

Focal segmental glomerulosclerosis: a single center study of over two decades

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Background: By sharing our quarter century of care on children with kidney biopsy-proven focal segmental glomerulosclerosis (FSGS), we hope to advance early recognition of this condition with its changing demographics in recent years and examine promising treatment modalities to slow its rate of progression.

Methods: Children fitting entry and exclusion criteria, who presented to our regional nephrology center, were enrolled into this retrospective study. The same criteria for kidney biopsies were uniformly applied under the same nephrologists in over 25 years of practice. Patients exited the study at the initiation of dialysis/transplantation or death. Kidney survival rate was determined by the Kaplan-Meier method.

Results: In 43 children (21 females and 22 males) enrolled, 15 were white and 28 black. The peak age at presentation was 10 to 15 years. Hypertension and heavy proteinuria were frequently seen as presenting features. Almost half of the patients showed serum creatinine concentrations minimally elevated above normal, indicating relatively early diagnosis of FSGS in the study population. Treatment consisted of one or more of the following medications: oral alternative-day prednisone, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, vitamin E, and intravenous methylprednisolone with cyclophosphamide or cyclosporine A.

Conclusions: In this study, with the early interest in FSGS, an opportunity became available to use the different treatment options over more than 2 decades. With the present combined therapy, the kidney survival was no better than the therapeutic regimen described earlier by others. Therefore attention must be focused on the efficacy and side effects of treatments which have been called into question: cyclophosphamide and intravenous methylprednisolone. We recommend a

modified treatment regimen, which is cost effective and with minimal side effects.

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Introduction

Nephrotic syndrome, with an annual incidence rate of 2 to 7 per 100 000 children younger than 18 years old,^[1] is a significant disease in childhood. The dramatic presentations of generalized edema and heavy, foamy proteinuria usually get the child to medical attention, appropriate diagnosis and treatment.^[1]

Primary focal segmental glomerulosclerosis (FSGS) is a clinically important component of childhood nephrotic syndrome because it is slowly progressive over a decade or less to chronic kidney failure.^[1] Recent data from South Africa^[2] clearly demonstrated that Asian and African nephrotic children are three to four times more likely to have FSGS, at an incidence of 20% and 27% respectively, in contrast to the incidence of 8% previously reported.^[3]

FSGS is characterized by lack of response to steroid treatment, and kidney biopsies in these children show sclerosis and collapse of the glomerular tufts.^[1] A quarter century's experience of the treatment and outcome of children with biopsy-proven FSGS at a single regional nephrology center in mid-Atlantic North America form the basis of this report.

Methods

Patients

All patients with biopsy-proven FSGS who had been referred to the pediatric nephrology division of Virginia Commonwealth University Health System, Richmond, Virginia between July 1977 and June 2002 were eligible for entry into this retrospective study. All clinical data were entered in "yellow sheets"^[4] as

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designed and advocated by Dr Frederick Bartter of the National Institutes of Health.

Kidney biopsy indications and study entry/exclusion/exit criteria

The criteria for kidney biopsies were steroid-resistant nephrotic syndrome, i.e., no response after 4 weeks of daily prednisone plus 4 weeks of every other day prednisone or steroid responsive but frequent relapsing nephrosis, i.e., more than two relapses in any 6-month period of follow-up.^[1,5] In addition, kidney biopsies were done by our board certified pediatric nephrologists in patients with proteinuria in excess of 2 g per day persisting over 3 months and without signs of nephrotic edema; all patients must meet two of the following parameters: unrelenting isolated hematuria persistent for over 2 years; hypertension; and evidence of elevated serum creatinine denoting chronic kidney insufficiency.^[5,6] Contraindications for biopsies are: solitary kidney, bleeding disorders, suspected tumors, acute infections or uncontrollable severe hypertension.^[5,6]

The entry criteria are kidney biopsy-documented FSGS in patients at or less than 18 years old.

Patients excluded from this study were secondary FSGS due to systemic lupus, anaphylactoid purpura, diabetes mellitus, HIV, sickle cell nephropathy, and dysplastic kidneys.

