Prevalence and Outcome of Focal Segmental Glomerulosclerosis in Iranian Children With Nephrotic Syndrome

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Introduction. Some evidence suggest an increase in the prevalence of focal segmental glomerular sclerosis (FSGS) in children. To date, there has been no study of the outcome in children with FSGS and its frequency over several decades in Iran. We aimed to report the changing trend of FSGS incidence and its outcome in a sample of Iranian children.

Materials and Methods. Between 1982 and 2008, all 716 kidney biopsies performed in children referred to Ali Asghar Children Hospital were recorded and confirmed cases with FSGS lesions were further evaluated. Baseline and clinical characteristics of all FSGS patients were assessed and the therapies and outcomes were reviewed.

Results. The incidence rate of FSGS was 10.1% between 1982 and 1990, which was significantly increased to as high as 20.5% after the year 2000 (P = .001). Among 64 children with FSGS, 20 progressed to end-stage renal disease with a mean survival time of 11.45 years (standard error of mean, 1.34 years). Kidney survival rates were 90.4%, 69%, and 47% at 1, 5 and 10 years of follow-up.

Conclusions. Our study demonstrates an increasing trend in FSGS incidence in Iranian children. However, kidney survival rates of our patients were similar to those reported by others in different countries.

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INTRODUCTION

Nephrotic syndrome, which is characterized by heavy proteinuria, hypoalbuminemia, hyperlipidemia, and often edema, is estimated to have an approximately overall prevalence rate of 2 to 5 cases per 100 000 children with the cumulative prevalence of 15.5 cases per 100 000 during childhood.[1] Focal segmental glomerular sclerosis (FSGS) is a cause of nephrotic syndrome characterized by proteinuria with and without renal insufficiency in children. Primary or idiopathic FSGS is considered when no etiology can be found. Primary FSGS was observed in about 7% of children who underwent kidney biopsy for evaluation of nephrotic syndrome in the report of the International Study of Kidney Disease in Children.[2]

The incidence of FSGS among children diagnosed with nephrotic syndrome has been increased in recent years in some studies.[3,4] In contrast, some other studies did not show any increase in the incidence of FSGS.[5] Since ethnicity seems to play an important role in the incidence of FSGS, multiple studies in different races should be done to determine disease frequency in various demographics. Additionally, the outcome of children with FSGS is also dependent on the genetic background and ethnicity.[6] Some races form a number of FSGS patients who progress to

end-stage renal disease (ESRD) more than other ethnic populations.[7]

To date, there has been no study of the outcome in children with FSGS and also its frequency over several decades in Iran. In this study, we determined the frequency of FSGS in children who underwent kidney biopsy over several decades in a major referral pediatric nephrology center in Tehran, Iran. Other aims of this study were to analyze clinical characteristics, course, resistance to steroid and other immunosuppressive medications, and outcome of Iranian children with primary FSGS referred to Ali Asghar Children Hospital.

MATERIALS AND METHODS

Patients Enrollment

During a 26-year period between 1982 and 2008, all kidney biopsies performed in children referred to Ali Asghar Children Hospital were recorded and assessed. It must be noted that all the biopsies were performed at Ali Asghar Hospital as a referral center for pediatric nephrology diseases. The specimens were taken for light microscopy and immunofluorescence assays and were indicated when the patient did not respond to steroid therapy. Reviewing these histopathological features, patients with a confirmed diagnosis of FSGS lesions (n = 84) were considered as the eligible ones to be enrolled for further assessment. The prevalence rate of FSGS was calculated year by year and also during different decades.

Medical records were not available for 20 cases. Children younger than 3 months with nephrotic syndrome (congenital nephrotic syndrome), reflux nephropathy, and any systemic disease were also excluded from the study. Finally, 64 children diagnosed as FSGS at Ali Asghar Children Hospital were evaluated and all medical records of these eligible cases were assessed in this study. After the enrollment, many variables were recorded for each patient including age at disease onset, gender, family history of nephrotic syndrome, choice of treatment, resistance to steroid and other immunosuppressive medications, microscopic and macroscopic hematuria, hypertension, and the final outcome.

