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The Effect of Parental Consanguinity on Clinical Course and Outcome of Children with Focal Segmental Glomerulosclerosis, a Report from Isfahan, Iran

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Introduction. Focal segmental glomerulosclerosis (FSGS) accounts for 20% of nephrotic syndromes among children as well as 75% of the steroid resistant nephrotic syndrome (SRNS). The aim of the present study was to evaluate the influence of parental consanguinity on clinical course and outcome of FSGS in children.

Methods. This historical cohort was carried out on 69 children affected by steroid resistant FSGS. Patients' data were recorded at the initial and the final analyses and response to therapeutic measures. Subjects were also questioned about the history of parental consanguinity.

Results. Forty-four participants (63.8%) were male with a male to female proportion of 1.76:1. Mean baseline age was 5.69 ± 2.39 (range: 1 to 10). Fifty-one patients (73.9%) reported consanguinity. A more significant resistance to cyclosporine A and cyclophosphamide was observed in participants denoting parental consanguinity than those with no kinship. The average renal survival time obtained significantly lower among those reporting consanguinity compared to the others (8.33 vs. 10.44 years, $P < .05$). According to univariate analysis results, parental consanguinity was a risk factor for developing chronic kidney disease (HR = 4.56, 95% CI: 1.06 to 19.47; $P < .05$).

Conclusion. Patients with FSGS plus parental consanguinity presented less renal survival time with more resistance to cures being more predisposed to the development of CKD.

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INTRODUCTION

As a clinical-pathological ailment, focal segmental glomerulosclerosis (FSGS) is represented by heavy proteinuria, edema, hypoalbuminemia, and hyperlipidemia.¹ Almost 20% of nephrotic disorders has been reported to occur in children due to FSGS, which also leads to 75% of steroid-resistant nephrotic syndrome (SRNS) cases in children.^{1,2} A considerable number of children with steroid-resistant FSGS are therefore influenced by end-stage renal disease (ESRD).³ The two classes of

FSGS include primary (idiopathic) and secondary (resulting from viruses, medications, structural pathologies, ischemia, and family/ genetic factors).¹

Reports indicate two inheritable kinds of genetic causes of FSGS, namely autosomal dominant and recessive,⁴ with the latter occurring at a young age showing more aggressiveness.⁵ Autosomal recessive heredity increases as a result of consanguine marriages.⁴ The more aggressiveness of autosomal recessive type of FSGS and the its elevated potential heredity because of consanguinity led

to the hypothesis that the parental consanguinity could influence the clinical course and therapeutic outcomes of children affected by FSGS.

Consanguine marriage has been a custom throughout the Middle East and also North Africa resulting from religious and culture-related beliefs.⁶ Despite the important and potential impact of cognation on the FSGS course, little related data are available. Indeed, most of Iranian and international investigations in the Middle East on children with FSGS or other SRNS cases scrutinized these ailments with regard to other factors.⁷⁻¹³ Even so, measurement of potential risk factors for chronic kidney diseases (CKD) development in children with SRNS has been investigated in a number of researches.^{8,14-19} Nevertheless, investigation on new factors (e.g. consanguinity) affecting this issue can helpfully complete the puzzle of influencing factors linked to renal failure development.

The aim of this trial to evaluate the influence of parental consanguinity on clinical course and therapeutic outcomes in children affected by FSGS. Furthermore, the risk factors of CKD development were assessed among the surveyed population and also children having or lacking parental consanguinity.

MATERIALS AND METHODS

Study Design and Population

This historical cohort study was conducted on children with steroid-resistant FSGS who admitted to the AL-Zahra and Imam-Hosseini children hospitals as two main tertiary care centers of pediatric nephrology diseases in Isfahan, Iran from January 2003 to January 2017. The inclusion criteria were as follows: 1) biopsy-proven steroid-resistant FSGS, 2) the age of younger than 16 years at onset, and 3) being at least 1 year under clinical follow-up. Patients with following characteristics were excluded from the study: 1) the presence of any cause of secondary FSGS including sickle cell disease, reflux nephropathy, viral infections, and renal agenesis, 2) the confirmed autosomal-dominant cases of FSGS, and 3) incomplete demographic, pathologic and laboratory data. All eligible patients and their medical records were evaluated by the same medical team. The study protocol was approved by the ethical committee of Isfahan University of Medical Sciences (Ethics Code: 191091). This research followed the tenets of

the Declaration of Helsinki. The informed consent was obtained from all parents/caregivers of the patients in this study.

