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Research Article

FOCAL SEGMENTAL GLOMERULOSCLEROSIS IN LIBYAN CHILDREN: TRIPOLI CHILDREN HOSPITAL EXPERIENCE (2000-2020)

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Abstract

Background: Focal Segmental Glomerulosclerosis (FSGS) is characterized by steroid resistant nephrotic syndrome. Pathologically it is consisted of glomerulosclerosis, which is both focal, involving a minority of glomeruli, and segmental, affecting a portion of the glomerular globe. **The aims** of this study are, to find out aLibyan experience on frequency, clinical presentations and outcomes among children with primary FSGS at Tripoli Children Hospital. **Patients and methods:** This is retrospective case series observational clinic-based study. Children who diagnosed as primary FSGS by renal biopsy were included in this study from 2000 to 2020 at Tripoli Children Hospital. The case sheet which used for data collection includes: Age at presentation, gender, Presence of hematuria, hypertension and renal impairment. Family history of nephrotic syndrome and FSGS, response to steroid therapy, choice of treatment and clinical outcomes. Typical presentation included the extreme of age at presentation from 2-8 years, absent of persistent hematuria or absence of macroscopic hematuria, absence of persistent hypertension, renal impairment and low serum complement. **Result:** Were viewed files of 41 children diagnosed by renal biopsy as FSGS, male composed of 65.9% of children. The age at diagnosis of nephrotic syndrome was 5.15 ± 3.29 [range 1 - 15 years]. 75.6% of children presented from 2-8 years of age. 15(36.6%) children had renal impairment, 9(22%) children had hematuria and 17(17.5%) had hypertension. 2 (4.9%) achieved remission initially, steroid resistant seen in 29 (70.7%) and 10 (24.3%) patients had steroid dependent and frequent relapse. Long-term follow-up showed complete remission in 24.4%. End-stage renal disease in 24.4%, and death in7.3%, 2.9%underwent successful renal transplantation, 7.3% transferred to adult for further follow up with adult nephrologist and 9.8% missed follow up. **Conclusion:** More than two third of the cases of FSGS in our population presented as steroid resistant nephrotic syndrome. 24.4% of FSGS progressed to ESRD.

Keywords: Libya, Nephrotic syndrome, Focal segmental glomerulosclerosis.

INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) is a podocyte disease. Pathologically it is consisted of glomerulosclerosis, which is both focal, involving a minority of glomeruli, and segmental, affecting a portion of the glomerular globe[1].Idiopathic nephrotic syndrome **(**INS) in children is classified according to the response to therapy into steroid-sensitive nephrotic syndrome (SSNS) and steroid-resistant nephrotic syndrome (SRNS) [2, 3].SSNS generally responds well to conventional oral corticosteroid therapy, and has a benign long-term renal prognosis even though it shows frequent relapses, while SRNS (which constitute 10-20% of nephrotic syndrome in children) does not achieve remission by oral corticosteroid therapy[4].Most SSNS is due to minimal change disease (MCD) and most SRNS is due to FSGS [2]. FSGS is estimated to account for around 7 to 20% of all forms of idiopathic nephrotic syndrome[5]. Over the last 20–30 years, the incidence and prevalence of FSGS has been increasing worldwide[6, 7].However, the absolute incidence and prevalence of FSGS are difficult to assess given the large variations between countries in referral policies for diagnostic renal biopsy [7, 8]. MCD is more common in male children, but most reports have found no clear gender difference in children with FSGS [9]. Race and ethnicity appears to play an important role in incidence and prevalence of FSGS in adult[9-11], and it has the same effect on pediatric patients [12].

