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Primary focal segmental glomerulosclerosis in children: prognostic factors

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Abstract To study the clinical course and the predictors of outcome in children and adolescents, 39 patients with nephrotic syndrome and primary focal segmental glomerulosclerosis (FSGS) were followed for a mean of 84.6 months. Thirty-six patients were treated with prednisone, either alone or in conjunction with cyclophosphamide. The clinical course was one of sustained remission in 4 patients, frequent relapse in 13, persistent non-nephrotic proteinuria in 5, and persistent nephrotic syndrome in 17; 2 patients had stable renal failure and 8 had progressive renal failure, 5 of them evolving to end-stage renal failure (ESRF). Resistance to prednisone was recorded in 76.6% of patients. The use of cyclophosphamide plus prednisone was of benefit in 42.8% of patients; 22.2% of the prednisone-resistant patients achieved remission of the nephrotic syndrome. A Kaplan-Meier analysis revealed a survival rate of 92% after 5 years, 86% after 10 years, and 76% after 15 years. Using both univariate and multivariate analysis, persistent nephrotic syndrome was associated with progression to ESRF and the remission of proteinuria with maintenance of renal function. As the outcome of the nephrotic syndrome in FSGS is significantly improved by remission of proteinuria, it is conceivable that immunosuppressive medication may be used in conjunction with prednisone in patients with steroid resistance.

Keywords Nephrotic syndrome · Focal segmental glomerulosclerosis · Predictors · Cyclophosphamide · Outcome

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Introduction

Focal segmental glomerulosclerosis (FSGS) is an important cause of proteinuria and chronic renal failure in children and young adults, accounting for 5%–15% of all cases of idiopathic nephrotic syndrome [1, 2, 3, 4, 5, 6]. Resistance to steroid therapy has been reported in around 70% of patients [1, 3, 7, 8, 9, 10, 11] and progression to end-stage renal failure (ESRF) in up to 60% after 10 years [4, 9, 12, 13, 14, 15]. Furthermore, in recent years an increase in the incidence of FSGS has been reported by many centers around the world. Despite having been first described more than 40 years ago [16], several aspects of its clinical course and treatment remain controversial, as most of the data has been based on retrospective analyses or on series with small numbers of patients.

The aim of this paper is to report the clinical course, the influence of treatment, and the predictors of outcome of nephrotic syndrome and FSGS in children and adolescents prospectively followed at a single institution.

Patients and methods

All patients younger than 18 years of age with idiopathic nephrotic syndrome and a biopsy-proven diagnosis of FSGS, who were followed for longer than 6 months in the Renal Service of the University Hospital/University of Bahia, Brazil, were included in the present report. In all instances the renal specimens were obtained by percutaneous biopsy, and sections containing at least 8 glomeruli were examined by a nephropathologist and classified according to Churg et al. [17].

At the time of initial evaluation a history was taken, a physical examination performed, and the following data were recorded: (1) evidence of systemic disease which could be related to renal disease, (2) blood pressure, (3) laboratory evaluation including urinalysis, 24-h urinary protein excretion, creatinine clearance, serum levels of creatinine, cholesterol, albumin, fasting blood glucose, and other tests to exclude systemic diseases, as appropriate.

The nephrotic syndrome was diagnosed by the presence of edema, urinary protein excretion greater than 30 mg/kg body weight per 24 h, serum albumin below 30 g/l, and serum cholesterol greater than 6.465 mmol/l. Hypertension was defined as

readings exceeding the 95th percentiles for systolic or diastolic blood pressure for age and gender, for patients younger than 12 years of age, and as blood pressure above 140/90 mmHg in older patients. Renal insufficiency was defined by serum creatinine levels above the age-related normal levels and end-stage renal disease (ESRD) by serum creatinine greater than 5 times the age-related normal upper limits or by the need for dialysis therapy.

The patients were treated with 1.0–2.0 mg of prednisone/kg body weight up to a maximum of 80 mg/day, divided into two or three doses, for 4–6 weeks, followed by single doses of prednisone, on alternate days, for 4 additional weeks, and the medication was then gradually discontinued over a period of 2–3 months. Remission was defined as the absence (complete) or reduction to non-nephrotic levels (partial) of the proteinuria, and resistance as the persistence of nephrotic-range proteinuria during 6 weeks of daily treatment. A relapse was denoted by recurrence of nephrotic-range proteinuria after the urine had been protein free for at least 4 weeks. A frequent relapse was defined as 3 or more relapses within 12 months in an initially steroid-responsive patient. The clinical response associated with steroid treatment was designated as steroid responsive (complete or partial remission of proteinuria during the steroid therapy, persisting for at least 6 weeks after therapy), steroid dependent (remission of proteinuria during therapy, but recurrence when the dosage was reduced below a critical level or relapse of proteinuria within the 1st month of stopping prednisone therapy), and steroid resistant (no remission of proteinuria during the 6 weeks of daily steroid therapy).

