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Clinical profile and treatment response of primary Focal Segmental Glomerulosclerosis (FSGS) in Eastern Indian Children

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Abstract
Currently, there is very little information about the spectrum of clinical profile and treatment response of children presenting with primary Focal Segmental Glomerulosclerosis in India and other South East Asian countries. This entity is an important component of childhood nephrotic syndrome because of its high chance of progression to Chronic Kidney Disease and End Stage Renal Disease. This retrospective study was conducted from June 2009-February 2014 to determine the spectrum and treatment response of primary Focal Segmental Glomerulosclerosis in children at a tertiary level hospital. All children aged between 6 months-14 years with biopsy proven Focal Segmental Glomerulosclerosis were included in the study. Their demographical, clinical and histopathological data were studied from case files. Treatment was given as per Indian Society of Paediatric Nephrology guidelines and responses that occurred were documented. Statistical analysis was done using Microsoft Excel software. We found that 31 (22.14%) children in our study had primary Focal Segmental Glomerulosclerosis with 64.51% being males. The mean age was 5.51 ± 3.82 years. Most of these cases had presented clinically with Steroid Resistant Nephrotic Syndrome (64.51%). Majority went into remission (90.3%) with immunosuppressive medications. Our results indicated that response to Cyclosporine-A is better compared to oral Cyclophosphamide (p= 0.00098). Hence, it maybe advocated in a paediatric patient with SRNS after renal histopathology primary Focal Segmental Glomerulosclerosis.
Keywords: Children, Cyclosporine A, Focal Segmental Glomerulosclerosis, Renal biopsy, Steroid Resistance

ABBREVIATIONS

FSGS: Focal Segmental Glomerulosclerosis

IF: Immuno-Fluorescence

LM: Light Microscope

SRNS: Steroid Resistant Nephrotic Syndrome

MCD: Minimal Change Disease

ESRD: End Stage Renal Disease

CRF: Chronic Renal Failure

CKD: Chronic kidney disease

GN: Glomerulonephritis

ISPN: Indian Society of Paediatric Nephrology.

INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) is a major cause of idiopathic steroid-resistant nephrotic syndrome and ESRD [1]. FSGS is a histopathological diagnosis characterised by sclerosis of focal (only some of the glomeruli) and segmental (part of the glomeruli) glomeruli (Fig.1) and IF is usually negative. It is more common in school-going children and has a heterogeneous course. The predominant presenting feature is that of nephrotic syndrome [2]. Recent data demonstrated that African and Asian nephrotic children are three to four times more likely to have FSGS than others. The clinical course of primary FSGS varies and there is a considerable controversy as to which factors are of importance in determining prognosis or response to therapy [3]. The clinical course is characterized by complete remission, persistent proteinuria and progression to renal failure. Progression to ESRD is significantly higher in patients who did not attain remission [4]. In long-term cohort studies in adults and children with primary FSGS, renal survival has been directly associated with degree of proteinuria control [5]. Various modalities of treatment have been used in treatment and control of FSGS. The immunosuppressive medications and miscellaneous therapies being used are corticosteroids, Cyclosporine A, Tacrolimus, Cyclophosphamide, Chlorambucil, MMF, Sirolimus and Plasmapheresis [5]. Many authors have found a rise in the prevalence of FSGS in children during the recent past, and since this lesion is associated with a significantly lower response to steroids than MCD, it is recommended to detect its presence on renal biopsy in order to better inform the patients about the long-term prognosis. The incidence of this lesion is increasing throughout the world not only in adults but also the children [6, 7]. In a country like ours, where most of the renal involvement in paediatric age group is due to nephrotic syndrome, malaria or septicaemia, it has become a necessity for us to determine the clinical profile and treatment response of FSGS which has a higher predilection of progression to CKD. This is the motivation for our study.

STUDY DESIGN AND METHODOLOGY

This retrospective and descriptive study was conducted in children aged 6 months to 14 years from June 2009- February 2014 at a tertiary care centre in India. A total of 140 renal biopsies were performed during this period in nephrotic children after parents were counselled regarding the need for renal biopsy. The indications of renal biopsy were SRNS, SDNS,FRNS, before starting Calcineurin inhibitors (CNI) and all patients with atypical presentations like gross hematuria, hypertension etc. Informed consent was obtained from the parents or

legal guardians before obtaining ultrasound-guided percutaneous renal biopsy specimens by automated biopsy gun. A total of 31 (22.14%) cases with biopsy proven primary FSGS were included in the study. The necessary demographical, clinical and laboratory data at the time of presentation and on last follow-up were noted. The histopathological findings, including LM and IF were documented from original renal biopsy forms. Standard definitions of the disease, investigation protocols and treatment responses were used as per the ISPN guidelines. The definitions used to assess the clinical course were as follows [8]:

Complete remission: Urine albumin trace or nil or urine Protein Creatinine ratio <0.2 mg/mg for 3 consecutive days.

