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ORIGINAL ARTICLE

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Differential risk of remission and ESRD in childhood FSGS

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Abstract Focal segmental glomerulosclerosis (FSGS) is the leading cause of steroid-resistant nephrotic syndrome in childhood and the most common form of end stage renal disease (ESRD) from glomerular disease. In order to assess the risk of progression of children with primary FSGS and the impact of proteinuria remission status on disease progression, we undertook this study to describe a cohort of 60 children and adolescents from the Glomerular Disease Collaborative Network. Of the 60 patients included in the cohort, 58% were African American. Median age was 16 years. Proteinuria ranged from 1.0–24.0 g/day/1.73 m^2; 57% were hypertensive, and the median estimated glomerular filtration rate (eGFR) was 90.2 ml/min/1.73 m^2. Complete remission was achieved in 20%, partial remission in 33%, and 47% have not achieved remission during follow-up with all prescribed therapy. Only ACE-I/ARB therapy was predictive of proteinuria remission in multivariate analysis (hazard ratio [HR] 3.35; 95% confidence interval [CI] 1.42–7.92). Renal survival was much improved in patients with complete or partial remission compared with no remission in univariate analysis. In multivariate analysis comparing no remission status, complete remission was associated with a 90% decreased risk of ESRD (HR 0.10, 95% CI 0.01–0.79, p =0.03). In summary, proteinuria remission status is a valid predictor of long-term renal survival in children with FSGS.

Keywords ESRD · Focal segmental glomerulosclerosis · Glomerular Disease Collaborative Network · Proteinuria

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Introduction

Focal segmental glomerulosclerosis (FSGS) is the leading cause of steroid-resistant nephrotic syndrome in childhood and the most common form of end-stage renal disease (ESRD) from glomerular disease [1]. The current first-line therapy for children with nephrotic syndrome of unknown etiology is treatment with corticosteroids [2].

Based upon the International Study of Kidney Disease in Children including 521 children with nephrotic syndrome but only 37 children with FSGS, we anticipate approximately 30% of children with FSGS to be corticosteroid-responsive. [3] For the remaining 70% of children and adolescents with FSGS, a proven therapeutic approach has not been established. The management goal for FSGS is the control of proteinuria and the preservation of kidney function. These two outcomes are linked in cohort studies of adult patients with primary FSGS [4, 5, 6, 7, 8, 9, 10]. These long-term, retrospective adult cohorts also show that a complete remission of proteinuria is linked to an excellent long-term renal survival.

In order to assess the risk of ESRD in children with primary FSGS and the impact of proteinuria-remission status on disease progression, we undertook this study to describe a cohort of children and adolescents from the Glomerular Disease Collaborative Network (GDCN).

Methods

Children and adolescents with biopsy-proven primary FSGS are included in this analysis. A total of 78 patients were eligible by biopsy. The biopsies were obtained between 1980 and 2004. At the time of diagnosis the patient age ranged from 1 to 21 years. Children with less than 1 year of follow-up were excluded. Children

Table 1 Description of baseline characteristics in pediatric FSGS patients (*FSGS* focal segmental glomerulosclerosis, *AA* African American, *eGFR* estimated GFR, *eProteinuria* estimated proteinuria, *NOS* not otherwise specified)

