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Original article

Racial differences in the incidence and renal outcome of idiopathic focal segmental glomerulosclerosis in children*

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Abstract. The North American Pediatric Registry reports that from 1987 to 1989 blacks and Hispanic children accounted for 23% of all renal transplants performed but 38% of those performed for focal segmental glomerulosclerosis (FSGS). From these data, we infer that blacks and Hispanics form a disproportionate number of FSGS patients who progress to end-stage renal disease (ESRD) compared with white children. To explore this hypothesis we assessed our single-center experience of FSGS comparing black and Hispanic with white children. Of 177 black and Hispanic children followed in our clinic for idiopathic nephrotic syndrome (NS) between 1974 and 1989, 57 were diagnosed as having FSGS (group I). The mean age at onset of NS of these group I patients was 7.3 ± 4.6 years and the mean duration of follow-up was 8.25 ± 4.3 years. During the same period, 13 of 65 white patients (group II) with idiopathic NS were found to have FSGS. Their mean age (7.8 ± 4.8 years) and duration of follow-up (8.8 ± 4.8 years) were similar. Therapeutic modalities in the two groups were also similar. Of group I patients, 78% (42/54) reached ESRD compared with 33% (4/12) of group II patients ($P < 0.01$). Life table analysis showed that 50% of black and Hispanic children will reach ESRD within 3 years of FSGS. In a subset of patients,, multiple regression analysis revealed that the higher the serum creatinine at the onset of NS ($P < 0.01$, $r = 0.519$), and the higher the serum cholesterol at the onset of NS ($P < 0.02$, $r = 0.511$), the more rapid the progression to ESRD. Based on our findings, a national survey to determine if FSGS is more virulent in black and Hispanic children is warranted.

Key words: Nephrotic syndrome – Focal segmental glomerulosclerosis – Racial differences – End-stage renal disease – Cholesterol

Introduction

Studies reporting the outcome of idiopathic nephrotic syndrome (NS) associated with Focal Segmental glomerulosclerosis (FSGS) are variable [1–3]. There has been little attempt to correlate this variability in outcome with racial differences. Easterling [4] reported that in southeastern Michigan states black adults account for a higher proportion of patients who reach end-stage renal disease (ESRD) compared with their percentage in the general population. Similar results have been reported from other parts of the country [5–7]. The incidence of ESRD in non-white patients was 2.7 times higher than in white patients in a national survey [8]. Although data from the pediatric population are not available, however, certain inferences can be made from the North American Pediatric Renal Transplant Cooperative Study [9]. The Registry (1987–1989) reported that black and Hispanic children accounted for 23% of all kidney transplants but 38% of renal transplants in which FSGS was the cause of ESRD [9]. These findings suggested that black and Hispanic children experience a disproportionate frequency of FSGS with progression to ESRD, hence we analyzed our single-center experience of FSGS comparing white and non-white children.

Materials and methods

We reviewed more than 2,000 records of children seen at our institution from 1974 to 1989 to identify children with NS. NS was defined by the presence of hypoalbuminemia (≤ 2.5 g/dl), proteinuria (>40 mg/m^2 per hour or >3 g/24 h) and edema. In order to identify patients with idiopathic NS, individuals with secondary causes of NS were excluded. Records were then reviewed to isolate patients with the histological diagnosis of FSGS, defined as segmental hyalinosis and sclerosis of one or more glomeruli seen under light microscopy, and immunofluorescence demonstrating segmental deposition of IgM and C_3 in capillary loops [3]. Careful questioning and toxicology screening were carried out at the time of clinic visits to exclude substance abuse as the etiological factor in our older patients.

The following variables were recorded for each patient at the onset of their NS: age, race, serum creatinine level, serum albumin level, serum cholesterol level, proteinuria, and blood pressure. Repeat measurements

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performed at the time of the histological diagnosis of FSGS. Treatment regimens employed, outcome, current status, and duration of follow-up were also recorded. Patients were then divided into groups according to race. The criteria for determination of race were based on chart documentation, and in cases where this was inadequate information from a family member was obtained.

Four drugs were utilized for the treatment of proteinuria in FSGS patients. At the onset of disease, prednisone was given according to the protocol of the International Study of Kidney Disease in Children [10]. Cyclophosphamide was administered orally to steroid non-responsive or toxic patients. In more recent years, intravenous pulse methylprednisolone and cyclosporine have also been used in resistant patients.

Using a biomedical programs proportional hazard model a life table analysis was carried out to determine the rate of progression to ESRD. Correlation coefficients were calculated using multiple regression analysis. Statistical analysis was carried out using Student's *t*-test comparing mean values, and a chi-squared analysis comparing patients in each group, as well as between groups. A P value of less than or equal to 0.05 was considered significant.

Results

Analysis of our data revealed that black and Hispanic children were almost identical, thus, the two patient populations were combined and formed group I. Over the years 1974–1989, 177 black and Hispanic children were followed in our clinic for NS. Of these, 57 patients (32.2%) were found to have idiopathic FSGS. Thirty-eight patients were black and 19 were Hispanic. The mean age at onset of NS was 7.3 ± 4.6 years (range 1.0–16.75 years). The mean duration of follow-up was 8.25 ± 4.3 years (range 1–15 years). Over the same period of time 65 Caucasian children were followed in our clinic for NS; 13 (20%) had FSGS and constituted group II. For group II patients the mean age of onset of NS was 7.8 ± 4.8 years (range 2–14.8 years) and the mean duration of follow-up was 8.8 ± 4.1 years (range 3.5–15.5 years).

