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Original Article

Internal Medicine Section

Clinicopathological Outcomes in Focal Segmental Glomerulosclerosis: A Retrospective Cohort Study

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ABSTRACT

Introduction: Focal Segmental Glomerulosclerosis (FSGS) is a nephrotic syndrome with a variety of clinicopathological presentations and varied responses to treatment. Hence, this study attempts to classify FSGS based on clinical presentation and pathological findings on kidney biopsy, which is essential for appropriate treatment and avoidance of inappropriate use of immunosuppressants.

Aim: To analyse clinicopathological findings and responses to immunosuppressants in FSGS.

Materials and Methods: A retrospective cohort study was conducted at Department of Nephrology, Vydehi Institute of Medical Sciences and Research Centre Bengaluru, Karnataka, India, to analyse clinicopathological parameters such as urine analysis, 24-hour urine protein, serum creatinine, serum albumin, lipid profile, renal biopsy details, and response to treatment in 97 patients. The study was planned, analysed, and executed between January 2023 and February 2023. All variables were expressed as mean±standard deviation or percentage. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) software version 16.0.

Results: Among a total of 97 patients, 64% were males. Sudden onset oedema was observed in 90% of the cases, while nephrotic proteinuria was seen in 71%. The Not Otherwise Specified (NOS) variant was noted in 60% of the cases. Complete remission was observed in 61%, suggesting a possible primary FSGS. Persistent nephrotic proteinuria with a poor response to therapy was noted in 32%, indicating a possible secondary/genetic FSGS, despite adequate immunosuppressive therapy. Therefore, differentiating between primary and secondary forms of FSGS has therapeutic and prognostic implications. Accurate diagnosis of each form of FSGS is vital to avoid unnecessary immunosuppressive-based therapy and establish appropriate treatment.

Conclusion: Resistance to steroid therapy was observed in one-third of FSGS patients. It is likely that unrecognised genetic FSGS or secondary FSGS were included among the study group of primary FSGS, leading to misinterpretation of treatment responses in primary FSGS. Hence, a clinicopathological approach for correctly differentiating between primary FSGS, secondary (maladaptive, viral, or toxic) FSGS, and genetic FSGS helps in making correct treatment decisions.

Keywords: Immunosuppressives, Nephrotic syndrome, Secondary

INTRODUCTION

The FSGS, which causes nephrotic proteinuria, is a spectrum of glomerular injury caused by various primary and secondary clinicopathological entities, each with different mechanisms of injury to the visceral epithelial cell podocyte. This leads to focal and segmental sclerosis in the glomeruli [1,2]. The incidence of FSGS is 1.2 to 1.5 times higher in men than in women [3,4]. Unlike primary FSGS, the genetic and secondary forms do not respond to immunosuppression [5]. In adults, responsiveness to steroids usually takes up to 16 weeks [6]. Differentiating the primary entity from the genetic and secondary entities has clinical and prognostic significance and prevents the use of inappropriate immunosuppressive treatment in non primary FSGS [1,2,7].

Light microscopy can diagnose the pattern of injury but cannot completely differentiate between primary and secondary forms [2]. Electron microscopy and genetic studies are required, but they are not easily accessible [2,5]. Currently, there is no 'gold-standard' biomarker that reliably identifies different subtypes of FSGS. Therefore, a combination of clinical, laboratory, and morphological features can be used to stratify patients until such biomarkers become available [2,8].

Hence, the present study aims to analyse the clinicopathological findings and the response to immunosuppressants in FSGS. This analysis is crucial for appropriate treatment, avoiding the inappropriate use of immunosuppressives, and also for conducting further therapeutic trials in FSGS [2-4,8].

MATERIALS AND METHODS

This retrospective cohort study was conducted at Department of Nephrology, Vydehi Institute of Medical Sciences and Research Centre Bengaluru, Karnataka, India, with an economical, service-oriented centre that provides nephrological services, including renal transplantation. The study was planned, analysed, and executed between January 2023 and February 2023. Institutional Ethics Committee approval was obtained with the IEC No: VIEC/2023/APP/003.

