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Original Article

Focal Segmental Glomerulosclerosis in Childhood: A Single-Center Experience

Çocukluk Çağı Fokal Segmental Glomeruloskleroz: Tek Merkez Deneyimi

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ABSTRACT

Aim: Focal segmental glomerulosclerosis (FSGS) is one of the common causes of nephrotic syndrome (NS) in children. This study aims to determine the demographical data, clinical course, treatment and renal outcome of children with primary FSGS and report the experience of a single center.

Material and Methods: A retrospective study of the long-term outcome of 38 patients with diagnosis of primary FSGS at a tertiary pediatric care hospital from the period July 2005 to July 2019 was conducted.

Results: The study included 38 patients (23 female and 15 male) with FSGS, and the mean age at diagnosis was 8.5 ± 4.2 years. The mean follow-up duration was 4.8± 4.1 (1-14.6) years. Seventeen (44.7%) patients were steroid-resistant NS (SRNS) and 21 (55.3%) patients were steroid-sensitive NS (SSNS) [12 (31.6%) steroid-dependent NS (SDNS) and 9 (23.7%) frequently relapsing NS (FRNS)]. There was no significant difference between these groups in age, gender, hematuria, serum albumin and urine protein level at presentation ($p > 0.05$). Long-term follow-up showed that 47% of SRNS patients achieved complete remission, 23.5% partial remission and 29.4% resistant to all therapies. ESRD was developed 15.8% of the FSGS patients. Risk factors for poor prognosis were the presence of hypertension (HT) at admission, female gender, and unresponsiveness to initial treatment.

Conclusion: Focal segmental glomerulosclerosis in childhood, shows changes in response to treatment and prognosis. In this study, we presented our data on risk factors affecting prognosis.

Keywords: Pediatric; Nephrotic Syndrome; Focal Segmental Glomerulosclerosis

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ÖZ

Amaç: Fokal segmental glomerüloskleroz (FSGS), çocuklarda nefrotik sendromun (NS) yaygın nedenlerinden biridir. Bu çalışma, primer FSGS'li çocukların demografik verilerini, klinik seyrini, tedavisini ve böbrek sonuçlarını belirlemeyi ve tek merkez deneyimini raporlamayı amaçlamaktadır.

Gereç ve Yöntemler: Üçüncü basamak bir pediatric bakım hastanesinde Temmuz 2005 ile Temmuz 2019 arasında primer FSGS tanısı alan 38 hastanın uzun vadeli sonuçlarına ilişkin retrospektif bir çalışmadır.

Bulgular: Fokal segmental glomerüloskleroz tanısı olan 38 çocuk (23 kız ve 15 erkek hasta) dahil edildi ve ortalama tanı yaşı 8.5 ± 4.2 yıldı. Ortalama takip süresi 4.8 ± 4.1 (1-14.6) yıldı. On yedi (%44.7) hasta steroide dirençli NS ve 21 (%55.3) hasta steroide duyarlı NS [12 (%31.6) steroid bağımlı NS ve 9 (%23.7) hasta sık tekrarlayan NS] idi. Başvuru anında bu gruplar arasında yaş, cinsiyet, hematüri, serum albumin ve idrar protein düzeyi açısından anlamlı fark yoktu ($p > 0.05$). Uzun süreli takipte SRNS'li hastaların %47'sinin tam remisyon, %23.5'inin kısmi remisyon ve %29.4 'ünün de tüm tedavilere dirençli olduğu görüldü. Hastaların %15.8'sinde SDBH gelişmişti. Kötü prognoz için risk faktörleri, başvuruda hipertansiyon (HT) varlığı, kadın cinsiyet ve başlangıç tedavisine yanıtsızlık olarak belirlendi.

Sonuç: Çocukluk çağında FSGS, tedaviye yanıt ve prognozda değişkenlik göstermektedir. Bu çalışmada prognozu etkileyen risk faktörleri ile ilgili verilerimizi sunduk.