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Furthermore, age appears to play an important role in the prevalence of FSGS[9]. The frequency of FSGS presenting before 6 years of age is less than 10%, but increases to 20–50% or more in patients presenting in teenage years[9]for instance 1.5% of Indian children with NS had FSGS in renal biopsy before 6 years of age and increased to 10.1% in adolescence patients [13]. FSGS classified in to primary or idiopathic FSGS and secondary FSGS[6, 10]. Children with INS may not frequently or routinely subjected to renal biopsy [2, 9, 14].The main indications of renal biopsy in children with NS was steroid-resistant nephrotic syndrome[9, 12]. The other indications for renal biopsy include children with frequent relapses after steroid therapy and older children. Thus, a biopsy series would tend to underestimate the relative frequency of minimal change disease and overstate that of other less steroid-responsive forms of glomerulonephritis including FSGS [12].Renal biopsy is required to further classify NS and to diagnose FSGS [2, 14, 15]. FSGS is a major contributor of SRNS and end-stage kidney disease (ESRD) [6, 16, 17].The clinical course of children with FSGS who do not achieve partial or complete remission have a 50% risk of progression to ESRD within 5 years whereas those who enter complete remission have a 5-year kidney survival rate is of 90%[18].FSGS accounting for around 14% of the dialysis patients [9, 16].FSGS is the third most common diagnosis for the transplant recipients preceded by aplastic/ hypoplastic/ dysplastic kidneys and obstructive uropathy accounting for approximately 11.5% [9, 16]unfortunately FSGS patients who progress to ESRD and who receive a renal transplant, cannot be reassured that the worst is behind them because FSGS can

recur in the transplanted kidney in 20–25% of cases [6].The aims of this study are, to find out a Libyan experience on frequency, clinical presentations and outcomes among children with primary FSGS at Tripoli Children Hospital.

MATERIALS AND METHODS

This is retrospective case series observational clinic-based study. Children who diagnosed as primary FSGS by renal biopsy were included in this study. These children were followed up in nephrology unit at Tripoli Children hospital (TCH), during the period between 2000 to 2020. TCH is a referral and teaching hospital covers 2/3 of pediatrics service in Libya. 41 children with primary FSGS diagnosed by renal biopsy were enrolled in this study. Children with minimal change disease, congenital and secondary nephrotic syndrome were excluded. Nephrotic syndrome was diagnosed according to the criteria of the international study of kidney disease in children (ISKDC)[19].The case sheet which used for data collection includes: Age at presentation, gender, Presence of hematuria, hypertension and renal impairment at presentation. Family history of nephrotic syndrome and FSGS and clinical outcomes. The specimens had examined by light microscopy, Immunofluorescence stained. Typical presentation included the extreme of age at presentation from 2-8 years, absent of persistent microscopic hematuria or absence of macroscopic hematuria, absence of persistent hypertension, renal impairment and low serum complement.

Definitions

SDNS was defined as two consecutive relapses during steroids therapy, or within two-weeks of ceasing therapy[20]. Infrequent relapse defined as one relapse within 6 months of initial response or one to three relapses in any 12 months' period[20]. Infrequent relapse defined as one relapse within 6 months of initial response or one to three relapses in any 12 months period[20]. SRNS was defined as an inability to achieve complete remission with corticosteroids therapy. A minimum of 8wks treatment with corticosteroids therapy[20]. Complete remission was defined as proteinuria < 0.3 g/day and clinical remission of the nephrotic syndrome. Partial response was defined as urinary protein excretion of > 0.3 g/day and < 1 g/day or, a 50% reduction of initial proteinuria. Chronic kidney disease (CKD) was defined based on estimated glomerular filtration rate (eGFR) (Schwartz formula): Stage-1 (renal injury) was defined as eGFR of > 90 mL/min per 1.73 m^2; Stage-2 (mild), eGFR of 60-89 mL/min per 1.73 m^2; Stage-3 (moderate), eGFR 30-59 mL/min per 1.73 m^2; Stage-4 (severe), eGFR of 15-29 mL/min per 1.73 m^2; Stage5 (ESRD), eGFR of < 15 mL/min per 1.73 m^2[21]. Blood pressure was standardized for age and gender using the Task Force tables and the 95th percentile was used as the cut-off point[22].

Statistical analysis

Data was analyzed by using IBM SPSS Statistics for Windows, version 20 (IBM Corp., Armonk, N.Y., USA). Descriptive statistics such as frequency, percentage and mean ± standard deviation were used to present all results. Chi-squared ($\chi 2$) and Fisher's exact tests were used as the test of significance for categorical variables. A p value < 0.05 considered significant. Data was anonymous, kept strictly confidential and was accessible only to the research team.