Inclusion and Exclusion criteria: Medical files of adult and adolescent patients (aged 13-60 years) with all types of biopsy-proven FSGS during the period from July 2011 to June 2022 were included in the study. All patients were treated with oral prednisolone for 24 weeks, with atleast six months of follow-up. Patients who did not receive steroid therapy, had poor compliance with drugs, or had follow-up for less than six months were excluded.

Study Procedure

Demographic profiles and laboratory parameters, such as urine analysis, 24-hour urine protein, serum creatinine, serum albumin, and lipid profile at the onset of the disease, as well as renal biopsy details, were analysed. The diagnosis of FSGS was made based on light microscopy and immunofluorescence.

Primary FSGS is caused by circulating permeability factors such as Serum Urine-like Plasminogen Activator Receptor (SuPAR), apoA1b, cardiotrophin-like cytokine factor, anti-CD40 antibody,

and Calcium/Calmodulin-serine Protein Kinase (CASK) that lead to podocyte foot process effacement. Secondary forms are due to maladaptive FSGS caused by glomerular hyperfiltration, such as in obesity or loss of nephron mass, and direct nephron toxicity in virus or drug-induced FSGS leading to podocyte injury. Genetic FSGS, due to mutations in various podocyte proteins, is diagnosed through careful evaluation in atypical primary or secondary FSGS [2].

FSGS was classified into five variants: collapsing variant, perihilar variant, maladaptive FSGS, tip variant, cellular variant, and the most common variant, Classic (NOS) variant [1]. Normal serum creatinine was defined as less than 1.4 mg/dL, and renal insufficiency was defined as greater than 1.4 mg/dL [9]. Nephrotic range proteinuria was defined as greater than 3.5 g/24 hr/1.73 m^2, and subnephrotic proteinuria was defined as less than 3.5 g/24 hr/1.73 m^2 of body surface area. Haematuria was defined as greater than five Red Blood Cells (RBCs) per high-power field. Hypertension was defined as Systolic Blood Pressure (SBP) greater than 140 mmHg or Diastolic Blood Pressure (DBP) greater than 90 mmHg [9].

All patients were started on oral prednisolone at a dosage of 1 mg/kg/day and continued for six months. The dosage was then tapered and stopped within one month. In patients who showed intolerance to steroids, the steroid dosage was reduced to 0.5 mg/kg/day. At the end of the study period, the response to therapy was classified as follows: 1) Complete remission (urine protein less than 200 mg/24 hrs); 2) Partial remission (urine protein greater than 200 mg/24 hrs but less than 3.5 g/24 hrs or a decrease in proteinuria of more than 50% from baseline); 3) No response (persistent proteinuria greater than 3.5 g/24 hrs); and 4) Chronic Kidney Disease (CKD)-CrCl <60 mL/min/1.73 m^2 after three months [6,10].

If there was no response to steroids at six months, patients were started on second-line drugs, which included oral cyclophosphamide or Calcineurin Inhibitors (CNI) like Cyclosporine A (CSA) or tacrolimus. All patients received the maximum tolerable dose of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

STATISTICAL ANALYSIS

All variables were expressed as mean±standard deviation or percentage. The statistical analysis was performed using SPSS software version 16.0.

RESULTS

A total of 97 patients were included, with a mean follow-up of two years. Approximately 63 (64%) were males, resulting in a male-to-female ratio of 1.9:1. The predominant age group comprised individuals between 25 and 50 years, accounting for 54% of the total patients. The most common symptom was sudden onset oedema, and the most frequent laboratory finding was nephrotic proteinuria, as shown in [Table/Fig-1].