Anahtar Kelimeler: Pediatrik; Nefrotik Sendrom; Fokal Segmental Glomerulosklerozis

Introduction

Nephrotic syndrome (NS) is one of the most common glomerular diseases of childhood characterized by leakage of protein into the urine through damaged glomeruli. Focal segmental glomerulosclerosis (FSGS) is one of the common causes of NS in children. Although some factors that may lead to FSGS have been identified, most of the patients are primary. Primary or idiopathic FSGS is, estimated to be responsible for 20% of pediatric NS, is a clinicopathologic diagnosis characterized by the presence of sclerosis in parts (segmental) of some (focal) glomeruli [1]. Proteinuria is the most common presenting feature of primary FSGS. It is often associated with hematuria, hypertension and some degree of renal failure in the pediatric age group, but it is indistinguishable from minimal change disease (MCD) in the early stages [2,3]. Although patients are usually considered steroid-resistant, 15-20% of FSGS patients may initially respond to steroids [4]. Focal segmental glomerulosclerosis is the most common form of glomerular disease, reaching end-stage renal disease (ESRD) in children. Previous studies have reported the risk factors, including significant proteinuria, decreased renal function, hypertension at diagnosis, tubulointerstitial lesions and glomerular sclerosis, to be associated with the prediction of long-term renal outcomes [1,3]. However, a consensus on the role of clinical and pathological risk factors in the pathogenesis or progression of FSGS yet lacks in children.

The aim of this retrospective cohort study is to determine the demographical data, clinical course, treatment and renal outcome of children with primary FSGS and report the experience of a single center.

Materials And Methods

This retrospective study was performed on 38 children aged 1-18 years diagnosed biopsy-proven primary FSGS, admitted to pediatric nephrology department of tertiary referral hospital over a fourteen-year period extending from July 2005 to July 2019. Inclusion criteria for the study were determined as patients whose sufficient histological findings could be reached retrospectively and who were followed up regularly for at least one year. Our study provides the results of the latest clinical follow-up findings of all our FSGS patients whose information we could access. Children who had a follow-up period of less than one year and had a history of a disease that could cause a secondary FSGS were excluded from this study.

Data, including age, sex, family history of proteinuria, hematuria or renal disease, presenting symptoms, 24-hour urine protein excretion and laboratory investigations, renal biopsy findings, treatment and responses to therapy, complications and renal outcomes, were recorded.

Renal biopsy criteria in children were determined as early or late-onset SRNS, SDNS and FRNS, being younger than one year or older than 12 years, persistent macroscopic hematuria, persistent hypertension, persistently decreased kidney function, and persistently decreased C3 complement level. All samples were evaluated by an experienced paediatric pathologist. The diagnosis of FSGS was based on the histological evaluation of kidney biopsy by light microscopy using hematoxylin and eosin, periodic acid-Schiff, Masson's trichrome and methenamine

silver staining and immunofluorescence microscopy staining with antibodies to IgG, IgA, IgM, C1q and C3.

The response to treatment and clinical definitions for FSGS were used according to KDIGO 2012 guidelines. Remission was defined as urinary protein/creatinine ratio <0.2 mg/mg. Partial remission was accepted as a 50% or more decrease in the urine proteinuria from baseline with protein/creatinine ratio >0.2 mg/mg. The following patients were considered steroid unresponsive: a. the patients who did not show a 50% decrease in protein excretion in the urine than the baseline b. Persistent protein/creatinine ratio > 2 mg/mg. SRNS was defined as the inability to achieve remission after 8 weeks of corticosteroid therapy. Also, we defined SDNS, after the achievement of remission as relapses occurring during the course of steroid tapering or within 2 weeks of stopping corticosteroid therapy. FRNS was defined as ≥2 relapses within 6 months of achieving initial remission or ≥4 relapses in any 12-month period.

The Schwartz formula was used to calculate the estimated glomerular filtration rate (eGFR) in all patients. We defined patients with persistent GFR <60 mL/min/1.73 m2 for at least three months as chronic kidney disease. ESRD was defined as a permanent GFR <15 mL/min/1.73 m2 or the onset of dialysis. Renal insufficiently was defined using KDIGO 2012 criteria with GFR and urine output.

Statistical analysis was performed using IBM SPSS Statistics for Windows v.22.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to determine the normality of the distribution of the study variables. Parametric variables are shown as mean ± SD, and nonparametric variables are shown as median and range. Categorical variables are presented as number and percentage. Student's t test was used to compare parametric variables and the Mann-Whitney U test was used to compare nonparametric variables. The $\chi 2$test or Fisher's exact test was used to compare categorical variables. The level of statistical significance was set at $p < 0.05$.

The research protocol of the study was approved by the ethics committee and the study was conducted in accordance with the Declaration of Helsinki Principles.

Results

The study included 38 children (23 female and 15 male) with FSGS, and the mean age at diagnosis was 8.5 ± 4.2 years. Four patients were under the age of two also seven were above the age of 12 at presentation. The mean follow-up time was 4.8 ± 4.1 years. A family history of proteinuria, hematuria or chronic kidney disease was determined in 5.2% of the patients. Baseline characteristics of the children diagnosed with FSGS were present in Table 1.