Median (range) or *n* (%)	Total cohort	Study cohort	Complete remission	Partial remission	No remission	*p* value
	(*n*=78)	(*n*=60)	(*n*=12)	(*n*=20)	(*n*=28)	
Age at biopsy	16.0 (3.0–21.0)	16.0 (3.0–21.0)	15.5 (5.0–21.0)	15.0 (3.0–21.0)	16.0 (4.0–21.0)	0.53
Male	36 (46%)	28 (47%)	3 (25%)	11 (55%)	14 (50%)	0.24
Race						0.43**
AA	45 (58%)	35 (58%)	7 (58%)	14 (70%)	14 (50%)	-
Caucasian	26 (33%)	18 (30%)	2 (17%)	4 (20%)	12 (43%)	
Hispanic	1 (1%)	1 (2%)	1 (8%)	0	0	
Other	6 (8%)	6 (10%)	2 (17%)	2 (10%)	2 (7%)	
Hypertension	36 (46%)	34 (57%)	5 (42%)	11 (55%)	18 (64%)	0.19
eProteinuria***	4.8 (1.0–24.0)	5.6 (1.0–24.0)	4.3 (1.0–14.8)	5.9 (1.4–20.0)	7.7 (1.5–24.0)	0.17
Baseline eGFR (ml/min/1.73 m^2)	90.2 (14.2–175.0)	90.2 (14.2–175.0)	94.0 (41.8–175.0)	91.0 (36.0–175.0)	67.6 (14.2–172.7)	0.09
FSGS variant						0.71****
Collapsing	17 (22%)	12 (20%)	2 (17%)	4 (20%)	6 (21%)	-
Perihilar	21 (27%)	17 (28%)	6 (50%)	5 (25%)	6 (21%)	
Tip	11 (14%)	9 (15%)	1 (8%)	3 (15%)	5 (18%)	
NOS	29 (37%)	22 (37%)	3 (25%)	8 (40%)	11 (39%)	

** AA vs others
*** eProteinuria based on 24-h protein excretion: g/day/1.73 m^2 or random urine protein/creatinine ratio g/g
**** Compare all FSGS variants by remission status

were retained in the analysis if a final outcome occurred prior to 1 year. Those under 1 year of age at presentation of proteinuria were excluded as a potential congenital nephrotic syndrome or syndrome-associated FSGS. Patients with a history of a disease that could cause a secondary FSGS were excluded from the study, including sickle cell disease, human immunodeficiency virus infection and reflux nephropathy. Patients were not excluded based on the body mass index (BMI) at diagnosis. The latter would require knowledge of an estimated dry weight in patients with significant edema at diagnosis, which was not available. In total, the eligible cohort included 60 children and adolescents with primary FSGS.

Patient-specific data were gathered as part of a larger GDCN patient registry. The GDCN is a group of 800 nephrologists from 300 private practice nephrology clinics and academic sites throughout the United States. The data-coordinating center is maintained at the University of North Carolina at Chapel Hill. The patients in this registry have allowed their medical records to be transferred to the GDCN coordinating center for data abstraction. Physician practices were reminded to update GDCN records for patients on a yearly basis. The GDCN patient registry contains data from over 2,500 participants with glomerular diseases, including 644 with FSGS. Of those with FSGS, 78 are children or adolescents. Patients were managed by their primary nephrologist.

Approximately 53% of patients identified with FSGS under 22 years of age consented to registry participation. Presenting signs, symptoms, family history of proteinuria and FSGS and laboratory parameters were recorded. Subsequent laboratory values, clinical information and therapies were abstracted for the registry. All treatment decisions and patient monitoring were at the discretion of the nephrologist in charge of individual patient management.

All patient kidney biopsies were reviewed by a single nephropathologist (D.B.T.) prior to publication to confirm the diagnosis of FSGS. Kidney biopsies were evaluated by light microscopy using hematoxylin and eosin, periodic acid Schiff and Masson trichrome staining. Immunofluorescence microscopy reports and interpretation were reviewed and prints of electron microscopy were examined. The diagnosis of FSGS was subclassified according to the working proposal histologic subclassification of FSGS [11]. Renal biopsy review was done without knowledge of patients' clinical outcome information.