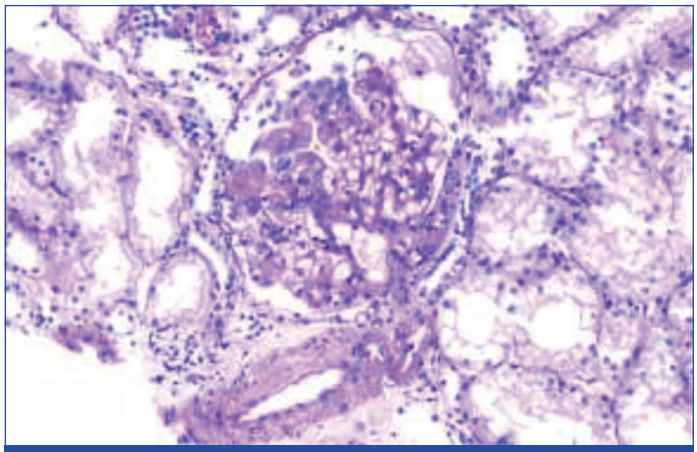
Parameters	Number (n)	Percentage (%)
Total patients	97	-
Gender distribution		
Male	63	64
Female	34	35
Age distribution		
<25 years	19	19
Predominant age group (25-50 years)	53	54
>50 years	25	25
Co-morbidities distribution		
Diabetes mellitus	4	4
Hypertension	8	8
Clinical features distribution		
Sudden onset oedema	88	90
Slow onset oedema	9	9
Renal failure	18	18
Nephrotic proteinuria	69	71
Microhaematuria	14	14
Subnephrotic proteinuria	29	29
Hypoalbuminaemia	71	73
Hypercholesterolaemia	70	72

[Table/Fig-1]: Baseline characters.

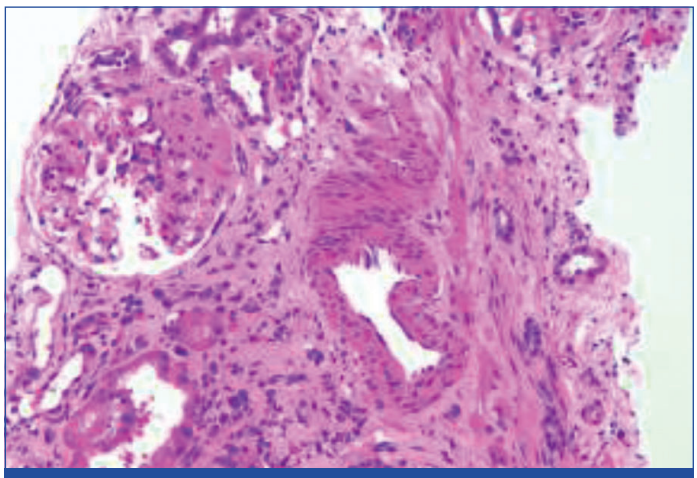
Among the histopathological varieties [Table/Fig-2-4], Not Otherwise Specified (NOS) was the most common lesion, present in 59 (60%) cases. Significant interstitial fibrosis and tubular atrophy were observed in 8 (8%) patients, affecting more than 20% of the cortical parenchyma. Immunofluorescence testing revealed Immunoglobulin M (IgM) positivity in 8 (8%) patients and C3 positivity in 8 (8%) patients. Treatment details [Table/Fig-5] indicated that all patients received Angiotensin-Converting Enzyme Inhibitor (ACEI)/Angiotensin receptor blocker (ARBs) and corticosteroids (prednisolone 1 mg/kg/day), with cyclophosphamide administered to 30 (30%) and CNI used in 34 (35%) cases.

Variant/Parameters	Frequency (n)	Percentage (%)
Not Otherwise Specified (NOS)	59	60
Tip	26	26
Perihilar	9	9
Tip+perihilar	1	1
Cellular	1	1
Collapsing	1	1
Interstitial fibrosis and tubular atrophy	8	8

[Table/Fig-2]: Histopathological varieties.