The patients exited the study at initiation of peritoneal or hemodialysis/transplantation procedures or death.

Treatment protocol

The treatment regimen was not uniform through these 25 years and changed over time. But the dosage of individual medications was the same as described below. Intravenous methylprednisolone was given at 30 mg/kg per week combined with a low dose of oral prednisone at 2 mg/kg on alternative days for various durations according to the severity of disease.^[1] Cyclophosphamide was given orally at 2 mg/kg body weight per day for 8 weeks combined with prednisone at 60 mg/sq meter body surface area on alternative days.^[1] Cyclosporine A was given orally at 5 mg/kg body weight per day.^[1] Angiotensin receptor blocker or angiotensin converting enzyme inhibitor was given orally on an ongoing basis until the disappearance of proteinuria and re-started with the return of proteinuria.^[1] Vitamin E was given orally at 400 to 800 units per day on a chronic basis as a renoprotective measure.^[7]

Statistical analysis

In this descriptive study, means/medians and proportions were used to describe characteristics of the study population. The Kaplan-Meier method was used to analyze kidney survival rates.

Results

A total of 43 patients met the entry and exclusion criteria. Their gender and age at the first clinic visit are presented in Fig. 1. The peak age of the patients was 10-15 years, and their gender was equally distributed. The racial backgrounds of these patients were 15 whites and 28 African American blacks.

Blood pressure at initial clinic visits showed that 32% of the patients had diastolic blood pressure in excess of 80 mmHg. Proteinuria was estimated by the ratio of urinary protein (mg per dl) divided by the urinary creatinine (mg per dl). The values in excess

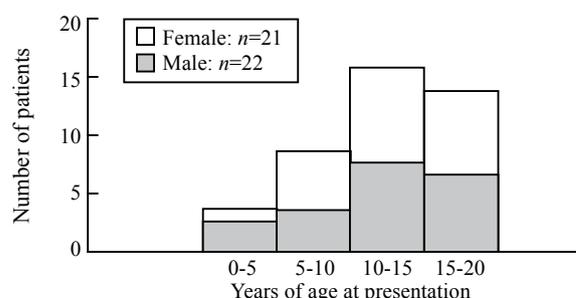


Fig. 1. The number of patients with biopsy-proven FSGS and age at time of first clinic visit.

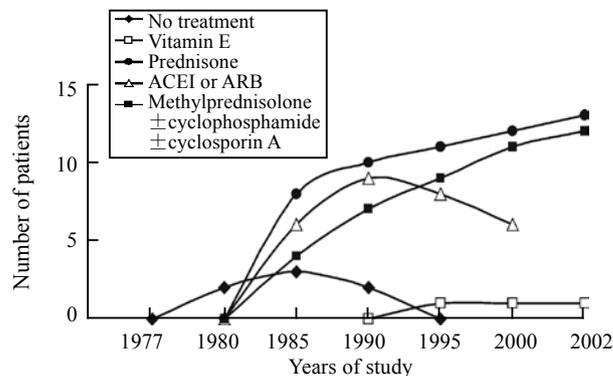


Fig. 2. The modalities of treatment given to the study subjects over the 25 years of this project. The patients who exited into dialysis/transplantation shortly after entering this study were not included in this graphic presentation.

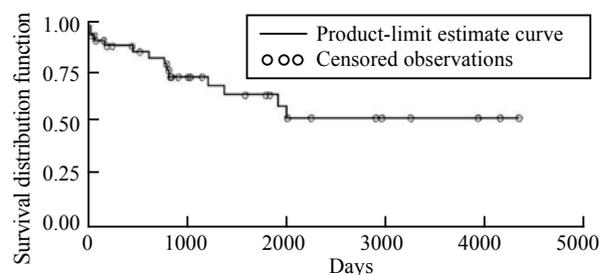


Fig. 3. The Kaplan-Meier analysis of kidney survival in forty-three FSGS children.