Table 1: Baseline characteristics of the children diagnosed with FSGS

Characteristic	Value
Gender female, n (%)	23 (60.5)
Patient age, years, mean ± SD	8.5 ± 4.2
Follow up time, years, mean ± SD	4.8 ± 4.1
Family history, n (%)	2 (5.2)
Presenting clinical symptoms, n (%)	
Edema	22 (57.9)
Macroscopic hematuria	2 (5.3)
Microscopic hematuria	18 (47.4)
Elevated blood pressure	13 (34)
Laboratory findings	
24-hour protein excretion (mg/m2/day)	194.75 ± 117.44
Nephrotic range proteinuria, n (%)	13 (34)
Serum albumin levels, gr/dl, mean ± SD	2.2 ± 1
Serum creatinine levels, mg/dl, mean ± SD	0.81 ± 0.79
eGFR, mL/min/1.73 m2, mean ± SD	84.04 ± 32.09
Renal insufficiency, n (%)	1 (2.63)
Steroid responses	
Steroid-resistant NS, n (%)	17 (44.7)
Steroid-dependent NS, n (%)	12 (31.6)
Frequent relapse NS, n (%)	9 (23.7)

eGFR: estimated glomerular filtration rate, NS: nephrotic syndrome

The first presentation symptoms of the patients were edema 22/38 (57.9%), macroscopic hematuria 2/38 (5.3%) and microscopic hematuria in 18/38 (47.4%). Thirteen (34.2%) patients were hypertensive at admission. Also, the mean 24-hour protein excretion was 194.75 ± 117.44 mg/m2/h and 84% of them had nephrotic range urine protein excretion. The mean serum albumin levels were 2.2 ± 1 gr/dL. At the presentation, the mean serum creatinine levels were 0.81 ± 0.79 mg/dL and the mean eGFR was 84.04 ± 32.09 ml/min/1.73 m2.

Biopsy was performed in 14 patients before initiating treatment and 24 patients underwent biopsy after starting treatment (at patients with SRNS, SDNS, FRNS). A median number of 23 glomeruli (range 10-68) was evaluated per biopsy specimen. Tubular atrophy was detected in 25/38 (65.7%) patients and mesangial enlargement in 24/38 (63.1%) patients. Fibrocellular crescent was shown in two (5.2%) patients. Twenty-one patients (55.3%) had glomeruli with global sclerosis, and 13 (34.2%) patients had glomeruli with segmental changes. Interstitial fibrosis was observed in 18.4%. Biopsy finding were given in Table 2.

Table 2: Biopsy findings

Characteristic	Value
Tubular atrophy, n (%)	25 (65.7)
Mesangial enlargement, n (%)	24 (63.1)
Fibrocellular crescent, n (%)	2 (5.2)
Global sclerosis, n (%)	21(55.3)
Segmental sclerosis, n (%)	13 (34.2)
Interstitial fibrosis, n (%)	7 (18.4)

Steroid therapy was initiated as 60 mg/m2/d (maximum: 60 mg/d) and continued for 4-8 weeks. Seventeen (44.7%) patients were SRNS and 21 (55.3%) patients were SSNS [12 (31.6%) SDNS and 9 (23.7%) FRNS]. Patients with SRNS, SDNS and FRNS were treated using cyclosporine, tacrolimus, mycophenolate mofetil (MMF) or cyclophosphamide. Cyclosporin was the most commonly used second-line therapy and preferred as the first cytotoxic agent in 19 (50%) patients. The number of patients who responded and induced complete remission with cyclosporine treatment in SRNS group were 5/13. Cyclosporine was discontinued because of cyclosporine toxicity clinical course in four of the patients, and their treatment was changed with other second-line agents. Cyclophosphamide was used 12 (31.5%) patients, MMF was used 8 (21%) patients and tacrolimus was used in 7 (18.5%) patients. Angiotensin-converting enzyme inhibitors (ACEIs)/ angiotensin receptor blockers (ARB) were used 30 (78.9%) patients. Long-term follow-up showed that 47% of SRNS patients achieved complete remission, 23.5% partial remission. Five (29.4%) of the patients were refractors to all therapies and were followed up with supportive therapy ACEIs/ARB.

ESRD was developed 15.8% of the patients. The median duration of ESRD was three years on average from the initial diagnosis. Risk factors for poor prognosis, presence of hypertension at presentation, female gender and unresponsiveness to initial treatment were determined. Multiple logistic regression analysis demonstrated that female gender (odds ratio 11.54 (1.15-115.39) p = 0.037), the presence of HT at presentation (odds ratio 6.75 (1.15-39.42) p = 0.034) and unresponsiveness to initial treatment (odds ratio 5.00 (1.14-21.79) p = 0.03) predicted poor prognosis of FSGS.