Patient Evaluation and Retrospective Data Collection

The medical records were evaluated and the following information was extracted: parental consanguinity, gender, age, age at disease onset, weight, height, hypertension and hematuria, serum creatinine, serum albumin and proteinuria at disease onset. Moreover, we evaluated the patients during follow-up period and in the last evaluation, their information, including serum creatinine and albumin, proteinuria, treatment outcome (CKD, ESRD, and death), progression time to CKD (if any) and response to treatments was recorded. In addition, pathologic types of FSGS in the participants were determined.

Definitions

FSGS diagnosis was based on pathologic criteria and pathologic variants of FSGS were classified as: not otherwise specified (NOS), perihilar variant, cellular variant, tip lesion and collapsing variant.²⁰ Parental consanguinity was defined as a union between two individuals with the inbreeding coefficient (F) greater than 0.016, which were including marriages between first cousins, double first cousins, second cousins, and double second cousins.⁶ Disease onset was considered as presentation of proteinuria in the patients. Hypertension was defined as systolic or diastolic blood pressure above the 95th percentile for age, gender, and height.¹⁰ Hematuria was established in patients with more than five red blood cells per high power field in microscopic urinalysis.¹⁰ The cut-off values for serum creatinine were considered in children less than 3 and 3 to 18 years of age as 0.6 and 1, respectively.²¹ Glomerular filtration rate (GFR) was estimated using the updated Schwartz equation.²² GFR < 60 mL/min/ 1.73 m² for more than three months was defined as CKD.²³ GFR < 15 mL/min/ 1.73 m² or need for renal replacement therapy was determined as ESRD.²³ Prednisolone was administered at the dosage of 60 mg/m²/d or 2 mg/kg/d for 4 weeks followed by taking for four more weeks at the same dosage every other day. Failure to remission after 4 weeks of therapy was determined as early nonresponder to steroids

and patients who initially responded to steroids and after that became resistant were defined as late nonresponders.²⁴ Early or late nonresponders to steroids were treated by cyclosporine A (CsA) and/or cyclophosphamide (CP). Patients who didn't respond properly to CsA or CP were treated with mycophenolate mofetil (MMF) and/or rituximab. Complete remission (CR) was defined as no proteinuria and also partial remission (PR) was determined as no edema and proteinuria between 4 to 40 mg/m²/h.²⁴ Response to treatment was considered when CR was occurred and partial remission or no remission was considered as resistance to treatment.²⁴

Statistical Analysis

Continuous data were expressed as mean ± SD and categorical values were described as percentages. The differences between patients with and without consanguinity were evaluated using independent sample t-test or Mann-Whitney U test. Categorical values were compared between groups using chi-square or Fisher's exact test. Renal survival analysis was performed using Kaplan-Meier life table survival analysis. The outcome in survival analysis was considered as CKD and also time from onset to CKD diagnosis was measured and included in the analysis. For comparison the renal survival rate in different subgroups Log-rank test was performed. Regarding survival analysis, data were expressed as mean ± SE and also, we calculated renal survival at 1, 5, and 10 years of follow-up. For determining the risk factors of CKD, we used cox regression analysis and both univariate and multivariate hazard ratios (HRs) were reported. A *P* value < .05 was considered significant. All statistical analyses were performed using MedCalc 15.8 software (*MedCalc*, Belgium).