of 0.2 mg/mg at initial clinic visits were observed in 42% of the patients. Nephrotic range proteinuria as defined by urinary protein to urinary creatinine ratio at or in excess of 2 mg/mg was found in 32% of the patients. At the initial clinic visit, the serum creatinine concentrations exceeding 1.2 mg/dl were found in 44% of the male patients and exceeded values of 1 mg/dl in 50% of the female patients. The treatment modalities used in the 25 years of this study are shown in Fig. 2. In the early period in the 1970s, up to 3 patients received no treatment, as advocated by Habib et al.^[8] But starting in the 1980s, alternative-day dose of prednisone alone,^[9,10] or intravenous methylprednisolone with alternative-day prednisone^[11,12] and sometimes with or without cyclophosphamide^[12,13] or cyclosporine A^[14-17] as well as angiotensin converting enzyme inhibitors or angiotensin receptor blockers^[12] were used. Finally, starting in 1990, vitamin E based on dosage used in a FSGS clinical trial^[18] was given as an adjunct therapy in our patients. The kidney survival rates were analyzed by the Kaplan-Meier method, with patients going into hemo- or peritoneal dialysis and kidney transplantation considered to be non-survivors and exiting the study (Fig. 3). No actual death was encountered in this study.

Discussion

The literature on FSGS describes a male predominance but in our single center study, the gender distribution is equal between male and female patients (Fig. 1). Although there was a male predominance during the earlier years in this study; however, when the period of follow up is extended to 25 years, the gender distribution became equalized. This is possibly one of the few 25-year follow-up studies in children with FSGS in North America. Most other papers using the current combination of medications reported on data collected over significantly shorter lengths of follow-up.^[19] Our study suggested that school-age girls have equal propensity to develop FSGS, but it needs confirmation by long-term studies.

African American blacks were in the majority in our study. This partly reflects the higher percentage of Africa-American patients residing in the catchment area of our regional referral center.^[20] But, it should be recognized that although FSGS is the primary pathological diagnosis in 8% of nephrotic syndrome cases in the International Study of Kidney Disease in Children (ISKDC),^[3] its incidence is tripled and quadrupled to 20% and 28% in Asian children and African children, respectively.^[2] Because, in our location, Asian-Americans and other non-black minority represent less than 3% of the general

population,^[20] we have had no Asian children with FSGS in this study population, which is one of the limitations of our study (*vide infra*).

We recognize hypertension as a diastolic blood pressure in excess of 80 mmHg. As a presenting feature in 32% of our patients, it was not different from the 40% incidence described in the ISKDC publication in 1981.^[3] Proteinuria as a presenting feature was present in 20% of the patients in the ISKDC^[3] compared with the 42% incidence in our study. In addition, 30% of the ISKDC patients^[3] presented with elevated levels of serum creatinine. In our patients, it was almost 50%, suggesting that more patients in our series had compromised glomerular filtration rates—albeit at the early stage, because most of them showed minimally elevated levels of serum creatinine at presentation. Thus, pediatricians need to be vigilant in recognizing that elevated blood pressure, minimal proteinuria, and minimally elevated levels of serum creatinine are characteristic features of FSGS.

Oral prednisone therapy is usually effective in achieving proteinuria-free status and remission in most of nephrotic children because of the minimally changed histology of nephrotic syndrome.^[1,12] But nephrotic syndrome due to FSGS is notoriously prone to being resistant to prednisone therapy or relapsing frequently.^[1,12] In addition, a number of FSGS patients progress without developing generalized edema which characterizes most nephrotic syndromes although significant proteinuria is often present, accompanied by asymptomatic hypertension. These are the features at the time of presentation illustrated in our study. These findings imply that clinicians must follow such children diligently and obtain the correct diagnosis by kidney biopsy, utilizing the criteria illustrated in this study. It is important to recognize that FSGS can present and progress silently.