Discussion

The present study presents a 14-year retrospective evaluation of pediatric primary FSGS patients. We identified the correlation between clinical and laboratory characteristics, findings with histologic lesions and obtained results about their response to treatment and factors affecting the prognosis of the disease with primary FSGS.

In this study, the mean age at presentation was 8.5 years, similar to previously reported studies [2,5,6]. Although male predominance was reported in other studies most of our patients (60.5%) in our study was female [1,5,7]. It was thought that this difference might be due to different geographical features and differences in the study groups (adult-child).

FSGS is associated with different clinical characteristics in childhood. The clinical features at the presentation of our patients were similar to the previous series [7,8]. In our study, 34.2% patients were hypertensive and 52.7% of patients have hematuria (5.3% macroscopic and 47.4% microscopic) at admission. Our rate of patients presenting with edema was 57.9%, and 84% of them had urinary protein excretion in the nephrotic range.

Arbus et al [9] reported 58 children with primary FSGS had a predominance of slightly increased mesangial matrix and mild/moderate tubular atrophy and fibrosis when looking at histological features. Yoshikawa et al [10] reported a segmental percentage of sclerotic glomeruli ranging from 16–22% and a percentage of globally sclerotic glomeruli ranging from 8.4–14%. In our study, we observed tubular atrophy 25/38 and mesangial enlargement 24/38 most frequently as histological findings. We observed that the rate of global sclerosis (55.3%) was higher than the rate of segmental sclerosis (34.2%). The reason for the higher detection of global sclerosis may be due to the delayed biopsy findings due to the late presentation of our patients.

In the literature, the initial response to corticosteroids was considered poor in patients with idiopathic FSGS, and approximately 20-25% were reported complete remission [11]. Another study showed that only 12 patients (16.7%) achieved complete remission; partial remission was achieved in 34 patients (47.2%), while 26 patients (36%) were resistant to all lines of therapy [5]. Also, the majority of published studies has shown that the response rate has been less than 30% [12,13]. In our study, 55.3% of our patients achieved complete remission with the initial corticosteroid treatment.

Various therapeutic strategies are applied with second immunosuppressants in patients with steroid-resistant FSGS. [2]. In our study, a second immunosuppressive treatment was tried in patients with SRNS, SDNS or FRNS. However, it is not clear an optimal therapy for SRNS patients, but the evidence supports the use of cyclosporine for first line therapy [13,14]. The response to cyclosporine is usually satisfactory. Lieberman et al [15] showed a significant decrease in proteinuria in all patients receiving cyclosporine. As a study shows that, the remission was observed in 40% of the 15 patients who received cyclosporin as the first cytotoxic therapy [13]. In the present study, cyclosporin was the most commonly used second-line therapy and preferred as the first cytotoxic agent in 19 patients. The number of patients who responded and induced complete remission with cyclosporine treatment was 5/13 (%38.5) in SRNS patient.

A cohort study reported that 53% of patients achieved a partial or complete remission due to all treatments [16]. Some studies showed that for FSGS in children, the frequency of ESRD was variable and ranged from 25% to 50% after 15 years of follow up [2,7]. In our study, long-term follow-up showed that 47% of SRNS patients achieved complete remission, 23.5% partial remission and 24.9% resistant to all therapies. ESRD was developed 15.8% of all the FSGS patients.

Age is a risk factor for kidney survival in FSGS [3,17]. Studies

of being diagnosed at a young age (especially <6 years) have shown more positive results concerning progression to ESRD [1,18]. However, age was not significant as a risk factor for ESRD in our study. Initial response to corticosteroids has been recognized as a strong predictor of kidney survival. With similar results, resistance to corticosteroids has been shown to be an important predictor of progression to ESRD [19,20]. We also found that unresponsiveness to initial treatment predicted poor prognosis of FSGS. In addition, other factors for poor prognosis in this study were the presence of hypertension at admission and female gender. determined.

The main limitation of our study was a retrospective nature, being a single center study and also the lack of genetic data.

Conclusion

In this study aims to investigate the effects of clinical and laboratory features at the presentation on response to treatment and long-term renal survival. We presented a significant association of female gender and presence of hypertension at presentation with poor prognosis in children with FSGS. Considering our cohort size and follow-up periods, we think that large-scale studies will contribute to the recommendations on this subject.

Declaration of conflict of interest

The authors have no conflicts of interest to declare. The authors received no funding for this work.

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