RESULTS

Patients' Characteristics

Eighty-five confirmed FSGS cases were evaluated for including to the study. Sixteen cases were excluded due to following reasons: five cases due to having secondary causes of FSGS, one because of autosomal dominant pattern, and ten subjects due to incomplete medical records. Ultimately, 69 patients were analyzed. Forty-four patients (63.8%) were male and male to female ratio was 1.7:1. The mean age at disease onset was 5.69 ± 2.39

Table 1. Baseline Characteristics of Patients with Focal Segmental Glomerulosclerosis

Variables	Value
Gender	
Male	44
Female	25
Age at disease onset, y	5.69 ± 2.39
Weight, kg	39.95 ± 18.17
Height, cm	131.18 ± 20.53
Parental Consanguinity, n (%)	51 (73.9)
Hypertension, n (%)	21 (30.4)
Hematuria, n (%)	14 (20.3)
Serum Creatinine at Presentation, mg/dL	0.8 ± 0.13
Serum Albumin at Presentation, g/dL	2.39 ± 0.89
Proteinuria at Presentation, g/d	3.38 ± 1.26

(range: 1 to 10) years. Fifty-one patients (73.9%) were born from consanguineous parents. Among patients with parental consanguinity, 40 patients (78.4%) were offspring of the first cousin marriages followed by a second cousin and double second cousin, which was seen in 8 (15.7%) and 3 (5.9%) patients; respectively. All patients in both groups had primary FSGS and there were no other FSGS cases in their families. The siblings of the children in consanguineous group did not have other confirmed genetic diseases including metabolic, neurological, and urological disorders. Table 1 summarizes the characteristics of studied patients at disease onset.

Outcome and Treatment Follow Up

The mean time of follow up was 5.76 ± 3.29 (range: 1 to 13) years. Forty-two patients (60.9%) were followed for more than 5 years and 12 patients (17.4%) were followed for more than 10 years. In the last evaluation, seven patients (10.1%) showed CKD and 18 patients (26.1%) showed ESRD. The mean time of progression to CKD was 3.63 ± 2.33 (range: 1 to 10) years. During follow-up, three patients (4.3%) expired and etiologies were septicemia in two patients and heart failure in one patient. Table 2 shows the features of patients and treatments through the last evaluation.

Comparison the Patients With and Without Consanguinity

Table 3 compares the characteristics of patients with and without consanguinity. According to the table, there were no significant differences in patients with and without parental consanguinity in

Table 2. Clinical Outcome at Last Evaluation and Response to Treatments in Children with Focal Segmental Glomerulosclerosis

Variables	Value
Age at Last Evaluation, y	12.15 ± 4.88
Time of Follow Up, y	5.76 ± 3.29
Serum Cr at Last Evaluation, mg/dL	1.74 ± 1.81
Serum Albumin at Last Evaluation, g/dL	3.74 ± 1.13
Proteinuria at Last Evaluation, g/d	0.88 ± 1.19
Progression to CKD, n (%)	7 (10.1)
Progression to ESRD, n (%)	18 (26.1)
Renal Transplantation, n (%)	8 (11.6)
Transplant Rejection, n (%)	2 (2.9)
Expired, n (%)	3 (4.3)
Progression Time to CKD, years from disease onset	3.63 ± 2.33
Pathologic Variants, n (%)	
NOS	30 (43.5)
Tip	18 (26.1)
Perihilar	11 (15.9)
Cellular	10 (14.5)
Collapsing	0
Response to Steroid, n (%)	
CR	19 (27.5)
PR	34 (49.3)
NR	16 (23.2)
Response to Cyclosporine A, n (%)	
CR	36 (63.2)
PR	13 (22.8)
NR	8 (14)
Response to Cyclophosphamide, n (%)	
CR	5 (10.9)
PR	0
NR	41 (89.1)
Response to Mycophenolate Mofetil, n (%)	
CR	5 (20.8)
PR	6 (25)
NR	13 (54.2)
Response to Rituximab, n (%)	
CR	2 (9.1)
PR	4 (18.2)
NR	16 (72.7)
Early Non-responders to Steroid, n (%)	50 (72.5)
Late Non-responders to Steroid, n (%)	19 (27.5)
Resistance to Cyclosporine A, n (%)	21 (36.8)
Resistance to Cyclophosphamide, n (%)	41 (89.1)
Resistance to Mycophenolate Mofetil, n (%)	19 (79.2)
Resistance to Rituximab, n (%)	20 (90.9)