Steroid-resistant patients and those with frequent relapse of the nephrotic syndrome received a daily oral cyclophosphamide dose of 2–3 mg/kg body weight for 12 weeks, along with the daily dose of prednisone during the first 4 weeks and on alternate days for 8 additional weeks. The clinical courses and final outcomes for each patient were evaluated at the end of the follow-up period by recording current medication, blood pressure, serum creatinine and albumin levels, urinalysis, and 24-h urinary protein excretion.

All data are expressed as mean values plus or minus standard deviation. Comparisons between groups were performed with Student's *t*-test for continuous data and the chi-squared test or Fisher's exact test for categorical data. The survival curve was drawn according to the Kaplan-Meier method [18]. Spearman's coefficient of correlation was used to identify variables predicting the development of ESRD and the response to therapy. These variables were identified from the patients' medical histories and baseline clinical evaluations, laboratory tests, and histological findings. They included gender, race, hypertension, renal function, hematuria, severity of proteinuria at the time of the first evaluation, proportion of glomeruli with segmental sclerosis, proportion of glomeruli with global sclerosis, presence or absence of interstitial infiltrate, interstitial fibrosis, hyperplastic arteriolosclerosis, and hyaline arteriolosclerosis. Variables that reached statistical significance in univariate analysis were subsequently included in a multivariate analysis, using the Cox proportional hazards model [19].

In order to study the correlation between the demographic, clinical, and histological variables at the time of baseline evaluation and the clinical course, a logistic regression model was used [20]. $P<0.05$ was considered statistically significant. The statistical analyses were performed using the Statistical Package for Social Science (SPSS) for Windows [21].

Results

A total of 39 patients, 18 male and 21 female, with the diagnosis of FSGS (Fig. 1) and nephrotic syndrome were included in the present study. At the time of the diagnosis of renal disease the mean age was 9.8±5.1 years (Table 1). Hypertension was recorded in 8 patients, microscopic hematuria in 14, and mild-to-moderate renal insufficiency in 7 patients (although it was transient and secondary to intravascular volume depletion in 3 of these).

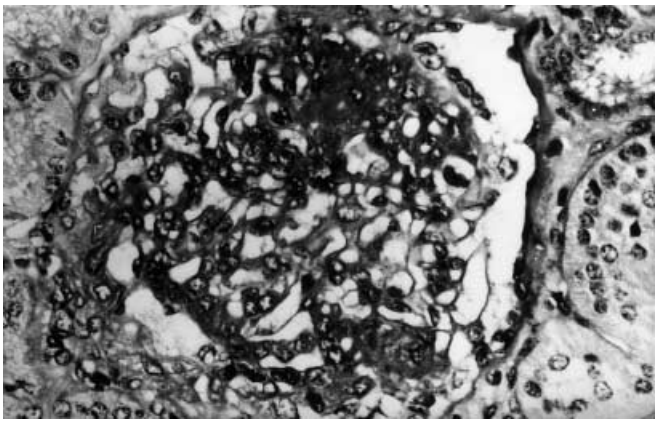

Fig. 1 Focal segmental glomerulosclerosis – light microscopic examination showing collapse of capillaries together with thickening of mesangial matrix. There is also adhesion of the affected lobule to Bowman's capsule (periodic acid-Schiff reagent, original magnification ×370)

Table 1 Demographic and clinical data from children and adolescent with focal segmental glomerulosclerosis

	n	%
Gender		
Male	18	(46.2)
Female	21	(53.8)
Race		
White	10	(25.6)
Non-white	29	(74.4)
Age (years)		
Mean±SD	9.8±5.1	
Median	10	
Range	2–18	
Duration of the nephrotic syndrome (months)		
Mean±SD	14.0±21.5	
Median	6	
Follow-up (months)		
Mean±SD	84.3±79.5	
Median	53	