It has been established by the ISKDC that the peak age of presenting FSGS was 6 years.^[3] The peak age at presentation in our study ranged from 10 to 15 years for both male and female patients (Fig. 1). This difference may be due to the decades between our study and the ISKDC. In the decade of the 1980s, our data also showed the predominance of male over female, but in the decades of the 1990s and 2000s, the gender distribution became equalized. It may be attributed to the restrictive criteria of kidney biopsies we have utilized or the higher number of black minority patients in our cohort or some other causes not yet identified.

Our over 25 years study at a single center provides a rare opportunity to survey changing therapeutic modalities in treating this progressive disease. The management philosophy of FSGS before the 1980s advocated by leaders in this field was no medical treatment,^[8] on the rationale that FSGS being

unresponsive to prednisone, there was no point to give this medication in order to avoid the often significant side-effects of long-term steroid therapy. However, starting in the 1980s, long-term alternative-day prednisone treatment was initiated because it was deemed to be beneficial in slowing the progression to kidney failure (Fig. 2). The short-term side effects of steroid were peritonitis and other risks of infections, and thromboembolism. Long-term therapy of steroids was complicated by growth retardation, metabolic bone disease, hypertension, and diabetes mellitus.

Tune, Lieberman and Mendoza^[11] demonstrated that intravenous methylprednisolone significantly ameliorated the progression of FSGS. Thus, nephrologists including those at this center in the 1980s routinely used intravenous methylprednisolone^[1,12] with and sometimes without cyclophosphamide and with or without cyclosporine A^[12] in an increasing number of patients. To monitor the risk of leucopenia occasionally encountered in the long-term administration of cyclophosphamide and/or cyclosporine A, white blood cell counts were examined regularly. These antimetabolites were discontinued until the white cell counts returned to normal.

In the 1990s (Fig. 2) angiotensin converting enzyme inhibitors or angiotensin receptor blockades^[1,12] were favored in preserving kidney function and we treated 9 patients with this regimen in the 1990s, but these medications declined to 6 patients by the late 1990s, as vitamin E began to be used as an adjunct therapy, based on experimental data from our group that this antioxidant can reverse FSGS in blind, controlled studies in rats.^[21] Thus we used a vitamin E dosage shown to be effective in children with IgA nephropathy, as established by our group.^[7] Controlled clinical trials in children with FSGS in the USA and elsewhere are beginning to address these proliferating and confusing treatment options.

Our data must be interpreted with the following limitations in mind. This is a retrospective study and the data are limited by what information was recorded on spread sheets. In addition, our tertiary specialist hospital received patients from all social economic classes, with substantial number of patients likely from less affluent and minority families. Finally, general population in our location is predominantly white (65%) and black (32%), with less than 3% from other ethnic origins.^[20] As a result, our project is limited by not having Asian children, who are the population at risk in other parts of the world.^[2] There is no general agreement upon histological classification of FSGS before 2004.^[22] Thus, our patient spread sheets collected over the previous 2 decades did not record whether the histology showed collapsing, tip, cellular or perihilar FSGS, which could have been useful as prognostic

factors. Finally, we did not have genetic markers. On the other hand, some advantages of our study are as follows: the use of the same criteria for kidney biopsies throughout the 25 years study; consistency maintained by utilizing the same data forms ("yellow sheets")^[4] and data entry by the same nephrologic attending, same care philosophy and follow-up.

Finally, treatment regimens for FSGS have been changing in these 3 to 4 decades. Initially in the 1970s, no treatment was recommended for FSGS on the rationale that steroids were ineffective and the side effects far outweighed the benefits.^[8] Then, in the 1980s, cyclophosphamide plus alternative-day prednisone regimen was used and best exemplified by the long-term Toronto study by Arbus et al.^[23] However, a recent study by Tarshish et al^[24] questioned the efficacy of cyclophosphamide.

