

The Spectrum of Focal Segmental Glomerulosclerosis from Eastern India: Is It Different?

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Abstract

Focal segmental glomerulosclerosis (FSGS) is a disease that is defined entirely by its histopathological appearance. The recent Columbian classification has grouped this disease into various types based on the light microscopic description. There is a paucity of data describing the distribution of its various subtypes from the Indian subcontinent. This study was undertaken with the aim to throw light on the epidemiology and clinical features of primary FSGS in Eastern India. This retrospective study includes our cohort of biopsy-proven FSGS who presented to us from June 2009 to July 2011 and the analysis of their presenting clinical and histopathological features from our center in East India. Out of 347 patients diagnosed with FSGS in this period, 224 patients were included in the study. A total of 167 cases were of not otherwise specified (NOS) variant (74.5%), 30 tip variant (13.39%), 14 perihilar (6.25%), 8 cellular (3.57%), and 5 to the collapsing variant (2.23%). The maximum proteinuria at presentation was seen with the tip variant (7.98 ± 6.6 g/24 h), and the renal functions were most deranged at presentation with the collapsing variant. These findings were different from those described in other populations including higher prevalence of the tip and the perihilar variant, significant difference in the degree of hypertension, proteinuria, and renal dysfunction among the different variants. The Columbian classification has helped to stratify the outcomes of this glomerular disease with respect to its clinical presentation as well as histopathological features. However, the characteristics of the various variants do show a distinctive pattern in various populations based on ethnicities.

Keywords: *Columbia classification, focal segmental glomerulosclerosis, Eastern India*

Introduction

Focal segmental glomerulosclerosis (FSGS) is a histopathological diagnosis, characterized by segmental sclerotic lesions. This disease has come a long way from its initial description by Fahr and Rich to the present day redefined and standardized pathological classification system based entirely on the light microscopy (LM) features (Columbian classification).[1-6] There have been various retrospective studies which have shown the varying distribution of the subtypes of FSGS as well as the clinical presentations and outcomes with regard to different ethnic cohorts.[7-11] Where most studies have described the Caucasian, Afro-American, and the European cohorts, there has been a paucity of data regarding this disease entity from the Asian continent, especially the Indian subcontinent. With the aim to gain better insight into the prevalence and clinical features of primary FSGS in the Indian population, we have retrospectively analyzed our cohort of 224 patients and compared their clinical and pathological spectrum.

Materials and Methods

This was a retrospective analysis of patients who had presented to our center from June 2009 to June 2011 and had focal and segmental glomerulosclerosis on kidney biopsy.

The cases included had no history or other conditions to suggest secondary features. The renal biopsies were confirmed by the same renal pathologist and were processed for LM and immunofluorescence (IF) before being categorized into one of the five subtypes according to the Columbian classification.[2] LM was carried out using hematoxylin and eosin, periodic acid-Schiff, Silver Jones, and trichrome stains. IF was carried out using polyclonal FTIC antibodies to IgG, IgA, IgM, C3, C1q, kappa, and Lambda chain and graded

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as per the intensity of staining from 0 to 3. Furthermore, the interstitial fibrosis and tubular atrophy (IFTA) was quantified as mild, moderate, or severe depending on the involvement of the core tissue <25%, 25%–50%, and >50%, respectively. A minimum of five glomeruli in the LM section was required for inclusion in the study. This number was chosen for a better comparison with previous studies by Chun *et al*.[8] The clinical records of all the cases were reviewed and relevant baseline demographic, clinical, and laboratory information was retrieved. The information included the gender, age, blood pressure, protein quantification, creatinine and estimated glomerular filtration rate (eGFR), serum albumin, urine routine examination, and serum cholesterol at presentation. The eGFR was calculated using the modified diet in renal disease study equation in patients ≥18 years of age and by the Schwartz equation in those <18 years of age.

Patients in whom complete data at presentation or those who had an inadequate sample (<5 glomeruli) on renal biopsy or showed features of FSGS due to a secondary disease were excluded.