Abbreviation: CKD, chronic kidney disease; ESRD, end stage renal disease; NOS, not otherwise specified; CR: complete remission; PR, partial remission; NR, no remission

terms of the following characteristics: gender, age at onset, hypertension, hematuria, serum creatinine at disease onset, and rate of CKD progression. In patients with and without consanguinity, the frequencies of age < 6 years, serum creatinine ≥ 0.8 mg/dL, albumin < 2.5 g/dL, and proteinuria ≥ 100 mg/m²/h at disease onset were as follows: 43.1% vs. 50% (*P* > .05), 68.6% vs. 44.4% (*P* > .05),

39.2% vs. 12.5% (*P* < .05), and 45.1% vs. 44.4% (*P* > .05); respectively.

Renal Survival Analysis

In all patients, renal survival rates were 95.7%, 72.5%, and 55.6% at 1, 5, and 10 years of follow-up; respectively. In patients with and without parental consanguinity, the renal survival rates at 1, 5, and 10 years of follow-up were as follows: 96.1%, 64.5%, and 44.1% vs. 94.4%, 92.8%, and 63% (*P* < .05); respectively (Figure). Table 4 shows the details of renal survival analysis in all patients and also subgroups with and without parental consanguinity.

Risk Factors of CKD

In univariate analysis for determining the risk factors associated with CKD in all patients, the following variables at baseline were statistically significant: parental consanguinity, hypertension, hematuria, serum creatinine ≥ 0.8 mg/dL, serum albumin < 2.5 g/dL, proteinuria ≥ 100 mg/m²/h, NOS pathologic variant and resistance to CsA (Table 5). In multivariate analysis, which was performed for all participants, proteinuria more than 100 mg/m²/h at disease onset (HR = 4.72, 95% CI: 1.16 to 19.1; *P* < 0.05) and serum creatinine > 0.8 mg/dL at onset (HR = 4.85, 95% CI: 1.06 to 22.18; *P* < .05) were still statistically significant, however parental consanguinity did was not significant (HR = 2.83, 95% CI: 0.52 to 15.33, *P* > .05). In multivariate analysis of the subgroup of patients with parental consanguinity, only proteinuria ≥ 100 mg/m²/h at disease onset (HR = 4.81, 95% CI: 1.16 to 19.84, *P* < .05) remained the independent predictor of CKD. By applying Cox regression analysis for patients without parental consanguinity, none of the examined variables were statistically significant.

DISCUSSION

In this historic cohort study, 69 Iranian children affected by primary FSGS were investigated; retrospectively. Further assessments included including patients' presentations, response to therapy, disease outcome, renal survival, and risk factors of CKD development. Additionally, these parameters were evaluated and compared in patients having or lacking parental consanguinity. To the best of our knowledge, the present survey

Table 3. The Characteristics Comparison of Patients With and Without Parental Consanguinity