Since the Kaplan-Meier kidney survival in our patients was not different from the equally long-term survival from the Toronto study,^[23] questions are raised concerning intravenous methylprednisolone,^[25] its cost, efficacy, and side effects of cataracts, hypertension, growth retardation and infectious complications. Because of the limited therapeutic options (Fig. 2), the clinical outcome in children with FSGS is still guarded, but it is better than that in the earlier 1970s.^[8] The use of tacrolimus^[26] and mycophenolate mofetil^[27,28] and important advances in delineating the genetic basis of FSGS have indicated that the future for children with FSGS is getting to be more hopeful.^[29]

In conclusion, the demographic characteristics of equal gender distribution instead of male predominance, the older age of presentation, and the prevalence of elevated levels of serum creatinine and proteinuria as presenting features in our study population may be due to the higher percentage of African-American children in our study compared to previous studies.^[3] The reasons for Kaplan-Meier survival rate in our study being not different from the earlier Toronto study,^[23] despite newer and more powerful regimen in the recent two decades, are surely multi-factorial. But the possibility that African-American children with FSGS are less responsive to therapy may need to be considered. Whether these observations are applicable to Asian nephrotic children, who show equal propensity to develop FSGS as African children, remains to be determined.

Oral treatment regimen with minimal side effects, consisting of vitamin E, alternative-day prednisone, and angiotensin converting enzyme inhibitor or angiotensin receptor blockade, would seem to be advisable. The addition of cyclophosphamide or cyclosporine A to the above regimen is an individualized decision. The side effects^[1,12] and long-

term follow-up of patients on this regimen of multiple medications require careful considerations.

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Ethical approval: The Institutional Review Board exempted this research project from review according to US federal regulation 45 CFR 46.101 (b)(2)(i)(ii). Informed consent from study participants were waived because the data analyses were from spread sheets.

Competing interest: None declared.

Contributors: CJCM proposed the project and wrote the paper. CJCM is the guarantor.