Data have been expressed as mean ± standard deviation or where indicated as median and ranges according to the variables. Chi-square test, Mann–Whitney U-test, and Kruskal–Wallis tests were applied as per requirement. $P < 0.05$ was considered statistically significant. All analyses were done using SPSS® software version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Out of 347 patients diagnosed with FSGS in this period, 224 patients were included in the study. A total of 167 cases were not otherwise specified (NOS) variant (74.5%), 30 tip variant (13.39%), 14 perihilar (6.25%), 8 cellular (3.57%), and 5 collapsing variant (2.23%). Details of demography and clinical presentation has been shown in Table 1. The mean age of presentation was the oldest in the collapsing variant predominantly younger in perihilar variant. There was no statistically significant difference among the different variants with regard to pediatric and adult population, gender distribution, nephrotic presentation, the presence of hypertension or hematuria, and the need for dialysis at the onset. However, the mean systolic and diastolic blood pressures were significantly higher in the collapsing variant followed by the NOS and tip variant. A similar statistically significant trend was seen in the presence of renal dysfunction (eGFR <1 ml/s/m^2) with 100% of the collapsing variant cases being involved. The eGFR at presentation was worst in the collapsing variant followed by the NOS and the tip variants ($P = 0.04$) [Table 2]. The mean presenting proteinuria was maximum in the tip variant (8 g) followed by the NOS variant (6 g). In contrast, the collapsing variant showed a lesser proteinuria (3.5 g). There was no statistical difference among the groups with regard to serum albumin and serum cholesterol. The mean number of glomeruli for evaluation by LM was 18 (range 5–43). Other details of histopathological parameter are shown in Table 3. The complete absence of IF was seen in 79% of patients. Segmental trapping of IgG, IgM, and C3 together was seen in 4.9% of patients and isolated IgM and C3 was seen in 8.48% and 2.23% of patients, respectively. IF of the biopsies did not show any statistically significant difference in staining patterns in different variants.

Discussion

In the present study, we have attempted to analyze the clinicopathological spectrum of our cohort of FSGS patients and categorized them in the lines of Columbian classification.[6] The frequency of variants compared in Indian, Chinese, Dutch, and multiethnic groups is

Table 1: Comparison between different focal segmental glomerulosclerosis variants based on demographic and initial presentation

Factors	Total	Histological variants					*P*
		NOS (%)	Tip variant (%)	Perihilar (%)	Cellular (%)	Collapsing (%)	
Number of patients	224	167 (74.5)	30 (13.3)	14 (6.25)	8 (3.57)	5 (2.23)	
Age (years)	28.0±16.6	28.4±16.3	33.2±15.1	13.2±18.8	20.6±10.6	33.8±20.2	0.02
Male: female	1.4:1	1.5:1	1.3:1	0.7:1	0.6:1	1:0	0.15
Onset of disease (years)							
<18	63	42 (25)	6 (20)	10 (71)	5 (62.5)	0	0.11
≥18	161	125 (75)	24 (80)	4 (29)	3 (37.5)	5 (100)	
Nephrotic presentation	197	148 (89)	26 (87)	13 (93)	5 (63)	5 (100)	0.2
Hematuria	95	71 (43)	11 (37)	2 (14)	8 (100)	3 (60)	0.76
Hypertension	96	74 (44)	12 (40)	2 (14)	3 (38)	5 (100)	0.3
Systolic BP (mmHg)	122.3±27	124.8±27.7	124.2±19	79.6±15.9	111.2±24.1	136±21.3	0.0001
Diastolic BP (mmHg)	77.1±15	78.9±15	77.3±13.3	53.3±9.8	71.2±15.5	78±10.9	0.0001
Renal dysfunction	117	89 (53)	16 (53)	2 (14)	3 (38)	5 (100)	0.03
Need for Dialysis	11	9 (5)	2 (7)	0	0	0	0.79

NOS: Not otherwise specified, BP: Blood pressure

shown in Table 4. It is obvious that while collapsing variant is seen much less frequently (range 2%–6.9%) in non-Afro-American ethnicities, the tip variant is seen much more commonly. Both the series from India including the present study and the study by Nada *et al*.[12] show similar patterns of distribution of various subtypes of FSGS, with the most common variant being the FSGS NOS followed by the tip variant. In contrast, the series by Silverstein and Craver, which had a predominant Afro-American population showed a complete absence of the tip variant and the perihilar variant and a relatively high prevalence of the collapsing subtype (24%), which is in accordance with various previously mentioned studies.[5,8,9,13]