Definitions

Hypertension was defined as a blood pressure higher than 95 percentile for age.[8] Moreover, the diagnosis of FSGS was based on pathologic changes. All of the patients were treated initially with prednisolone, 2 *mg/kg/d*, for one month. Complete response was defined as proteinuria of 4 *mg/m²/h or more*, while partial response was considered when a urinary protein excretion less than 50% of baseline proteinuria occurred. Also, resistance to steroid therapy was defined by the absence of remission after 4 weeks of treatment.[8] Immunosuppressive drugs were given to steroid-resistant patients. Patients who were initially steroid sensitive and subsequently became steroid resistant were defined as late nonresponders.[8]

Statistical Analyses

Data were analyzed using the the SPSS software (Statistical Package for the Social Sciences, version 16.0, SPSS Inc, Chicago, Ill, USA). In descriptive reports, mean, standard deviation, and standard error of mean were used for quantitative variables and frequency rates were reported to describe qualitative characteristics. Standard deviation was calculated and used to present the discrepancy of each baseline continuous variable, while standard error of mean was used to show the variance of calculated continuous outcomes (survival time) in order to generalize the findings to the target population. The prevalence rates were calculated by dividing the number of new cases with FSGS to the total number of biopsied patients during each period of time. Afterward, the chi-square test was used to evaluate the significance of any differences in the prevalence rates of FSGS within different decades.

The Kaplan-Meier procedure was used to perform survival analysis of renal outcomes in children with FSGS. In survival analysis, the outcome was considered as ESRD and survival rates and means were calculated. The log-rank test was also used to evaluate the significance of the difference between survival mean in different subgroups of the study. The Cox regression analysis was used to assess multivariable association between different variables and kidney survival mean. In all analytic procedures, a *P* value less than .05 was considered significant.

RESULTS

Prevalence Rate

Between 1982 and 2008, a total of 716 kidney

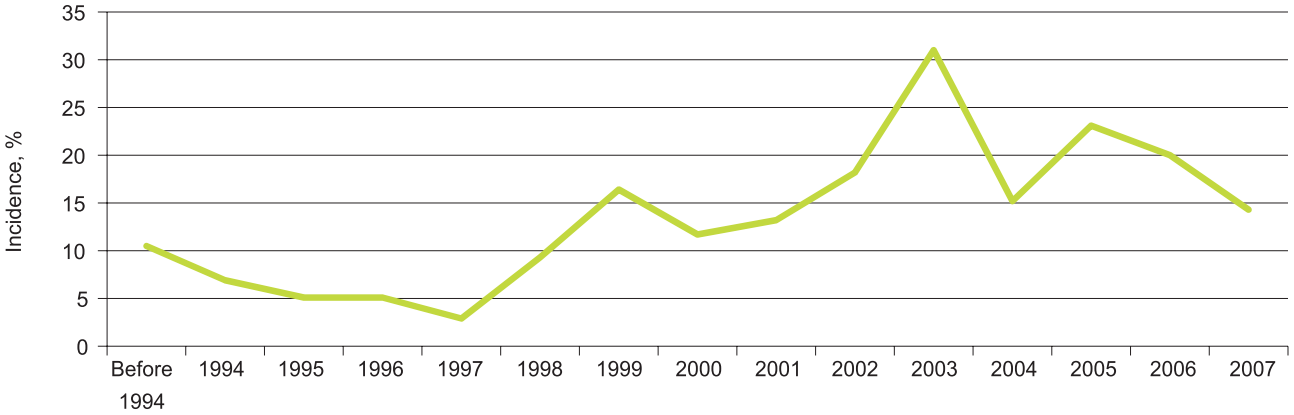

Figure 1. Changing trend in the prevalence rate of focal segmental glomerulosclerosis among Iranian children biopsied for nephritic syndrome

biopsies were performed in Ali Asghar Children Hospital. Eighty-four children (11.7%) were diagnosed with FSGS at this referral hospital. The changing trend of FSGS prevalence rate during this 26-year period is illustrated in Figure 1. Moreover, the prevalence of FSGS in patients who underwent kidney biopsy was evaluated in 3 periods of time. The prevalence of FSGS was 10.1% (boys, 61.5%; mean age at onset, 7.00 ± 5.66 years) between 1982 and 1990 and 9.2% (boys, 61.5%; mean age at onset, 6.81 ± 4.09 years) between 1991 and 2000, while after the year 2000, the prevalence rate increased significantly (P = .001) and reached as high as 20.5% (boys, 66.7%; mean age at onset, 7.96 ± 3.83 years). With regard to the population with idiopathic nephrotic syndrome, the prevalence rate of FSGS was 5.3% between 1982 and 1990, 13.7% between 1991 and 2000, and 26.1% after 2000.