Thirty patients were initially treated with prednisone and 6 with prednisone in conjunction with cyclophosphamide. Among the patients treated with prednisone, complete remission of the proteinuria was recorded in 6 patients (20.0%), partial remission in 1 (3.4%), and resistance in 23 patients (76.6%). Twenty-two patients were subsequently treated with prednisone in conjunction with cyclophosphamide. Of 18 prednisone-resistant patients, complete remission was achieved in 3 (16.6%) and partial remission in 1 (5.6%), although 2 other patients had remission of proteinuria during the final period of gradual tapering of prednisone. A decrease in the frequency of relapses was observed in both patients with frequently relapsing nephrotic syndrome. Two steroid-dependent patients treated with both drugs achieved par-

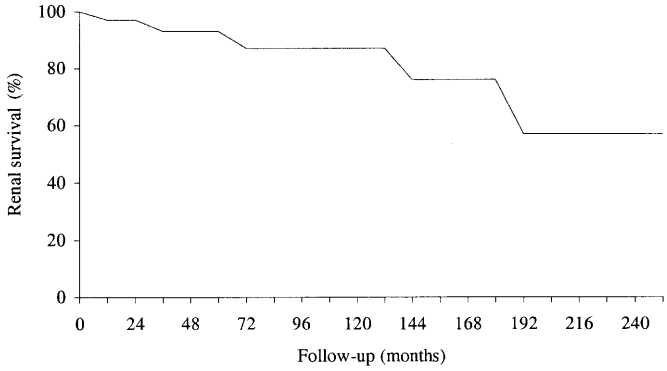

Fig. 2 Renal survival in children and adolescents with nephrotic syndrome and primary focal segmental glomerulosclerosis

Table 2 Clinical course of the nephrotic syndrome in patients with focal segmental glomerulosclerosis

	n	%
Renal insufficiency		
At diagnosis	7[a]	17.9
At end of follow-up	10	25.6
Progression of renal insufficiency	8	20.5
Hypertension		
At diagnosis	8	20.5
At end of follow-up	12	30.8
Clinical course		
Remission/relapse	17	43.6
Persistent nephrotic syndrome	17	43.6
Persistent non-nephrotic proteinuria	5	12.8

[a] Transient in 3 patients

tial remission; 1 of them recently evolving with a course of remissions and relapses.

Among the patients treated with prednisone and cyclophosphamide from the beginning, the response to therapy was complete remission in 3, partial remission in 1, and was absent in 2. The treatment was well tolerated and no patient presented side effects requiring the discontinuation of medication.

Three patients were treated conservatively: spontaneous remission was recorded in 1 patient and persistent nephrotic syndrome in 2, of whom 1 evolved to advanced renal failure.

The patients were followed for a mean of 84.6±79.8 months. The clinical course was characterized by sustained remission in 4 patients, remissions and relapses in 13, persistent non-nephrotic proteinuria in 5, and persistent nephrotic syndrome in 17. At the time of the final clinical evaluation, 12 patients had hypertension, 2 had stable renal failure, and 8 had progressive renal failure. Five patients had reached advanced renal failure (Table 2).

A Kaplan-Meier survival analysis revealed a mean survival of 232 months (95% confidence interval= 180–284). The survival rate after 5 years was 92%, after 10 years 86%, and after 15 years 76% (Fig. 2). The Cox model of multivariate analysis did not reveal any clinical, laboratory, or histological feature at the time of the initial evaluation to be a predictor of outcome.

In a logistic regression analysis, however, the clinical course characterized by persistent nephrotic syndrome was associated with advanced renal failure at the time of the final evaluation. Among the variables that could influence the clinical course of the disease, responsiveness to therapy was associated with a prolonged remission and a relapsing and remitting course with maintenance of the renal function. None of the clinical, laboratory, or histological features at the time of presentation was predictive of the response to immunosuppressive therapy.

Discussion

Poor response to steroid therapy and the progressive loss of renal function evolving into ESRD have been emphasized in FSGS. A review of several studies showed an overall response rate to steroid therapy in 27% of cases, with a range of 0%–70% [1, 3 ,7, 8, 9, 10, 11, 22, 23], and a progression rate to renal failure of 40%, with 28% progressing to end-stage renal failure [12, 24, 25, 26, 27, 28]. In the present study we found a mean survival time of 232 months and a survival rate of 92% after 5 years, 86% after 10 years, and 76% after 15 years, which is somewhat higher than reported in several other series. The reasons for the relatively good survival rate observed in the present study are not clear. Except for the series of Mongeau et al. [15] and Cattran and Rao [4], in most reports the mean observation time has been relatively short and the number of patients small.