The other difference seen in our population was the prevalence of the tip variant and the perihilar variant. The tip variant was seen as commonly as in 32% of patients in the Dutch cohort as compared to our population (13%).[11] The perihilar variants have been described in the Dutch population as well as the multiethnic cohort of Thomas *et al*. to be as high as 26%. However, we had a much lesser prevalence of this subtype (6.2%) in our cohort.[9,11] Despite exclusion of secondary FSGA in all the studies including ours, we still had a much lesser incidence of peri-hilar variety. Furthermore, we had a very small percentage of patients belonging to the cellular variant (3%), which again was in contrast to the prevalence of this subtype in the

Table 2: Comparison between different focal segmental glomerulosclerosis variants based on initial laboratory parameters

Parameters	Total cohort	Histological variants					*P*
		NOS	Tip variant	Perihilar	Cellular	Collapsing	
Serum creatinine (μmol/L)	1.55±1.09	1.58±1.09	1.44±0.61	0.69±0.47	1.57±1.22	2.89±1.0	0.9
Average eGFR (ml/min/m^2)	54.49±23.9	55.08±24.5	50.89±21.5	67.6±16.7	49.7±28.1	28.7±10.17	0.04
Serum albumin (g/L)	19.8±5.5	19.9±5.5	1.94±0.53	17.6±3.2	20.5±7.9	18.4±3.2	0.95
Serum cholesterol (mmol/L)	8.9±2.7	9.09±2.57	8.28±2.72	9.97±4.32	7.86±1.91	7.34±1.19	0.20
24 h urine protein (g/day)	5.86±3.78	5.89±3.14	7.98±6.6	3.7±0.63	3.42±0.66	3.54±0.07	0.0001

eGFR: Estimated glomerular filtration rate, NOS: Not otherwise specified

Table 3: Comparison between different focal segmental glomerulosclerosis variants based on histopathology

Features	Histopathological variants of FSGS on renal biopsy					*P*
	NOS	Tip variant	Perihilar	Cellular	Collapsing	
Number of patients (%)	167 (74.5)	30 (13.39)	14 (6.25)	8 (3.57)	5 (2.23)	
Average number of glomeruli	18±8	18±8	23±7	19±8	22±8	0.11
Glomerular (percentage of total glomeruli)						
Global sclerosis (%)	12.7±17.8	5.9±13.9	11.1±20.7	0	7.8±7.1	0.007
Segmental sclerosis (%)	24.5±18.1	25.7±26.8	18.6±13.1	18.8±10	22.6±17.4	0.75
Involved glomeruli (%)	37.4±25.5	31.6±34.8	30±23.9	18.8±10	30.4±17.5	0.05
Vascular (%)						
Mild	24 (14.37)	0	0	0	0	0.02
Moderate	11 (6.5)	2 (6.6)	0	0	0	
Severe	5 (2.9)	1 (3.3)	0	0	0	
Tubulointerstium (%)						
No IFTA	116 (69.4)	26 (86.66)	12 (85.71)	8 (100)	3 (60)	0.04
<25% IFTA	28 (16.76)	3 (10)	2 (14.28)	0	2 (40)	
25%-50% IFTA	21 (12.57)	1 (3.33)	0	0	0	
>50% IFTA	2 (1.1)	0	0	0	0	
Acute tubular injury (%)	13 (7.7)	2 (6.66)	0	0	0	0.68

FSGS: Focal segmental glomerulosclerosis, IFTA: Interstitial fibrosis and tubular atrophy, NOS: Not otherwise specified

Table 4: Comparative prevalence of various variants of focal segmental glomerulosclerosis in different ethnicities

Variant	Present (%)	Nada (%) India	Shi (%) Chinese	Thomas (%) Multiethnicity	Deegan (%) Dutch	Silverstein (%) Afro-American
NOS	74.5	72.5	55.9	42	32	44
Tip	13.3	13.5	4.8	17	37	0
Cellular	3.57	8	25.5	3	0	32
Perihilar	6.25	4	6.9	26	26	0
Collapsing	2.23	2	6.9	11	5	24