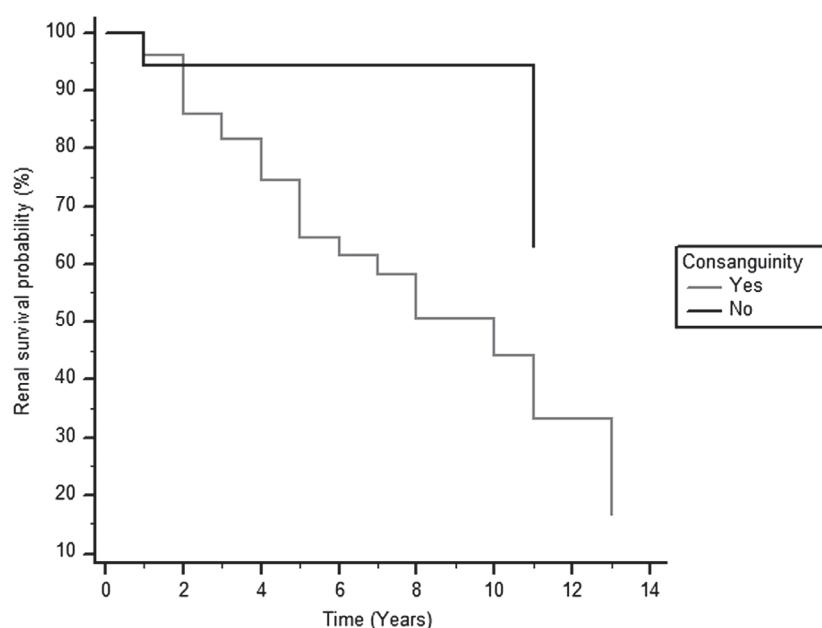
Variables	Patients with Parental Consanguinity (n = 51)	Patients Without Parental Consanguinity (n = 18)	P
Gender			
Male	32	12	> .05
Female	19	6	
Age at Disease Onset, y	5.68 ± 2.52	5.72 ± 2.02	> .05
Hypertension, n (%)	19 (37.2)	2 (11.1)	> .05
Hematuria, n (%)	12 (23.5)	2 (11.1)	> .05
Serum Creatinine at Onset, mg/dL	0.81 ± 0.12	0.75 ± 0.15	> .05
Serum Albumin at Onset, g/dL	2.22 ± 0.92	2.88 ± 0.6	< .05
Proteinuria at Onset, g/d	3.62 ± 1.67	2.7 ± 0.85	< .05
Serum Creatinine at Last Evaluation, mg/dL	2.05 ± 1.99	0.87 ± 0.55	< .05
Serum Albumin at Last Evaluation, g/dL	3.54 ± 1.17	4.32 ± 0.8	< .05
Proteinuria at Last Evaluation, g/d	1.12 ± 1.37	0.2 ± 0.33	< .05
Pathologic Variants, n (%)			
NOS	23 (45.1)	7 (38.9)	> .05
Tip Lesion	13 (25.5)	5 (27.8)	
Perihilar	7 (13.7)	4 (22.2)	
Cellular	8 (15.7)	2 (11.1)	
Collapsing	0	0	
Progression to CKD, n (%)	6 (11.7)	1 (5.5)	> .05
Progression to ESRD, n (%)	17 (33.3)	1 (5.5)	< .05
Transplant Rejection, n (%)	2 (3.9)	0	> .05
Expired, n (%)	3 (5.8)	0	> .05
Progression Time to CKD, years from Disease Onset	3.88 ± 2.34	1.5 ± 0.7	> .05
Response to Steroid, n (%)			
CR	10 (19.6)	9 (50)	< .05
PR	26 (51)	8 (44.5)	
NR	15 (29.4)	1 (5.5)	
Response to Cyclosporine A, n (%)			
CR	24 (54.5)	12 (92.3)	< .05
PR	13 (29.5)	0	
NR	7 (16)	1 (7.7)	
Response to Cyclophosphamide, n (%)			
CR	2 (5.3)	3 (37.5)	< .05
PR	0	0	
NR	36 (94.7)	5 (62.5)	
Response to Mycophenolate Mofetil, n (%)			
CR	2 (9.5)	3 (100)	< .05
PR	6 (28.5)	0	
NR	13 (62)	0	
Response to Rituximab, n (%)			
CR	2 (10.5)	0	> .05
PR	4 (21)	0	
NR	13 (68.5)	3 (100)	
Early Non-responders to Steroids, n (%)	41 (80.4)	9 (50)	< .05
Late Non-responders to Steroids, n (%)	10 (19.6)	9 (50)	< .05
Resistance to Cyclosporine A, n (%)	20 (45.5)	1 (7.7)	< .05
Resistance to Cyclophosphamide, n (%)	36 (94.7)	5 (62.5)	< .05
Resistance to Mycophenolate Mofetil, n (%)	19 (90.5)	0	< .05
Resistance to Rituximab, n (%)	17 (89.5)	3 (100)	> .05

Abbreviations: CKD, chronic kidney disease; ESRD, end stage renal disease; CR, complete remission; PR, partial remission; NR, no remission.

has compared FSGS children having or lacking consanguinity concerning different aspects of FSGS

for the first time.