Outcome of the cohort was assessed as nadir proteinuria and estimated GFR (eGFR). GFR was estimated using the Schwartz formula for children age $\leq$18 and Cockroft-Gault equation for ages 19 and above [12, 13, 14, 15]. Three of 60 had eGFR greater than 175 ml/min/1.73 m^2. Neither the Schwartz nor Cockroft-Gault formulas have been validated in the extremely high range or in patients for whom hyperfiltration may be manifest. Consequently, for these three patients with eGFR >175, the eGFR was defined as 175 ml/min/1.73 m^2 for analysis to prevent an excessive influence by these values. Complete remission was defined as urine protein/creatinine ratio (UP/C) <0.2 g/g or 24 h urine protein excretion <0.2 g/24 h, adjusted for body surface area. Partial remission was equal to >50% reduction of proteinuria from baseline, and no remission was defined as all others. UP/C results were reported from ambulatory specimens according to the monitoring standard of the primary nephrologists. Twenty-four-hour urine collections were determined to be adequate if the urinary creatinine excretion was 20 mg/kg/day ± 5 mg/kg/day. If the specimen did not meet this criteria, a protein–creatinine ratio was computed from the sample. The UP/C values are used as an estimate of 24-h protein excretion when the 24-h sample was not obtained or was not complete. For Table 1, values are provided for *estimated* 24-h urine protein excretion. For analysis, the estimated proteinuria (eProteinuria) value was represented by either a 24-h urine protein g/24 h adjusted for body surface area or a UP/C (g/g). This approach is supported by publications that document the correlation of these two measurements [16, 17]. ESRD was defined as the onset of dialysis or transplant dependence. Patients were censored at the time of last follow-up or in January 2005.

Statistical analysis

Demographic and clinical characteristics were compared between groups defined by proteinuria remission status (complete remission, partial remission or no remission). Mantel-Haenszel statistics were calculated for categorical variables. *T*-tests or Wilcoxon rank-sum tests were performed for continuous variables. Kaplan-Meier estimator was used for estimating renal survival probability according to the remission status.

Proportional hazards models were used to assess factors associated with proteinuria remission status and renal survival status [18, 19, 20]. In univariate analysis, potential predicators of proteinuria remission or risk factors of renal survival were identified using a significance value of p <0.05. These potential predictors or risk factors were then included in the multivariate model. Backward selection method was also used to evaluate for potential predictors. Hazard ratios (HR) with a 95% confidence interval (CI) were re-

Table 2 Description of therapy and renal survival after diagnosis of FSGS in childhood

Median (range) or *n* (%)	Complete remission (*n*=12)	Partial remission (*n*=20)	No remission (*n*=28)	*p* value
Number of therapies	3 (2–3)	2 (1–4)	2 (1–4)	0.24
ACE-I/ARB use	8 (67%)	16 (80%)	4 (14%)	0.0001
Calcineurin inhibitors use	3 (25%)	8 (40%)	2 (7%)	0.01
ESRD	1 (8%)	2 (10%)	18 (64%)	<0.0001
Month of follow-up	37.9 (13.2–232.7)	46.1 (3.0–129.7)	30.9 (5.4–206.5)	0.71

(*ACE-I/ARB* angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, *ESRD* end-stage renal disease)

ported. Patients who did not reach outcomes of interest (complete or partial remission, dialysis or renal transplant) were censored at the last follow-up date. Since there were rare instances of measures with missing data and data were missing at random, missing data points were excluded. All management and statistical analyses were conducted using the SAS software version 8.2 (Cary, NC, USA).

The GDCN registry and this study were reviewed and approved by the Institutional Review Board of the University of North Carolina. Informed consent was obtained from the patients and guardians of the study participants.

Results

The total cohort included 78 pediatric patients with a racial distribution of 58% black, 33% white and 8% other. Males accounted for 46% of the study population and the median age at biopsy was 16.0 years (range 3.0–21.0). Kidney biopsy data included 13.1% from the years 1980–1990 and the remaining 86.9% from 1991-2003. Long-term follow-up was available for 60 identified patients with a minimum of 3 months and maximum 233 months (median 33 months). Of the 60 patients included in the cohort, 58% were black, 30% white, 2% Hispanic and 10% other races. This racial distribution compares with our overall GDCN registry population, 31% black, 49% white, 1% Hispanic and 2% other races, highlighting the predominance of FSGS in African Americans. The children and adolescents ranged in age from 3–21 years, median 16 years. A family history of proteinuria was reported in 8% of the cohort and a family history of FSGS in 3% of the cohort. Biopsy review yielded 22 cases of FSGS not otherwise specified (NOS), 17 FSGS perihilar variant (PH), 0 FSGS cellular variant (CELL), 9 FSGS tip lesion variant (TIP), and 12 FSGS collapsing variant (COL).