Table 1. Demographic and Clinical Characteristics of Children With Focal Segmental Glomerulosclerosis

Parameter	Value
Age at disease onset, y	6.97 ± 4.10
Gender, %	
Girl	34.4
Boy	65.5
Family History, %	14.0
Clinical features, %	
Microscopic hematuria	34.3
Gross hematuria	6.0
Hypertension	37.5
Steroid resistance, %	
Initial	8.6
Late	8.6
Treatment, %	
Cyclophosphamide	43.4
Cyclosporine A	82.7
Mycophenolate mofetil	50.0

Baseline Characteristics

We reviewed 64 records of children with FSGS during a period of 26 years. Baseline, demographic and clinical characteristics of the FSGS patients are shown in Table 1. Forty-two patients (65.6%) were boy and the boy-girl ratio was 1.9:1. The mean age at disease onset was 6.97 ± 4.1 years. Familial history was positive in 9 of 64 children (14%). Twenty-two patients (34.3%) had microscopic hematuria, and gross hematuria was presented in 4 patients (6%) at initial presentation. Blood pressure was high in 24 patients (37.5%).

Treatment Follow-up

Fifty-eight patients were followed for a median of 5.7 years (range, 3 months to 20 years). Eight patients were followed for more than 10 years. Among these 58 children, initial steroid resistance was seen in 47 (81.3%) and late resistance in 5 patients (8.6%). In contrast, 2 patients completely recovered and responded to steroid without any recurrence. They were followed for 5 and 7 years, respectively. The other 4 patients responded to steroid but suffered the recurrence. Finally, all of these 4 patients recovered. One of these patients received cyclosporine A with partial response, but responded to a combination of cyclosporine A and mycophenolate mofetil and recovered completely.

The clinical status at the last visit in patients with initial and/or late steroid resistance showed that 14 patients (26.9%) gained complete recovery, while 32 patients (61.5%) were resistant to

immunosuppressive drugs other than steroid. Among 14 patients who recovered, 9 responded completely to cyclosporine A. Four patients had recurrence on cyclosporine therapy and responded completely to the combination of cyclosporine A and mycophenolate mofetil. Additionally, 1 patient received mycophenolate mofetil only and recovered.

Survival

Twenty patients (20 of 58; 34.4%) progressed to ESRD after a mean time of 4.9 years (range, 3 months to 12 years), and the mean survival time was 11.45 years (standard error of mean, 1.34 years). The kidney survival rates were 90.4%, 69%, and 47% at 1, 5, and 10 years of follow-up, respectively (Figure 2). Death occurred in 4 patients. The causes of mortality were septicemia in 2 of them and ESRD and cardiopulmonary complications in the other 2 patients.

As shown in Table 2, the univariable relationship between kidney survival and some other factors were also assessed. These factors were included: age at presentation, gender, initial resistance to steroid and other immunosuppressive medications, microscopic and macroscopic hematuria, and hypertension. Children with initial resistance to the treatment had a significantly lower mean kidney survival (7.66 years; standard error of mean, 0.72 years versus 18.00 years; standard error of mean, 1.85 years; P = .009). In addition, FSGS patients with a positive family history had also suffered from a significant lower kidney survival time (5.50 years; standard error of mean, 0.98 years versus 13.16 years; standard error of mean, 1.56 years; P = .006). Although the mean survival time of kidney in FSGS children was calculated longer in girls (9.91 years; standard error of mean, 1.87 years in girls versus 9.52 years; standard error of mean, 0.87 years in boys) and patients with the age at diagnosis less than 8 years (11.03 years; standard error of mean, 1.50 years versus 8.73 years; standard error of mean, 0.96 years in those aged 8 years and older), these differences failed to meet a significance level (log-rank test P = .28 and P = .47, respectively). Multivariable analysis was performed to assess the independent factors affecting kidney survival by means of Cox regression model. The only significant factor was initial resistance to treatment (odds ratio, 8.80; P = .04).