In the studied cohort, 18 patients (26.1%)



Renal Survival in Children with History of Parental Consanguinity Versus Without Parental Consanguinity

presented ESRD in the end, which was less than that of a research in Iran (34.4%),¹⁰ while it is consistent with the report from Tunis.¹¹ In fact, an ESRD prevalence of 4.9%¹⁸ to 34%¹⁰ has been reported in FSGS children with the utmost prevalence of around 20%.^{7,8,11,17, 23} Differences in ESRD frequencies in children with FSGS can most probably be attributed to the follow up period. Actually, researches performed via lengthier follow-up recounted a greater rate of ESRD.¹⁰ The findings revealed that a higher ESRD rate in children belonged to parents with consanguinity was significant than the other children with FSGS, demonstrating that such children had undesirable consequences as opposed to those with no history of parental cognation. The recorded renal survival rate were 95.7%, 72.5%, and 55.6% at 1, 5, and 10 years of follow-up; respectively, with an incidence somewhat higher than that reported recently in Iran by Hoseini *et al.* who found renal survival rates of 1, 5, and 10 for follow-up as 90.4%, 69%, and 47%; respectively.¹⁰ Furthermore, the present survival rates were more satisfactory than those (50%, 20% at 5 and 10 years of follow-up, respectively) reported in the United Kingdom in 1978.²⁵ On the other hand, the current findings concerning kidney survival rates were less than those of other assessments done in South Korea,²⁶ Egypt,⁹ and Brazil.¹⁷ Besides, this research demonstrated that the lower renal survival rate in children with a record

of parental cognation was significant than those with FSGS. Therefore, as consanguine marriage can be considered as a cause of less renal survival rate in the examined participants. In particular, by determination of renal survival rate in children with no parental consanguinity revealed that the renal survival prevalence in this subgroup is in line with the abovementioned surveys. Nevertheless, there were less significant outcomes among FSGS children with consanguinity; hence; the special reason for the less frequent renal survival in our research than those of others was the elevated parental consanguinity frequency. Fluctuations in population, age at disease incidence, and ahead-of-time response to corticosteroids could probably be the other causes concerning the discrepancies between renal survival rates.

In addition, therapy response was assessed in the children with FSGS. In our study, 72.5% of subjects were early non-responders to corticosteroids, which were reported to be 85.29%,¹³ 81.3%,¹⁰ 76.6%,¹⁷ 63.8%,¹² and 47.8%²⁶ in the literature. According to the findings, 10.9% of the surveyed participants presented CR after treating with CP, with a resistance frequency of 89.1% to CP therapy. The CR frequency using CP revealed very smaller levels than other researches, reporting 20.8%,²⁶ 37%,⁸ and 69.4%.¹² At present, CP is not recommendable to treat SRNS²⁷ due to elevated resistance rate and side effects. Regarding CsA,