At diagnosis of FSGS, proteinuria ranged from 1.0–24.0 g/day/1.73 m^2. Twenty-three percent had urine protein excretion less than 2.0 g/day/1.73 m^2 at diagnosis. Fifty-seven percent were hypertensive at diagnosis. The estimated glomerular filtration rate (eGFR) ranged from 14.2–175 ml/min/1.73 m^2, median 86.4 ml/min/1.73 m^2. At the time of diagnosis, one of 60 had an eGFR less than 15 ml/min/1.73 m^2. In the patient with renal failure at diagnosis, follow-up was monitored to assure that this represented a chronic renal failure rather than an acute, transient condition. ESRD was confirmed in this patient.

Beginning at the diagnosis of FSGS through the time of last observation or ESRD, therapy included corticosteroids, in those not treated before biopsy, in 35 of 60 (58%), angiotensin-converting enzyme inhibitors (ACE-I)/angiotensin receptor blockers (ARB) 47%, calcineurin inhibitors 23%, cyclophosphamide 7%, mycophenolate mofetil 8%, and lipid lowering agents 17%. It should be noted that lipid lowering agents have only recently been approved for use in children by the US Food and Drug Administration.

Proteinuria remission

Complete remission was achieved in 20%, partial remission in 33% and 47% have not achieved a remission during follow-up. For patients who reached a complete remission, therapy included between one and three, median two, therapeutic agents to achieve complete remission. For patients with partial or no remission the median number of agents was two, with a maximum of four agents used in their therapy to the end of the follow-up period. One patient did not receive therapy based on submitted records. This patient presented in ESRD. Four patients did not have treatment data in the registry. Two of these patients have achieved complete remission and had renal survival at the end of the study. Two patients did not have a remission of proteinuria and reached ESRD. Of the 35 patients with initial exposure to corticosteroids after biopsy, only one achieved a remission. This patient had the tip variant of FSGS and achieved a complete remission.

Table 1 summarizes the baseline characteristics of patients by remission status. Subsequent therapies, follow-up time, and renal survival is reported in Table 2. In univariate analysis, ACE-I/ARB (HR 3.96, 95% CI 1.69–9.29) and calcineurin therapy (HR 2.54, 95% CI 1.20–5.35) increased the likelihood of a complete or partial remission of proteinuria. Variables that were not predictive included patient age, black race, male gender, protein excretion, FSGS variant, and baseline eGFR (Table 3). In multivariate analysis, only ACE-I/ARB therapy was associated with proteinuria remission. In those treated with ACE-I/ARB, the risk ratio for remission was 3.35 times greater than patients who did not receive this therapy.

Table 3 Predictors for complete and partial remission and risk factors for ESRD in primary FSGS (*ACE-I/ARB* angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, *eGFR* estimated GFR, *ESRD* end-stage renal disease, *FSGS* focal segmental glomerulosclerosis)

Characteristic	Predictors for complete and partial remission				Risk factors for ESRD			
	Univariate hazard ratio (95% confidence interval)	*p* value	Multivariate hazard ratio (95% confidence interval)	*p* value	Univariate hazard ratio (95% confidence interval)	*p* value	Multivariate hazard ratio (95% confidence interval)	*p* value
Age at biopsy	0.99 (0.92, 1.06)	0.77	-	-	1.03 (0.94, 1.12)	0.57	-	-
African American	1.68 (0.78, 3.60)	0.19			0.75 (0.31, 1.82)	0.52		
Male	1.09 (0.54, 2.21)	0.81			2.46 (1.00, 6.07)	0.05		
eGFR	1.00 (0.99, 1.01)	0.23			0.99 (0.98, 1.00)	0.06		
Proteinuria	1.00 (1.00, 1.00)	0.99			1.00 (1.00, 1.00)	0.30		
Hypertension	0.67 (0.33, 1.38)	0.28			0.35 (0.05, 2.66)	0.08		
Collapsing variant	0.86 (0.35, 2.11)	0.74			2.25 (0.85, 5.94)	0.10		
ACE-I/ARB	3.96 (1.69, 9.29)	0.0016	3.35 (1.42, 7.92)	0.0059	0.23(0.07, 0.79)	0.02	0.45 (0.12, 1.72)	0.24
Calcineurin therapy	2.54 (1.20, 5.35)	0.01	1.48 (0.67, 3.30)	0.33	0.35 (0.05, 2.66)	0.31		
Complete remission	-				0.09 (0.01, 0.68)	0.02	0.10 (0.01, 0.79)	0.03
Partial remission	-				0.14 (0.03, 0.62)	0.01	0.21 (0.04, 1.04)	0.06