Partial remission: Urine albumin 1+ or 2+ or Urine Protein Creatinine ratio 0.2 mg/mg to 2 mg/mg.

Non-responder: No remission.

Relapses: Urine albumin 3+ or 4+ or protein creatinine ratio ≥2 mg/mg for 3 consecutive days.

SRNS: Lack of remission despite daily therapy with oral prednisolone at a dose of 2 mg/kg/day for 4 weeks.

SDNS: Relapses on alternate day steroid therapy or within 2 weeks of its cessation.

FRNS: ≥2 relapses in 6 months of initial response or ≥4 relapses in any 12 month period.

Hypertension: Blood pressure readings exceeding the 95th percentiles for systolic or diastolic blood pressure for age and gender.

Descriptive statistics for continuous variables were expressed as mean (SD) and medians. We compared categorical data and proportions using the chi-square test. A value of $p<0.05$ was considered statistically significant. All the data was compiled, analyzed and tabulated using Microsoft Office Excel 2007 software.

The mean duration of follow up was 12 months with a range of 8-14 months.

RESULTS

Out of 140 renal biopsies performed, renal histopathology was compatible with FSGS in 31 (22.14%) children, 20 (64.51%) were males and 11(35.48%) were females with a male-to-female ratio of 1.8:1. The mean age was 5.51 ± 3.82 years (range 6 months-14 years). The youngest child was aged 9 months and he presented with Infantile NS. 7 (22.58%) out of these 31 were aged between 10-14 years. Out of 31 children, 20 (64.51%) children were steroid resistant, 9 (29.03%) had a steroid dependent (SDNS) course and 2 (6.45%) had frequent relapsing nephrotic syndrome (FRNS) as shown in Chart-1. 8 (25.8%) children were hypertensive and all children had normal kidney function test at the time of renal biopsy. The mean serum Albumin at presentation was 1.49 ± 0.29 gm/dl.

All the children received prednisolone. 13 children had received combination of oral prednisolone and oral CYP. Of those, 5 children went into remission and remained relapse free for next 6 months. The remaining 8 children were switched over to CyA because of no response to CYP and one patient among them had drug toxicity to CYP. Out of 31 children, 4 (12.9%) children responded to MMF, 2 (6.45%) children responded to Tacrolimus and 12 (38.71%) children were treated with oral CyA. Our analyses indicate that response to oral CyA is better compared to oral CYP (p value=0.00098) with a

95% C.I of 11.6% to 64.38% for responders to CYP and 35% to 88% for non-responders.

Follow–up:

During follow up, 28 (90.3%) children were in remission, only 2 (6.45%) children were in partial remission and one patient died because of septicaemia during the study period.

DISCUSSION AND CONCLUSION

Clinical surveys from North America and the United Kingdom have reported the incidence of NS to be between two and four new cases per 100,000 children per year, with biopsy-confirmed FSGS comprising 15–20% of the total [9]. A study from Canada reported an incidence of FSGS of 0.37 to 0.94 new cases per 100,000 children per year [10]. The results of our study are generally similar to those previously reported in the literature extensively searched by us. All the previously reported studies have observed a higher prevalence of FSGS in SRNS [13, 14, 15]. The incidence of FSGS is not uniform across the world, as presented in Chart-2. A similar incidence rate was also reported in the studies from Saudi Arabia and Tunisia also [12, 13]. A study from India found FSGS in 58% of cases of SRNS children [14]. In contrast, FSGS was less common in studies from Japan (which is also a part of South East Asia) [18] and Kuwait [19]. The reasons for these variations may be hard to point out currently but these differences in the results may be due to racial, genetic, or environmental factors. Inter-observer variation and differences in disease definitions and inclusion criteria also affect the final results of such studies.

Corticosteroids are the mainstay of treatment and the therapeutic response to steroids appears to be the best predictor of long-term outcome and prognosis [20]. In our cohort, we found that SRNS 20(64.5%) is the most common clinical presentation of FSGS while 9(29%) showed SDNS pattern. This is in contrast to the data found out by studies conducted in Egypt and Pakistan where SDNS was the most common clinical presentation [21, 22]. As the outcome of the nephrotic syndrome in FSGS is significantly improved by remission of proteinuria, it is conceivable now that immunosuppressive medication may be used in conjunction with prednisone in patients with steroid resistance [23]. FSGS reveals a variety of histopathological subtypes, variable responses to therapy and its outcome [24, 25]. Anti-proteinuric agents like renin antagonists, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone antagonists that antagonize the renin-angiotensin II-aldosterone axis have proven to be very beneficial. There is an emerging recognition that viewing FSGS as a T-cell driven disease and the subsequent focus solely on immunosuppressive agents as potential treatments may be misguided and hindering advances in therapeutics [26]. Other agents like rituximab has been found to be safe and effective in inducing and maintaining remission in a significant proportion of patients with difficult SRNS and SDNS [27]. Tacrolimus has also been shown to be effective in small studies involving paediatric and adult patients with an overall response rate of approximately 50–75% [28]. MMF has also been used in some trials but relapses were common and more studies are needed in order to

accept this modality of treatment [29]. Currently two agents – adalimumab (anti-TNF-α antibody and Galactose) are undergoing evaluation compared to standard conservative medical therapy (combined treatment with lisinopril, losartan, and atorvastatin) [30].