Table 4. Renal Survival in Different Subgroups of Patients

Characteristics	All Patients (n = 69)				Patients with Parental Consanguinity (n = 51)				Patients Without Parental Consanguinity (n = 18)			
	Renal Survival Time (Years)				Renal Survival Time (Years)				Renal Survival Time (Years)			
	Mean	SE	Median	P	Mean	SE	Median	P	Mean	SE	Median	P
Consanguinity												
Yes	8.33	0.7	10	< .05								
No	10.44	0.76	-									
Gender												
Male	9.14	0.53	11	< .05	8.4	0.69	11	> .05	11	0	-	> .05
Female	7.76	1.08	7		7.23	1.16	6		6	0.91	-	
Age												
< 6	7.39	0.79	-	> .05	6.4	0.93	5	< .05	9	0.94	-	> .05
≥ 6	8.52	0.44	11		8.11	0.54	11		11	0	-	
Hypertension												
Yes	5.91	1.01	4	< .001	5.86	1.03	4	< .05	3.75	1.94	1	< .05
No	10.68	0.66	13		10	0.87	10		6	0	-	
Hematuria												
Yes	6.20	1.38	5	< .05	6.22	1.46	5	> .05	4.5	2.47	1	< .05
No	9.87	0.63	11		8.94	0.78	11		7	0	-	
Serum Creatinine at Disease Onset												
< 0.8 mg/dL	10.06	0.5	11	< .05	8.94	0.83	10	> .05	11	0	-	> .05
≥ 0.8 mg/dL	8.04	0.75	8		7.72	0.82	8		9.75	1.65	11	
Serum Albumin at Disease Onset												
< 2.5 g/dL	4.15	0.57	4	< .001	4.13	0.58	4	< .001	1	0	1	< .001
≥ 2.5 g/dL	9.69	0.2	13		9.53	0.31	13		1	0	11	
Proteinuria at Disease Onset												
< 100 mg/m ² /h	10.99	0.61	13	< .001	10.63	0.78	13	< .001	11	0	11	> .05
≥ 100 mg/m ² /h	5.92	0.77	5		4.87	0.73	5		9.75	1.16	-	
Pathologic Variants												
NOS	6.88	0.75	8	< .05	5.8	0.79	5	< .001	7	0	-	< .05
Tip Lesion	8.08	0.76	10		7.39	0.94	7		10	0	-	
Cellular	10	0.94	13		10	0	13		11	0	-	
Perihilar	11	0	11		10	0	-		11	0	11	
Resistance to Steroids												
Early	7.58	0.56	10	< .05	6.75	0.55	8	< .05	9.88	1.48	11	> .05
Late	13	0	-		11	0	-		11	0	-	
Resistance to Cyclosporine A												
Yes	4.93	0.58	4	< .001	4.56	0.58	4	< .001	1	0	1	< .001
No	11.74	0.6	13		11.62	0.82	13		11	0	11	
Resistance to Cyclophosphamide												
Yes	7.73	0.72	8	> .05	7.55	0.77	7	> .05	9	2.5	11	> .05
No	11	0	-		7	0	-		11	0	-	
Resistance to Mycophenolate Mofetil												
Yes	6.4	0.87	6	< .05	6.4	0.87	6	> .05	-	-	-	-
No	11	0	11		10	0	-		11	0	-	
Resistance to Rituximab												
Yes	4.02	0.59	3	> .05	4.17	0.6	4	> .05	1	0	1	-
No	7	0	-		7	0	-		-	-	-	

Abbreviations: SE, standard error; NOS, not otherwise specified.

the response rate of the subjects was satisfactory relative to the recently published one (about

50%).^{8,12} MMF resistance frequency and rituximab were determined at 79.2% and 90.9%, respectively.

Table 5. Risk Factors of CKD in All Patients and Children With and Without Parental Consanguinity

Variables	All Patients (n = 69)		Patients with Parental Consanguinity (n = 51)		Patients Without Parental Consanguinity (n = 18)	
	HR (95 % CI)	P	HR (95 % CI)	P	HR (95 % CI)	P
Parental Consanguinity (Yes vs. No)	4.56 (1.06 to 19.47)	< .05				
Gender (Male vs. Female)	-	> .05	-	> .05	-	> .05
Age at Disease Onset (< 6 years vs. ≥ 6 years)	-	> .05	-	> .05	-	> .05
Hypertension (Yes vs. No)	4.03 (1.79 to 9.08)	< .05	2.99 (1.28 to 6.98)	< .05	-	> .05
Hematuria (Yes vs. No)	2.99 (1.33 to 6.76)	< .05	-	> .05	-	> .05
Serum Creatinine at Presentation (< 0.8 mg/dL vs. ≥ 0.8 mg/dL)	4.06 (1.21 to 13.56)	< .05	-	> .05	-	> .05
Serum Albumin at Presentation (< 2.5 g/dL vs. ≥ 2.5 g/dL)	39.31 (9.07 to 170.35)	< .001	24.64 (5.66 to 107.1)	< .001	-	> .05
Proteinuria at Presentation (< 100 mg/m ² /h vs. ≥ 100 mg/m ² /h)	5.55 (2.28 to 13.5)	< .001	7.29 (2.65 to 20.04)	< .001	-	> .05
Pathologic Variant (NOS vs. Other Pathologic Variants)	3.52 (1.4 to 8.8)	< .05	4.34 (1.64 to 11.48)	< .05	-	> .05
Pathologic Variant (Tip Lesion vs. Other Pathologic Variants)	-	> .05	-	> .05	-	> .05
Pathologic Variant (Perihilar vs. Other Pathologic Variants)	-	> .05	-	> .05	-	> .05
Pathologic Variant (Cellular vs. Other Pathologic Variants)	-	> .05	-	> .05	-	> .05
Resistance to Steroids (Early vs. Late)	-	> .05	-	> .05	-	> .05
Resistance to Cyclosporine A (Yes vs. No)	27.77 (6.4 to 120.46)	< .001	18.78 (4.29 to 82.1)	< .001	-	> .05
Resistance to Cyclophosphamide (Yes vs. No)	-	> .05	-	> .05	-	> .05
Resistance to Mycophenolate Mofetil (Yes vs. No)	-	> .05	-	> .05	-	> .05
Resistance to Rituximab (Yes vs. No)	-	> .05	-	> .05	-	> .05