[Table/Fig-3]: FSGS tip variant, PAS stain (40X).



[Table/Fig-4]: FSGS tip variant, haematoxylin and eosin stain (40X).

A favourable response to corticosteroid treatment was observed in 59 (60%) patients, possibly indicating primary FSGS. A response to

Medications use	Frequency (n)	Percentage (%)
ACEI/ARB	97	100
Corticosteroids	97	100
Cyclophosphamide	30	30
CNI	34	35

[Table/Fig-5]: Treatment details.

Disease response to corticosteroids	Frequency (n)	Percentage (%)
NOS	35	59
Tip	22	37
Perihilar	1	1.7
Mixed Tip-perihilar	1	1.7
Cellular	0	0
Collapsing	0	0
Corticosteroid-resistant group		
Response to cyclophosphamide	6	20
Response to CNI	13	38

[Table/Fig-6]: Response to treatment details.

cyclophosphamide was seen in 6 (20%) patients, while CNI treatment showed a response in 13 (38%) patients. Response to treatment [Table/Fig-6] revealed that the highest response to corticosteroid treatment was observed in 35 (59%) cases of the NOS variant. Among corticosteroid-resistant patients treated with CNI, a disease response was seen in 13 (38%) cases. Among corticosteroid-resistant patients treated with cyclophosphamide, a disease response was observed in 6 (20%) cases. Resistant proteinuria was seen in 31 (32%) patients, possibly indicating secondary/genetic FSGS, as shown in the outcome details [Table/Fig-7].

Disease response	Frequency (n)	Percentage (%)
Complete Remission (CR)	60	61
Partial Remission (PR)	5	5
Relapse	8	8
Steroid dependency	4	4
Steroid resistance	31	32
Response to cyclophosphamide	6	20
Response to CNI	13	38
CKD incidence	16	16

[Table/Fig-7]: Outcome details.

The most common complication was infection, followed by cushingoid features due to corticosteroid therapy. For the seven patients who were multidrug resistant, treatment with mycophenolate and Rituximab was offered, and they are yet to follow-up.

DISCUSSION

Out of the total 97 subjects included in the study, 63 (64%) were male (male-to-female ratio of 1.85:1), similar to the study conducted by Dhanapriya J et al., where 65% were males, and also similar to the study by Wani AS and Zahir Z, where most of the patients were male [11]. The predominant age group was between 25 and 50 years, accounting for 53 (54%) of the total patients, similar to the findings of Dhanapriya J et al., [6]. Out of the total 97 subjects included in the study, the most common symptom was sudden onset oedema, observed in 88 (90%) patients, similar to the findings of Dhanapriya J et al., where it was seen in 98% [6]. Nephrotic proteinuria was observed in 69 (71%) of the subjects, also similar to the study by Dhanapriya J et al., where it was seen in 79% [6].

Pathology: Significant interstitial fibrosis and tubular atrophy (>20% of cortical parenchyma) were present in 8 (8%) of the patients in the current study. The incidence of various histological variants and interstitial fibrosis and tubular atrophy varied among different studies [6,9]. In the study by Dhanapriya J et al., among FSGS subtypes, the perihilar variant showed a lower incidence of microscopic haematuria and nephrotic proteinuria compared to other variants like NOS ($p<0.001$) and the cellular variety ($p<0.001$). The cellular variant of FSGS showed a higher incidence of renal failure ($p<0.05$). The NOS variant showed a higher incidence of interstitial fibrosis and tubular atrophy ($p=0.007$) compared to the cellular variant [6,12].