In the present analyses we could not identify any demographic, clinical, or histological data at the time of diagnosis of the renal disease that could predict the progression to end-stage renal failure, using either univariate or multivariate analysis. Cattran and Rao [4] differed from other authors [11, 14, 29, 30] in finding no significant correlation between renal function at the time of the initial evaluation and progression to end-stage renal failure. It is possible that the small number of patients progressing to end-stage renal failure in the present series could explain such a difference.

The persistence of the nephrotic syndrome, however, was associated with progression towards advanced renal failure and the need for dialysis therapy. In contrast, patients who achieved remission had a significantly better prognosis. Nevertheless, in the present study we could not explore any difference in outcome dependent on the clinical course characterized by sustained remission, remissions and relapses, or partial remission. The best clinical predictor of prognosis in FSGS was the response to therapy, as only 1 patient in the present series had spontaneous remission. Unfortunately, none of the presenting features could predict the response to therapy.

The poor response rate to steroid therapy (76.6%) observed in the present series was not unexpected, since only children with steroid-resistant nephrotic syndrome undergo renal biopsy at our institution. The influence of the

addition of cyclophosphamide to steroid therapy is difficult to analyze. It seemed to be of benefit in 42.8% of patients (12 of 28 patients treated with cyclophosphamide and prednisone experienced remission of proteinuria, with reductions of the rate of relapse in 2). It is noteworthy that 22.2% of the steroid-resistant patients had remission of the nephrotic syndrome with the addition of cyclophosphamide. Although similar to reports in the literature [4, 8, 23, 27, 31, 32], the small number of patients does not allow us to draw definitive conclusions. Tarshish et al. [32] prospectively studied patients with steroid-resistant FSGS randomly treated with prednisone or prednisone plus cyclophosphamide and concluded that cyclophosphamide therapy was not recommended for steroid-resistant FSGS. These authors did not find any significant differences between the two groups regarding treatment failure and remission of proteinuria, despite the relatively small number of patients studied. Other authors [8, 23, 31, 33], however, report that cyclophosphamide seems to confer some benefit in patients with nephrotic syndrome and FSGS, as some steroid-resistant patients achieve remission. Further randomized and prospective studies with larger numbers of patients are necessary to better demonstrate the beneficial effect of the addition of cyclophosphamide to steroid therapy in the treatment of FSGS.

In conclusion, remission of the proteinuria predicts a good long-term outcome in children with nephrotic syndrome and FSGS. The use of immunosuppressive medication in conjunction with prednisone seems beneficial in the treatment of steroid-resistant FSGS.