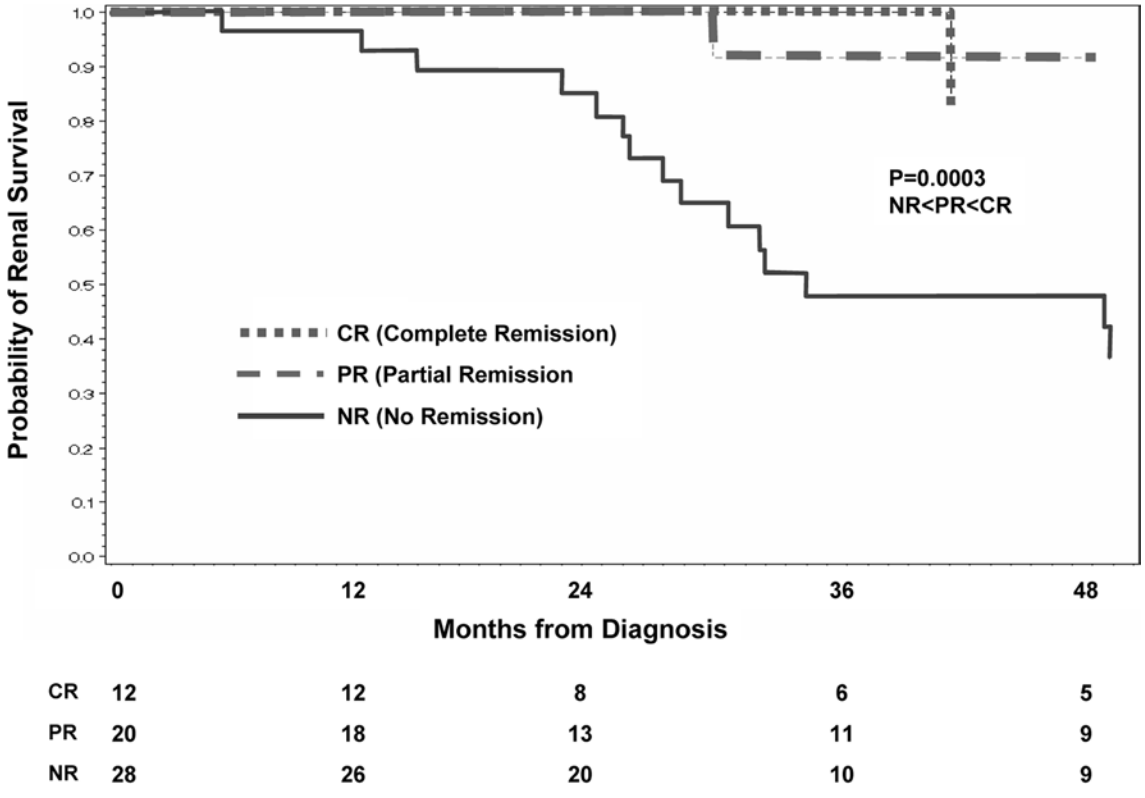

Fig. 1 Kaplan-Meyer analysis of the risk of ESRD by proteinuria remission status in primary FSGS (*FSGS* focal segmental glomerulosclerosis, *ESRD* end-stage renal disease)

Renal survival

Thirty-five percent of the children and adolescents reached ESRD during the study period. The risk of ESRD was assessed in relation to remission status, shown in Fig. 1. This figure suggests that both complete and partial remission status are associated with a better renal survival than the no remission group ($p<0.003$). In univariate analysis, potential predictors of ESRD were assessed (Table 3). ACE-I/ARB and remission status were identified as potential predictors of ESRD. Patient age at biopsy, race, male gender, eGFR, proteinuria, hypertension, collapsing variant, and calcineurin therapy were not univariate predictors of ESRD and were not included in multivariate analysis. In multivariate analysis, only remission status was associated with a risk of renal failure.