There are not many controlled studies and there is no consensus on the optimal treatment of patient with FSGS. The clinical spectrum and treatment outcome in our study is as presented in Table-1. As far as we know, this study defines the true spectrum of FSGS in children in Eastern India. Our analyses show a better response to oral Cyclosporine A (p=0.00098) compared to oral Cyclophosphamide. It is also important to note that almost 90% of the patients went into complete remission with various Immuno-suppressants and consequently exhibit an excellent prognosis and hence they maybe advocated for a paediatric patient with SRNS after renal histopathology shows FSGS. However, a larger cohort and genetic studies from our country are needed before forming definite treatment protocols.

DISCLOSURES

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Human and animal rights: Not applicable

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Table 1: Spectrum and Treatment Outcome in our study

Gender	20 males (64.51%)
Age at onset	5.51 + 3.82 years
Adolescents	7 (22.58%)
Mean serum Albumin	1.49 ± 0.29 gm/dl
Hypertension	8 (25.8%)
Prednisolone + CYP	5 (16.13%)
Non responders to CYP	8 (62% of total patients on pred+CYP)
Prednisolone + CyA	20 (64.51%)
Prednisolone + Tacrolimus	2 (6.45%)
Prednisolone + MMF	4 (12.9%)
Remission	28 (90.3%)
Partial remission	2 (6.45%)

Fig.1: Renal biopsy of 3 year 6 months boy; LM showing segmental sclerosis of glomerular tuft, accompanied by aggregation of foam cells and proliferation of podocytes, while remaining are within normal limits of morphology. Basement membrane is not thickened. The tubules show patchy atrophy with hyaline casts. The Interstitium shows moderate mixed inflammatory cell infiltrate. The blood vessels are unremarkable (magnification x200).

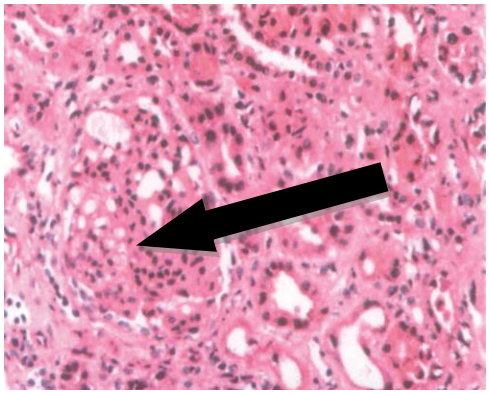


Chart-1: Clinical presentations of FSGS in our study (n=31)

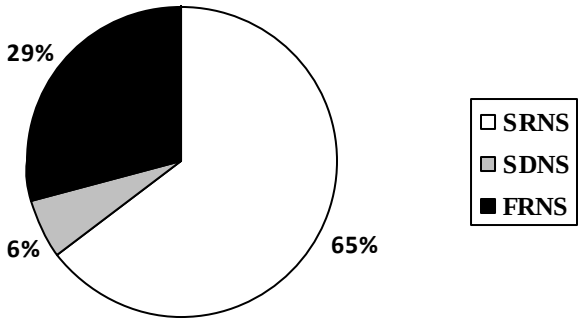
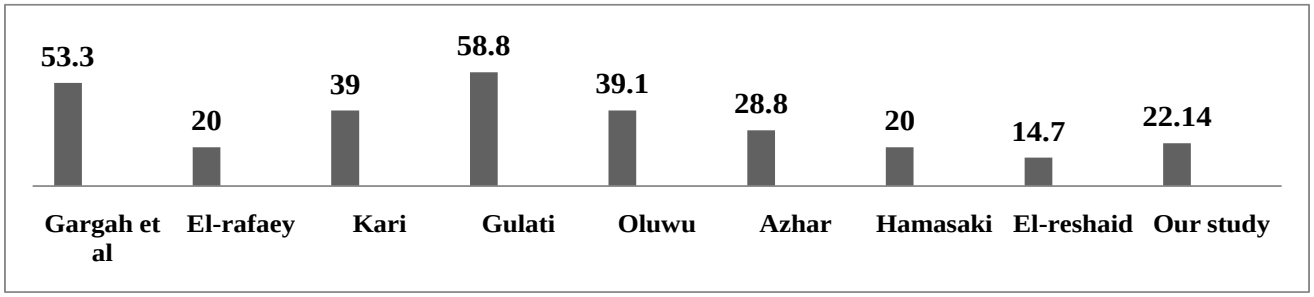


Chart 2: Comparison of incidence of FSGS in our study with other international studies (all figures are in percentages of total biopsies done)



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