Table 2. Univariable Analysis of Factors Potentially Associated With Kidney Survival Time in Children with Focal Segmental Glomerulosclerosis

Parameter	Survival Time, y (Mean ± SEM)*	*P*
Age at disease onset, y		
< 8	11.03 ± 1.50	
≥ 8	8.73 ± 0.96	.47
Gender		
Girl	9.91 ± 1.87	
Boy	9.52 ± 0.87	.28
Family History		
Negative	13.16 ± 1.56	
Positive	5.50 ± 0.98	.006
Hematuria		
Negative	8.29 ± 0.91	
Positive	14.61 ± 2.00	.20
Hypertension		
Negative	11.64 ± 1.67	
Positive	9.51 ± 1.23	.90
Initial drug resistance		
Negative	18.00 ± 1.85	
Positive	7.66 ± 0.72	.009

*SEM indicates standard error of mean.

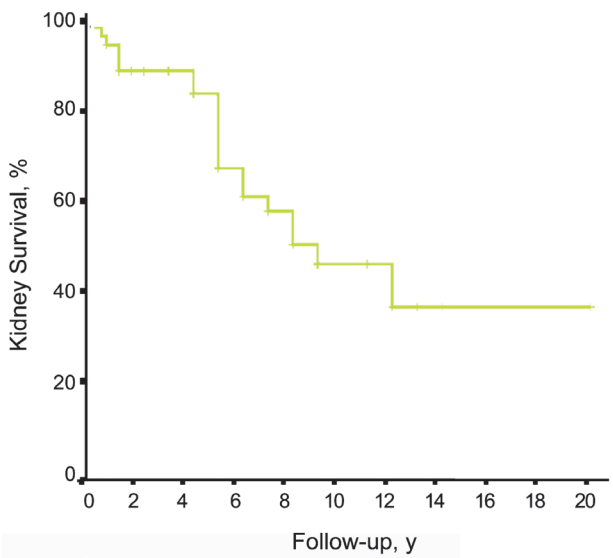

Figure 2. Kidney survival rate in Iranian children with focal segmental glomerulosclerosis

DISCUSSION

Reports of the International Study of Kidney Disease in Children in 1970 and 1978 showed that the incidence of FSGS was 7% to 9% in patients who were systematically biopsied with the diagnosis of nephrosis.[2,9] However, recent studies have shown an increased incidence of FSGS

in children.[4,5,10,11] Our series also depicted that there was an increasing trend in the prevalence of FSGS in our sample of Iranian children, which seems to be slowed down a bit after 2006. This prevalence is approximately doubled from 10% to 20% during more than 2 decades in Iranian children with idiopathic nephrotic syndrome. Similarly, Gulati and colleagues concluded a shift toward an increasing prevalence of FSGS (from 20% to 47%) over the years in the Indian children.[11] Moreover, a Canadian study of Caucasian children found the incidence of FSGS to have increased from 0.37 to 0.94 per 100 000 per year between the years 1985 and 2002.[4] A separate biopsy-based study of North American children in Southwestern United States demonstrated an increase of FSGS from 11% in the years between 1985 and 1995 to 25% in the following decade.[12] With regard to the prevalence of idiopathic nephrotic syndrome, more than 65% of all biopsies in our series were performed due to nephrotic syndrome alone or in combination with other manifestations such as nephritic syndrome. In a 10-year retrospective study by Bazina and colleagues,[13] the main indication for kidney biopsy in children was also nephrotic syndrome (41.5%).