Compared with no remission status, the complete remission status was associated with a 90% decreased risk of ESRD (HR 0.10, 95% CI 0.01–0.79, p=0.03) (Table 3). Two of 60 (3%) patients died during the observation period. Both deaths occurred after reaching ESRD.

Discussion

Primary FSGS is a disorder with a poor prognosis and no proven therapy. Although corticosteroids are considered an accepted first-line therapeutic agent for children with this disorder, at best 30% of the children with primary FSGS will achieve a complete remission with corticosteroids alone. Indeed, in our predominantly African American cohort, only one of 35 (3%) had a complete remission when initial corticosteroid therapy occurred after biopsy. This patient was Caucasian, with FSGS tip lesion variant.

Previous published studies have documented a 4–5% spontaneous remission rate in primary FSGS. [21] In this cohort a full 53% achieved a partial or complete remission in this study as a result of all prescribed therapy, and no spontaneous remissions were documented. A combination therapeutic approach was evident based on the number of agents used to treat these patients. Complete remission predicted an improvement in renal survival compared with no remission. Those with a complete remission had a 100% renal survival at 3 years, and those with a partial remission had a 92% 3-year renal survival, compared with the 47% 3-year survival in the no remission category. This is in agreement with recently published data from the Toronto Glomerulonephritis Registry of adults with FSGS [4, 5]. Unfortunately, 47% of our patients are non-remitters with the use of traditional therapies. The management of persistently proteinuric patients with FSGS has developed to include a combination regimen of ACE-I, ARB, statin agents, and blood pressure control. More precise anti-fibrotic therapies have been evaluated in animal models but have not translated into human investigation.

ACE-I and ARB therapy was associated with proteinuria remission, and remission of proteinuria was identified as a factor predictive of renal survival in the present cohort. In studies of glomerular diseases in general and FSGS specifically, similar findings of proteinuria reduction as a consequence of ACE-I therapy have been documented. In a recent study of children with steroid-resistant nephrotic syndrome, the effects of low- and high-dose enalapril were documented, with a dose-dependent diminution in urinary protein excretion [22]. In a post hoc analysis of ramipril efficacy in nephropathy trial, ramipril was associated with a renoprotective effect manifest as improved renal survival [23]. The effects of ACE-I/ARB therapy have been recently reviewed and shown to be associated with reduction in proteinuria and improved renal survival in studies of nondiabetic kidney disease [24].

The effects of cyclosporin therapy were not associated with an improved renal survival in the 23% of patients receiving this therapy. The comparison group included patients who received alternate therapies. This suggests that the other therapies may be associated with a similar renal survival. Comparison of cyclosporin to chlorambucil in a randomized clinical trial was not shown to have a greater rate of remission or renal survival [25]. However, comparisons of cyclosporine to placebo or low-dose corticosteroids have shown improved control of proteinuria and renal survival [26, 27]. Alternate explanations may include a limitation in power to detect a difference that is truly present. A larger cohort or randomized control trial is the optimal route to determine efficacy of cyclosporin therapy.

Our study does not include an analysis of recently described genetic mutations in studies of international cohorts of children with FSGS and corticosteroid-resistant nephrotic syndrome [28, 29, 30]. In our cohort, it was uncommon to have a family history of FSGS (3%) or proteinuria (8%). The published genetic studies do not include a significant number of children from North America or specifically those of African American race. Consequently, we do not know the potential genetic contribution to the etiology of FSGS or to the therapeutic response in our study.

The variability of management styles for this disease is the result of a lack of randomized clinical trials to support a specific and optimal therapeutic approach. The NIH-supported FSGS-Clinical Trial which is now underway should provide a first step toward advancement in the therapeutic strategy for corticosteroid-resistant FSGS. As part of an ancillary to this national study, the prevalence of known FSGS-associated genetic mutations may further define the relationship between specific genetic mutations and therapeutic responsiveness. For those resistant to first- and second-line agents (non-remitters), novel therapeutic strategies should be explored to prevent or delay the progression to ESRD.

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