RESULTS

Between 2000 and 2020 a total of 75 kidneys biopsies were performed on children with nephrotic syndrome, 41(54.6%) consist of FSGS. These children presented and followed up in nephrology clinic at Tripoli Children Hospital. We reviewed 41 records of children with FSGS during a period of 20 years. 27 boys (65.9%), male: female ratio was 1.9. The age at diagnosis of nephrotic syndrome was 5.15 ± 3.29 [range 1 - 15 years]. Of these, 19 children (46.3%) had atypical presentation, 15(36.6%) children had renal impairment, 9(22%) children had hematuria and 17(17.5%) had hypertension. Family history of NS were noticed in 10 (24.4%) children and 6(14.6%) child had positive family history of FSGS. Renal biopsy was repeated in two children (4.88%).GFR at presentation accounted as 18(43.9%) of children stage I and stage V (ESRD) accounted as 3(7.3%), GFR at last presentation 17(41.5%) of children still in stage I and 10(24.4%) reached ESRD. Demographic and clinical characteristics of the FSGS patients are shown in Table 1:

Table 1. Socio-demographic characteristics of children with FSGS

Character		Frequency	%
Sex			
Male		27	65.9
Female		14	34.1
Age groups (year)			
< 2		1	2.4
2-8		31	75.6
>8		9	21.9
Clinical type			
SSNS in place of NSSSNS		2	4.9
SDNS and FR		9	22
SRNS		30	73.1
Clinical features			
Hematuria		9	22
Hypertension		17	41.5
Renal impairment		15	36.6
GFR at Presentation (ml/min/1.73m^2)			
Stage I CKD	>80	18	43.9
Stage II CKD	60-79	11	26.8
Stage III CKD	30-59	5	12.2
Stage IV CKD	15-29	4	9.8
ESRD	< 15	3	7.3
Family History of NS		10	24.2
Family History of FSGS		6	14.6
GFR lastpresentation (ml/min/1.73m^2)			
Stage I CKD	>80	17	41.5
Stage II CKD	60-79	4	9.8
Stage III CKD	30-59	4	9.8
Stage IV CKD	15-29	1	2.4
ESRD	< 15	10	24.4
Missed		5	12.2

SSNS: Steroid sensitive nephrotic syndrome, SD NS and FR: steroid dependent and frequent relapse nephrotic syndrome, SRNS: Steroid resistant nephrotic syndrome.

At presentation hematuria was detected in 9 (22%) patients. Hypertension was found in 17 (41.5%) patients. Renal impairment was present in 15 (36.6%) patients. Steroid therapy was given to all patients, of whom 2 (4.9%) achieved remissioninitially, steroid resistant seen in 29 (70.7%) and 10 (24.3%) patients had steroid dependent and frequent relapse. When we found the relation between clinical types and age groups, patient gender and clinical presentation there were no statistically significance between them except renal impairment and the clinical types as seen in table 2. This is may be related to the small number of sample.

Table 2. Clinical Steroid response and its relation to age groups, sex, initial hematuria, hypertension and renal impairment at time of presentation

	SSNS	SRNS	SDNS	Total	P value
Frequency	2(4.9%)	30(73.1%)	9(22%)	41 (100%)	
Age groups					
< 2 years	0 (0%)	1 (2.4%)	0 (0%)	1 (2.4%)	
2-8 years	2 (4.9%)	20 (48.8%)	9 (22%)	31 (75.6%)	
> 8 year	0 (0%)	8 (19.5%)	1 (2.4%)	9 (21.9%)	
Sex					
Males	2(4.9%)	19 (46.3%)	6 (14.6%)	27 (65.9%)	0.551
Females	0 (0%)	10 (24.4%)	4 (9.8%)	14 (34.1%)	
Hematuria	0 (0%)	8 (19.5%)	1 (2.4%)	9(22%)	0.380
Hypertension	1(2.4%)	13(31.7%)	3 (7.3%)	17(41.5%)	0.692
Renal impairment	0 (0%)	14 (34.1%)	1 (2.4%)	15 (36.6%)	0.052

SSNS: Steroid sensitive nephrotic syndrome, SD NS and FR: steroid dependent and frequent relapse nephrotic syndrome, SRNS: Steroid resistant nephrotic syndrome.

The outcomes of studied cases included 10 (24.4%) were found to have complete remission, 9 (22%) had continue follow up with CKD and gradual had deterioration of renal function while 10 (24.4%) progressed to ESRD, 2 (2.9%) underwent successful renal transplantation and kept on follow up, 3(7.3%) transferred to adult for further follow up with adult nephrologist, 3(7.3%) died after reaching ESRD and 4(9.8%) missed follow up.