References

- Roth KS, Amaker BH, Chan JC. Nephrotic syndrome: pathogenesis and management. *Pediatr Rev* 2002;23:237-248.
- Adhikari M, Bhimma R, Coovadia HM. Focal segmental glomerulosclerosis in children from KwaZulu/Natal, South Africa. *Clin Nephrol* 2001;55:16-24.
- A report of the International Study of Kidney Disease in Children. The primary nephrotic syndrome in children. Identification of patients with minimal change nephrotic syndrome from initial response to prednisone. *J Pediatr* 1981;98:561-564.
- Chan JC. Lessons from 20 years of leading a pediatric nephrology program. *Nephron* 1998;78:378-388.
- Chan JC. Indications for kidney biopsies. *Clin Pediatr (Phila)* 1978;17:488-489.
- Chan JC, Brewer WH, Still WJ. Renal biopsies in children under ultrasound guidance: 100 consecutive biopsies in children. *J Urol* 1983;129:103-107.
- Chan JC, Mahan JD, Trachtman H, Scheinman J, Flynn JT, Alon US, et al. Vitamin E therapy in IgA nephropathy: a double-blind, placebo controlled study. *Pediatr Nephrol* 2003;18:1015-1019.
- Habib R. The major syndromes. In: Royer P, Habib R, Mathieu H, Broyer M, eds. *Pediatric Nephrology*. Philadelphia: W. B. Saunders Co, 1974: 246-290.
- Latta K, von Schnakenburg C, Ehrich JH. A meta-analysis of cytotoxic treatment for frequently relapsing nephrotic syndrome in children. *Pediatr Nephrol* 2001;16:271-282.
- Ichikawa I, Fogo A. Focal segmental glomerulosclerosis. *Pediatr Nephrol* 1996;10:374-391.
- Tune BM, Lieberman E, Mendoza SA. Steroid-resistant nephrotic focal segmental glomerulosclerosis: a treatable disease. *Pediatr Nephrol* 1996;10:772-778.
- Lee EK, Chan WK, Lai WM, Chiu MC. Nephrotic syndrome: long term management. In: Chiu MC, Yap HK, eds. *Practical Paediatric Nephrology. An update of current practices*. Hong Kong: Medcom Ltd, 2005: 116-129.
- Report of Arbeitsgemeinschaft für Padiatrische Nephrologie. Cyclophosphamide treatment of steroid dependent nephrotic syndrome: comparison of eight week with 12 week course. *Arch Dis Child* 1987;62:1102-1106.
- Lieberman KV, Tejani A. A randomized double-blind placebo-controlled trial of cyclosporine in steroid-resistant idiopathic focal segmental glomerulosclerosis in children. *J Am Soc Nephrol* 1996;7:56-63.
- Kher KK. Nephrotic syndrome. In: Kher KK, Makker SP, eds. *Clinical Pediatric Nephrology*. New York: McGraw Hill Inc, 1992: 137-174.
- Niaudet P. Steroid resistant idiopathic nephrotic syndrome in children. In: Avner ED, Harmon WE, Niaudet P, eds. *Pediatric Nephrology*. Philadelphia: Lippincott Williams and Wilkins, 2004: 557-573.
- Waldo FB, Benfield MR, Kohaut EC. Therapy of focal and segmental glomerulosclerosis with methyl prednisolone, cyclosporine A, and prednisone. *Pediatr Nephrol* 1998;12:397-400.
- Tahzib M, Frank R, Gauthier B, Valderrama E, Trachtman H. Vitamin E treatment of focal segmental glomerulosclerosis: results of an open-label study. *Pediatr Nephrol* 1999;13:649-652.
- Gipson DS, Chin H, Presler TP, Jennette C, Ferris ME, Massengill S, et al. Differential risk of remission and ESRD in childhood FSGS. *Pediatr Nephrol* 2006;21:344-349.
- Goldman DI, Chan JC. Kidney disease in the child. *Va Med Q* 1993;120:202-205.
- Hahn S, Kuemmerle NB, Chan W, Hisano S, Saborio P, Krieg RJ Jr, et al. Glomerulosclerosis in the remnant kidney rat is modulated by dietary alpha-tocopherol. *J Am Soc Nephrol* 1998;9:2089-2095.
- D'Agati VD, Fogo AB, Bruijn JA, Jennette JC. Pathologic classification of focal segmental glomerulosclerosis: a working proposal. *Am J Kidney Dis* 2004;43:368-382.
- Arbus GS, Poucell S, Bachevie GS, Bauml R. Focal segmental glomerulosclerosis with idiopathic nephrotic syndrome: three types of clinical response. *J Pediatr* 1982;101:40-45.
- Tarshish P, Tobin JN, Bernstein J, Edelmann CM Jr. Cyclophosphamide does not benefit patients with focal segmental glomerulosclerosis. A report of the International Study of Kidney Disease in Children. *Pediatr Nephrol* 1996;10:590-593.
- Tune BM, Kirpekar R, Sibley RK, Reznik VM, Griswold WR, Mendoza SA. Intravenous methylprednisolone and oral alkylating agent therapy of prednisone-resistant pediatric focal segmental glomerulosclerosis: a long-term follow-up. *Clin Nephrol* 1995;43:84-88.
- Segarra A, Vila J, Pou L, Majo J, Arbos A, Quiles T, et al. Combined therapy of tacrolimus and corticosteroids in cyclosporin-resistant or -dependent idiopathic focal glomerulosclerosis: a preliminary uncontrolled study with prospective follow-up. *Nephrol Dial Transplant* 2002;17:655-662.
- Barletta GM, Smoyer WE, Bunchman TE, Flynn JT, Kershaw DB. Use of mycophenolate mofetil in steroid-dependent and -resistant nephrotic syndrome. *Pediatr Nephrol* 2003;18:833-837.
- Montane B, Abitbol C, Chandar J, Strauss J, Zilleruelo G. Novel therapy of focal glomerulosclerosis with mycophenolate and angiotensin blockade. *Pediatr Nephrol* 2003;18:772-771.
- Gipson DS, Gibson K, Gipson PE, Watkins S, Moxey-Mims M. Therapeutic approach to FSGS in children. *Pediatr Nephrol* 2007;22:28-36.

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