Since these studies did not consider clinical variables, the potential confounding clinical characteristics such as age at diagnosis, gender, and ethnicity may have influenced their results. On the other hand, there is a longitudinal difference in biopsy selection bias in these reports which influence the incidence of FSGS in patients with nephrotic syndrome. Boyer and coworkers did not show any increase in FSGS incidence longitudinally, and this result can be secondary to a similar distribution of age, gender, and race of patients over time.[12] There was a predominance of males in our study (65.5%). This finding was similar to other studies,[6,14] especially the most recent ones in our region which reported that 67.6% and 66.7% of Turkish and Egyptian children with FSGS were male, respectively.[15,16] The mean age at presentation was 6.97 years in our patients. Most studies have demonstrated that the mean age at presentation is 6 to 7 years.[16-18] Additionally our findings depict that although the mean age at the onset of disease has nonsignificantly slightly increased, the male dominance has not changed during recent decades.

Overall, having evaluated 716 kidney biopsies within a period of 26 years, our study is one the largest reports of FSGS children in Iran since yet. In a previous single-center investigation by Ahmadzadeh and colleagues,[19] of 231 biopsied children during a 7-year period, FSGS was the most common pathology in children with steroid-resistant nephrotic syndrome (37.5%). In another series of 400 evaluated biopsy specimens in all age groups between 2006 and 2007 by Mohammadhoseiniakbari and associates,[20] FSGS was found to be the most common glomerulonephritis (37.1%) in all age groups including children. A higher cross-sectional prevalence of FSGS (41%) was also reported in a series of 44 Iranian children with nephrotic syndrome by Safaei and colleagues[21] during a 7-year period.

The initial response to steroid in patients with FSGS is poor. Seventy percent to 80% of these patients are steroid resistant.[22] In our study, initial steroid resistance was seen in 81.3% and only 5 patients (7.8%) received prednisolone as the only therapy and recovered completely. Full data on the treatment outcome of our FSGS patients are previously published.[23] However, since mild and steroid-sensitive FSGS patients were not biopsied in most studies, it is impossible to determine the true incidence of steroid sensitivity in these patients.

The outcome of FSGS is variable. In different reports, renal insufficiency is reported in 20% to 65% of patients.[24,25] According to the North American Pediatric Renal Trials and Collaborative Studies report, FSGS is the most common etiology of ESRD in some races, accounting for 23% of children with ESRD. The studies that assessed survival analysis are few.[6,24,26-28] Kidney survival rate in these studies are variable and depend on the race of patients, age at presentation, and the initial response to corticosteroids.[6,7,28] We showed that 34.4% of our patients progressed to ESRD. Our kidney survival rates (90.4%, 69%, and 47% at 1, 5, and 10 years, respectively) were similar to those reported by Canadian studies,[26,27] but more than the estimate of survival rate from Cameron,[26] and less than that reported from Brazil and Egypt.[6,16,24] Evaluating 72 biopsy-proven FSGS Egyptian children between 1995 and 2008, El-Refaey and colleagues reported kidney survival rates of 93% and 68% at 5 and 10 years, respectively.[16]

In different studies, the relationship between some prognostic factors and outcome of patients with FSGS was determined. The overall kidney

survival seems to be more favorable in younger patients, white patients, and patients with initial response to corticosteroid. Some studies in pediatric population did not show any relationship between histologic variants and the response to steroids and outcome of patients with FSGS. This finding is in contrast with studies performed in adult patients. Our analysis to evaluate the factors affecting kidney survival showed that a positive family history and initial resistance to steroid were significantly associated with a poor outcome and lower kidney survival. However, in further multilevel analysis, initial resistance to steroids was the only significant indicator of kidney survival in FSGS children. As mentioned, this was confirmed with some previous studies in other races, too.[6,7,28]

It must be noted that our report had some limitations associated with the retrospective design of the study and some missing data in medical records of the patients. However, to the best of our knowledge, this is the largest report of FSGS prevalence in Iranian children. The considerable prevalence of FSGS in children necessitates performance of further studies focusing on the factors affecting short-term and long-term prognosis in order to improve the outcome in these patients.

CONCLUSIONS

Our study demonstrates an increasing trend in FSGS incidence in Iranian children. However, kidney survival rates of our patients were similar to those reported by others in different countries.

CONFLICT OF INTEREST

None declared.

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