DISCUSSION

This is the first retrospective case series observational clinic-based study of Libyan children with FSGS presented to Nephrology unit at Tripoli Children Hospital. The incidence of FSGS has been a rising in children and adults worldwide in the past two decades[9].Our hospital data showed that FSGS accounted as 41(54.6%) of biopsied nephrotic children. Bakr et al showed that 16.2% of 741 biopsied nephroticsyndrome of Egyptian children had FSGS[23]. Different studies from the United Kingdom and North America had reported a proven biopsy with FSGS in 15%–20% of nephrotic syndrome cases[9]. In our study only 2(4.9%) had steroid sensitive initially, 9(22%) developed steroid dependent with frequent relapse and 30(73.1%) had steroid resistant. Our data is higher than that found in a Tunisian pediatric study of 30 children, Gargah et al reported that FSGS was most frequently occurring in the steroid-resistant nephrotic syndrome accounted as 53% of cases[24]. However a a cohort study from Pakistan found that the common presentation of FSGS was SDNS children[15], In contrast, FSGS was less common in studies from Japan (which is also a part of South East Asia)[25]. and Kuwait[26].A study done in Jordan[27], they found SRNS was the most common clinical presentation of FSGS as in the Egyptian study done by El-Refaey et al[28]**.** This difference in prevalence can be explained by difference of indications for renal biopsy in some studies and also small sample size. The mean age of presentation in our children was 5.15 ± 3.29 [range 1 - 15 years].3.71 years which is younger than other studies from Egypt and Turkey that reported a mean age of 6–7 years at baseline[28, 29]. In our study, there was a predominance of male patients (60%) as observed in other studies[28-30]. In our study 27 (65.9%) were males, male: female ratio was 1.9. Earlier studies have shown that there is male predominance and majority of the patients with FSGS present with microscopic hematuria and hypertension[30-32].A study done by Jellouli et al showed that 14 (47%) females and 16 (5%) males. The mean age of disease onset was 7.3±4.6 years range (1.3-14 years)[33]. On the other hand, a study done by Almardini et al showed that 60 % were males, with a male to female ratio of 1.8:1. Mean age at presentation was 3.71 ± 2.59 years with a range of two months and 14 years[27].In a cohort study, 67.6% of the patients were male[29]. The clinical features at presentation of our patients were similar to other studies. Of these children 19 (46.3%) children had atypical presentation, 15(36.6%) children had renal impairment, 9(22%) children had hematuria and 17(17.5%) had hypertension. In a study from Turkey showed that 3 (10%) patients had microscopic hematuria, 6(18%) had elevated serum creatinine and 15 (44.1%) had hypertension[29]. In our current study, 29.3% achieved complete remission at last follow-up and partial remission was achieved in 31.3%. El-Refaey et al[28]reported in his 72 cohort of Egyptian children that only 16.7% achieved complete remission while 47.2% had partial remission, whereas a study from the Turkish pediatric nephrology FSGS study group of 148 patients reported complete remission in 33.8%[34]. On the other hand, Data from previous cohort studies of FSGS in children have shown that the outcome is variable and the frequency of end-stage renal disease ranges widely from 25% to 50%[29],[34, 35]after 15 years of follow-up. In our series 9 (22%) progressed to ESRD, 2 (2.9%) underwent successful renal transplantation which is less than other study from Jordan showed that children progressed toend stage renal disease accounted as 30% of the children[27]**.**While in Tunisian study they found that 12(40%) patients had renal failure and 8(27%) of them had end stage renal disease[33].

Study limitation

The study had several limitations like small sample size and also absence of genetic testing of children with FSGS nephrotic syndrome. Future multicenter study with larger number of patients is needed.

Conclusion

As this is the first retrospective study that document patterns of renal pathology from Libyan children with nephrotic syndrome. Of the group 54.6% had FSGS. More than two third of the cases of FSGS in our population presented as steroid resistant nephrotic syndrome. Positive family history of nephrotic syndrome in 24% of our patient. At presentation 36.6% patients had presented with renal impairment only 24.4% of FSGS progressed to ESRD.

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