References

1. White RHR, Glasgow EF, Mills RJ (1970) Clinicopathologic study of nephrotic syndrome in childhood. Lancet I:1353–1359
2. Habib R, Kleinknecht C (1971) The primary nephrotic syndrome of childhood. Pathol Annu 6:417–474
3. International Study of Kidney Disease in Children (1981) The primary nephrotic syndrome in children. Identification of patients with minimal change nephrotic syndrome from initial response to prednisone. J Pediatr 98:561–564
4. Cattran DC, Rao P (1998) Long-term outcome in children and adults with classic focal segmental glomerulosclerosis. Am J Kidney Dis 32:72–79
5. Korbet SM (1999) Clinical picture and outcome of primary focal segmental glomerulosclerosis. Nephrol Dial Transplant 14 [Suppl 3]:68–73
6. Srivastava T, Simon SD, Alon US (1999) High incidence of focal segmental glomerulosclerosis in nephrotic syndrome of childhood. Pediatr Nephrol 13:13–18
7. Newman WJ, Tisher CC, McCoy RC, Gunnells JC, Krueger RP, Clapp JR, Robinson R (1976) Focal glomerular sclerosis: contrasting clinical patterns in children and adults. Medicine (Baltimore) 55:67–87
8. Mongeau JG, Corneille L, Robitaille PO, O'Regan S, Pelletier M (1981) Primary nephrosis in childhood associated with focal glomerular sclerosis: is long-term prognosis that severe? Kidney Int 20:743–746
9. Southwest Pediatric Nephrology Study Group (1985) Focal segmental glomerulosclerosis in children with idiopathic nephrotic syndrome. Kidney Int 27:442–449
10. Pei Y, Cattran D, Delmore T, Katz A, Lang A, Rance P (1987) Evidence suggesting under-treatment in adults with idiopathic focal segmental glomerulosclerosis. Am J Med 82:938–944
11. Korbet SM, Schwartz MM, Lewis EJ (1994) Primary focal segmental glomerulosclerosis: clinical course and response to therapy. Am J Kidney Dis 23:773–783
12. Beaufils H, Alphonse JC, Guedon J, Legrain M (1978) Focal glomerulosclerosis: natural history and treatment. Nephron 21:75–85
13. Tejani A, Nicastri AD, Sem D, Chen CK, Phadke K, Adamson O, Butt KMH (1983) Long-term evaluation of children with nephrotic syndrome and focal segmental glomerular sclerosis. Nephron 35:225–231
14. Ingulli E, Tejani A (1991) Racial differences in the incidence and renal outcome of idiopathic focal segmental glomerulosclerosis in children. Pediatr Nephrol 5:393–397
15. Mongeau JG, Robitaille PO, Clermont MJ, Merouani A, Russo P (1993) Focal segmental glomerulosclerosis (FSG) 20 years later. From toddler to grown up. Clin Nephrol 40:1–6
16. Rich AR (1957) A hitherto undescribed vulnerability of the juxta-medulary glomeruli in lipoid nephrosis. Bull Johns Hopkins Hosp 100:173–187
17. Churg J, Bernstein J, Glassock RJ (1995) Renal disease. Classification and atlas of glomerular diseases, 2nd edn. Igaku-Soin, New York, pp 49–65
18. Kleinbaum DG (1996) Survival analysis. Springer, New York Berlin Heidelberg
19. Cox DR (1972) Regression methods and life tables (with discussion). J R Stat Soc B 34:187–220
20. Hosmer DW Jr, Lemeshow S (1989) Applied logistic regression. Wiley, New York
21. Norusis MJ (1993) SPSS for windows: base system user's guide, release 6.0. SPSS, Chicago
22. Arbus GS, Poucell S, Bacheyie GS, Baumal R (1982) Focal segmental glomerulosclerosis with idiopathic nephrotic syndrome: three types of clinical response. J Pediatr 101:40–45
23. Yoshikawa N, Ito H, Akamatsu R, Matsuyama S, Hasegawa O, Nakahara C, Matsuo T (1986) Focal segmental glomerulosclerosis with and without nephrotic syndrome in children. J Pediatr 109:65–70
24. Cameron JS, Turner DR, Ogg CS, Chantler C, Williams DG (1978) The long-term prognosis of patients with focal segmental glomerulosclerosis. Clin Nephrol 10:213–218
25. Velosa JA, Holley KE, Torres VE, Offord KP (1983) Significance of proteinuria on the outcome of renal function in patients with focal segmental glomerulosclerosis. Mayo Clin Proc 58:568–577
26. Morita M, White RHR, Coad NAG, Raafat F (1990) The clinical significance of glomerular location of segmental lesion in focal segmental glomerulosclerosis. Clin Nephrol 33:211–219
27. Tune BM, Kirpekar R, Sibley RK, Reznik VM, Griswold WR, Mendoza AS (1995) Intravenous methylprednisolone and oral alkylating agent therapy of prednisone-resistant pediatric focal segmental glomerulosclerosis: a long-term follow-up. Clin Nephrol 43:84–88
28. Cameron JS (1996) The enigma of focal segmental glomerulosclerosis. Kidney Int 50:S119–S131
29. Wehrmann M, Bohle A, Held H, Schumm G, Gendziorra H, Pressler H (1990) Long-term prognosis of focal sclerosing glomerulonephritis: an analysis of 250 cases with particular regard to tubulointerstitial changes. Clin Nephrol 33:115–122
30. Chan PCK, Chan KW, Cheng IKP, Chan MK (1991) Focal sclerosing glomerulopathy: risk factors of progression and optimal mode of treatment. Int Urol Nephrol 239:619–629
31. Geary D, Farine M, Thorner P, Baumal R (1984) Response to cyclophosphamide in steroid-resistant focal segmental glomerulosclerosis: a reappraisal. Clin Nephrol 22:109–113
32. Tarshish P, Tobin JN, Bernstein J, Edelman CM Jr (1996) Cyclophosphamide does not benefit patients with focal segmental glomerulosclerosis. A report of the International Study of Kidney Disease in Children. Pediatr Nephrol 10:590–593
33. Rennert WP, Kala UK Jacobs D, Goetsch S, Verhaat S (1999) Pulse cyclophosphamide for steroid-resistant focal segmental glomerulosclerosis. Pediatr Nephrol 13:113–116