NOS: Not otherwise specified

Chinese and the Afro-American cohorts which showed it to be 25% and 32%, respectively.[13,14] However, on the whole, the other cohorts showed a relatively rare prevalence of this subtype ranging from 0% to 8%. The two studies from Asian cohorts (Indian and Chinese) and our study re-emphasize the fact that the study population affects the prevalence of various variants.[13-16]

The collapsing and the tip variant of FSGS have been described to be seen more commonly among the teenagers and adults as compared to children.[8-10,15] However, out cohort had a majority of adult population. This finding suggests that NOS patients may have had longer duration of FSGS, perhaps owing to subclinical disease, correlating with their higher prevalence of subnephrotic proteinuria.[15]

A varying degree of hypertension was also documented among the variants [Table 1], and the difference between the degree of hypertension between variants was statistically significant ($P = 0.0001$). Thomas *et al*. also have described a significant difference in the degree of hypertension between different variants.[9] In their series, the percentage of hypertensive patients was more in perihilar and NOS (80% each) and least in tip variant (54% cases) ($P = 0.05$), while in other studies, the difference was not significant.[8,10] We also have collapsing and the NOS variant showing the highest blood pressures, and the perihilar variant least blood pressures. In the present study, a majority of the cases were males (M:F = 1.4:1). The male:female ratio in various variants ranged from 1.5:1 in NOS variant to 1:0 in collapsing variant. However, the difference in the sex ratio between variants was statistically not significant, as is documented in the literature.[8-10] The average serum creatinine at the time of biopsy was 1.56 ± 1.1 mg/dl with the highest levels seen with collapsing variant and the lowest in the perihilar variant, but the difference between variants was not statistically significant ($P = 0.9$). In other studies, average serum creatinine level varied between 2 and 2.5 mg% with highest levels in collapsing as in the present study; however, it was lowest in the tip variant.[8-10] The average 24 h urine protein excretion rate was 5.86 ± 3.78 g/day. The degree of proteinuria was highest in patients of tip variant (7.98 ± 6.6 g/day) and lowest in patients with cellular variant (3.42 ± 0.66 g/day). The comparison between different variants for the degree of proteinuria was statistically significant ($P = 0.0001$). This is in contrast with the study by Thomas *et al*.[9] where the degree of proteinuria was highest in patients of cellular, collapsing, and tip variants (16 ± 15, 10 ± 5.3, 9.7 ± 7 g/day, respectively) and lowest in patients with perihilar variant (4.4 ± 3.3 g/day). In the series by Deegens *et al*.,[11] highest proteinuria was in collapsing and tip variants (10.4 ± 6.7, 10.0 ± 5.7 g/day, respectively) and lowest in patients with perihilar variant (5.2 ± 2.6 g/day). Shi *et al*.[14] also observed that the level of proteinuria in cellular and tip variants was much higher than NOS. Nada *et al*.[12] reported the highest proteinuria in patients of collapsing variant (6.17 ± 4.67 g/day) and lowest in patients with perihilar variant (1.94 ± 0.94 g/day).

Hematuria at presentation was seen most commonly in the collapsing and cellular variants in 42% of patients. The other study from the Indian subcontinent showed the presence of hematuria only in 26.7% of patients and was also most commonly seen in the cellular variant. In the study by Stokes *et al*., the tip variant showed the hematuria in 58%, and in the study by Nada *et al*., it was seen in 20.8% of patients.[10,12] However, our cohort of tip variant showed hematuria in 37% of patients, and the difference in the presence of hematuria was not statistically significant among the various variants ($P = 0.76$).

The availability of electron microscopy reports would have helped us to interpret the data better but was unavailable due to economic constraints. This was a limitation of this study.

Conclusion

Our population showed the in FSGS, NOS was the most common variant followed by the tip variant. Collapsing FSGS was uncommon in our population. Further, the characteristics of the various variants do show a distinctive pattern in various populations based on ethnicities.

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Conflicts of interest

There are no conflicts of interest.

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