Abbreviations: HR, hazard ratio; NOS, not otherwise specified.

There is controversy concerning the impact of MMF and rituximab on SRNS in previous researches,^{28,29} poor treatment success was obtained by these two drugs in our study. It was found here that FSGS children with consanguine parental marriage had more significant early non-responses to steroids and resistance to CsA, CP, and MMF than the other ones. Based on these observations, these children had higher risk of resistance to SRNS standard therapies, which was shown for CsA recently; a report by Buscher *et al.*³⁰ indicated that children with genetic factors for SRNS presented a low response rate to CsA as opposed to non-genetic participants, which may consistent with the present observations as consanguinity can raise the risk of the FSGS autosomal recessive type and ultimately its genetic factor.

Consanguine marriage has been a customary prevalence in the Middle East and North Africa, including Iran, because of religious and culture-related beliefs.⁶ In our investigation, 73.5% of the

subjects with FSGS recounted parental cognation. Parental consanguinity rates of 20%⁷ and 43.3%¹¹ were found in FSGS children in Jordan and Tunis, respectively. Both ours and the two aforesaid studies demonstrated high rates of this marriage in the parents of patients affected by FSGS across the Middle East and North Africa. Here, it was detected that renal survival rates were lower in these patients and that they showed higher resistance to a variety of cures with greater at risk of developing renal failure. Therefore, keeping records of parental consanguinity in such cases can helpfully determine the prognostics of such patients and the use of more specific genetic screening in these cases. Assessments of NPHS1, NPHS2, PLCE1, and MYO1E genes are recommended for genetic screening of the FSGS children with consanguine parents.⁴ It should be noted that genetic testing of children with FSGS could help to predict the response to treatments and overall the outcome.³¹ Unfortunately, we did

not perform the genetic assessment of autosomal recessive FSGS genes and cannot confirm our assessment of treatment response and outcome in patients with and without consanguinity. Additionally, because consanguine marriage can amplify the risks of multiple diseases, such as renal diseases that are not evaluated in pre-marriage screenings, it is necessary to inform individuals regarding potential threats of consanguine marriage more effectively together with governmental policies for declining the encumbrance of such illnesses.

There are limitations here, namely: a) the retrospective study form had some limits, but attempts were made to strengthen the study through assessing patients and by treatment using the same medical team, b) a high consanguineous rate in the investigated subjects revealed that most of them were born from consanguine parents and few numbers of patients were found with no parental cognation (This might influence the statistical analysis, in particular for determination of the renal survival and CKD risk factors among subjects lacking cognation as part of the statistical analyses did not approach the significance levels), c) this was a regional trial and caution should be taken for generalization of the findings to other provinces in Iran, and d) At last, analysis of mutations in autosomal recessive genes was not done among subjects with consanguine parents to confirm the outcome concerning the influence of consanguinity on clinical course and therapeutic outcomes of FSGS.

CONCLUSION

To sum up, the consanguine marriage rate was relatively higher in Iranian children affected by steroid-resistant FSGS. Subjects with consanguine parents presented less renal survival time and were more resistant to treatments, with elevated possibility of developing CKD. Therefore, having records of consanguine parents in children affected by FSGS could be valuable for prediction of prognosis in such patients.

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None

CONFLICT OF INTEREST

The authors declare no conflict of interests.

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تازه های آموزش
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