Treatment response and outcome: In the remaining patients who were multidrug resistant, treatment with mycophenolate and rituximab was offered, and they are yet to follow-up. Other studies have shown that a majority of patients achieved high rates of sustained remission with second- and third-line immunosuppressive drugs [6]. The tip variant showed a higher complete remission rate ($p<0.001$) compared to other variants, as observed in the study by Kwon YE et al., [13]. The NOS variant exhibited lower remission rates and higher progression to CKD ($p=0.003$) compared to the tip lesion ($p=0.009$) [6]. Response to treatment varied among different histological entities in various studies [6,9]. In contrast to the present study, other studies by Dhanapriya J et al., and Pradhan SK et al., showed a higher incidence of hypertension, a higher cellular variant subtype, higher steroid resistance, and a higher incidence of CKD due to chronicity in the form of interstitial fibrosis and tubular atrophy at the entry level [6,10]. This could be a reason for the contrasting outcomes and responses observed in different studies, including varied incidences of relapse, steroid dependency, steroid resistance, and response to cyclophosphamide and calcineurin inhibitors in different histologic variants.

In the present study, since genetic screening and electron microscopy were not performed, it is likely that unrecognised cases of genetic FSGS were included among the primary FSGS cases. This could lead to misinterpretation of treatment responses, as mentioned in other literature, since relying solely on light microscopy is insufficient [2,3,8]. The study by Shabaka A et al., demonstrated that steroid resistance should raise suspicion of an underlying genetic disease, which can be diagnosed through genetic testing [1,8]. Given that the term FSGS encompasses a wide range of diseases, it is important to have measurable biomarkers that accurately differentiate between primary and secondary FSGS [4,8]. Proper patient characterisation at the beginning of a study requires details such as quantification of urine protein (nephrotic range proteinuria in primary podocyte foot process FSGS, genetic FSGS, toxic/viral forms of secondary FSGS, and subnephrotic proteinuria in maladaptive FSGS/FSGS of undetermined cause), serum albumin measurements with specification of the biochemical assay (low serum levels in primary podocyte foot process FSGS, normal levels in other forms), electron microscopy evaluation of foot process effacement (generalised in primary podocyte foot process FSGS, segmental/diffuse in genetic FSGS, mild/segmental in maladaptive FSGS/FSGS of undetermined cause), and genetic analysis using the most recent FSGS gene panels or whole exon sequencing [2,5].

Factors influencing the exact stratification of FSGS types remain unclear, including history elicitation of disease onset (sudden onset proteinuria in primary podocyte foot process FSGS, insidious onset in other forms, unavailability of electron microscopy and genetic studies), inability to test causative factors like circulating permeability factor in primary podocyte foot process FSGS, or failure to recognise the causative factor in maladaptive FSGS, or unavailability of genetic testing [2]. Proper patient characterisation at the end of a study requires details such as response to Renin-angiotensin System (RAS) inhibition (non response in primary podocyte foot process FSGS, good response in maladaptive FSGS, genetic FSGS, FSGS of undetermined cause), and response to glucocorticoids/calcineurin inhibitors (response in primary podocyte foot process FSGS, poor response in maladaptive FSGS, genetic FSGS, FSGS of undetermined cause), which will aid in FSGS stratification [2]. Therefore, differentiating between primary and secondary forms of

FSGS has therapeutic and prognostic implications [14]. Accurately diagnosing each form of FSGS is crucial to avoid unnecessary immunosuppressive therapy and establish appropriate treatment [3,4].

Limitation(s)

The main limitation of the present study was the inability to perform electron microscopy and genetic studies on these cases due to the unavailability of these facilities at the centre and the poor affordability of the patient population. Other limitations included the small sample size and the fact that it was a single-centre study, which restricts the generalisability of the findings.

CONCLUSION(S)

Resistance to steroid therapy was noted in one-third of FSGS patients. The present study supports the need for a clear definition of "primary" FSGS and a clinicopathological approach to correctly differentiate between primary FSGS, secondary (maladaptive, viral, or toxic) FSGS, and genetic FSGS. This not only helps in making correct treatment decisions but also guides the rational design of therapeutic trials. Future studies should aim to identify biomarkers that will more precisely indicate the underlying pathophysiological process.

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