All patients in groups I and II received at least one course of prednisone. Eighty-four percent of the black and Hispanic patients and 85% of the white patients received at least one course of cyclophosphamide. Of group I patients, 40% were given pulse methylprednisolone therapy while 38% of group II also received this treatment. Cyclosporine was administered to 35% of group I patients and 38% of group II patients.

Table 1 summarizes the demography, the clinical parameters at the onset of NS and the renal outcome in the two groups. More group I patients progressed to ESRD (78%) compared with group II (33%) patients $P < 0.01$.

Twenty-nine group I patients and 4 group II patients were found to have FSGS on an initial biopsy performed following the onset of NS. These patients were classified as having primary FSGS. The remaining 28 group I and 9 group II patients were initially steroid responsive, were dignosed as having minimal change disease (MCD) upon renal biopsy, and later became steroid resistant. A second, or in many instances a subsequent biopsy performed years later revealed the lesion of FSGS, thus excluding the possibility of sampling error. These patients were classified as having secondary FSGS. Table 2 compares the demography, clinical features and renal outcome of primary and secondary FSGS patients in group I. A similar analysis for group II patients was not carried out because of the small numbers. Group I patients classified as primary FSGS were older at the onset of NS (10.1 ± 3.9 years) compared with secondary FSGS patients (4.4 ± 3.2 years, $P < 0.001$). However, surprisingly the mean age of both primary and secondary patients was similar once FSGS was diagnosed (10.1 ± 3.9 and 9.3 ± 4.0 years, respectively). Primary FSGS patients had a higher serum creatinine at onset of NS compared with secondary FSGS patients. Interestingly, once FSGS was diagnosed, the time for progression to ESRD was similar in both subsets (primary 2.8 ± 1.3 years, secondary 2.1 ± 1.5 years).

Table 1. Demography, clinical parameters and renal outcome in black and Hispanic (group I) and white (group II) children with idiopathic nephrotic syndrome (NS)

	Group I	Group II
Rate FSGS/idiopathic NS	57/177	13/65
(%)	32.2	20
Age FSGS (years)		
mean	7.3 ± 4.6	7.8 ± 4.8
range	1–16	2–14.8
Follow-up (years)		
mean	8.25 ± 4.3	8.8 ± 4.1
range	1–15	3.5–15.5
Data at presentation		
Serum cholesterol (mg/dl)	372	421
Serum albumin (g/dl)	1.65	1.52
Serum creatinine (mg/dl)	0.778	0.746
Proteinuria (g/24 h)	5.55	5.08
Outcome		
Lost to follow-up	3	1
Remaining patients	54	12
ESRD (*n**)	42	4
(%)	78	33

* $P < 0.01$

FSGS, Focal segmental glomerulosclerosis; ESRD, endstage renal disease

Table 2. Demography, laboratory data and renal outcome in primary (early) and secondary (late) FSGS in group I patients

	Primary FSGS ($n = 29$)	Secondary FSGS ($n = 28$)	P value
Race: blacks	20	18	NS
Hispanics	9	10	NS
Sex: males	13	19	NS
females	6	9	NS
Age at NS (years)	10.1	4.4	<0.001
Age at FSGS (years)	10.1	9.3	NS
Serum albumin at NS (g/dl)	1.6	1.6	NS
Serum creatinine at NS (mg/dl)	0.96	0.59	<0.001
Serum cholesterol at NS (mg/dl)	430	412	NS
Proteinuria at NS (g/24 h)	5.4	5.7	NS
HTN at NS (*n*)	6	3	NS
ESRD, *n* (%)	22 (75)	20 (71)	NS
Age at ESRD (years)	12.3	11.8	NS
Duration of NS (years)	2.8	7.3	<0.001
Duration of FSGS (years)	2.8	2.1	NS

HTN, hypertension

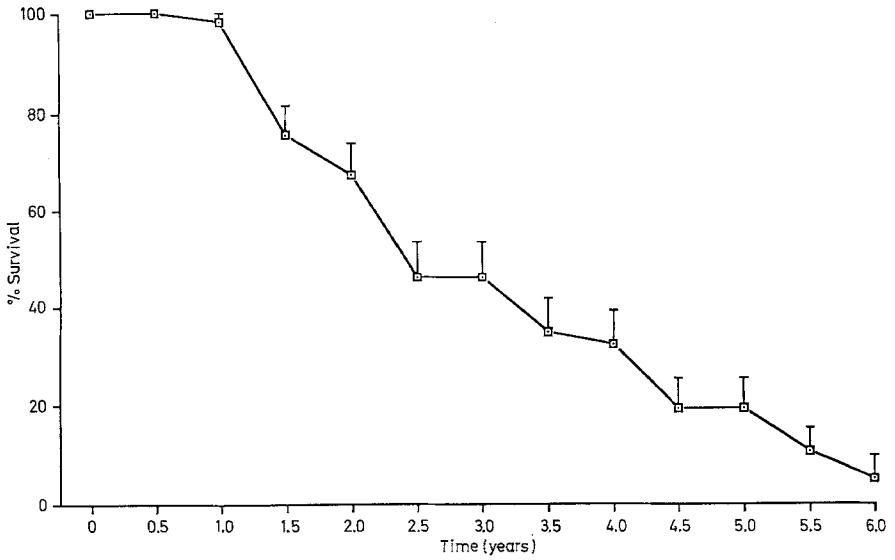

Fig. 1. Cumulative proportion of kidney survival over 6 years after the diagnosis of focal segmental glomerular sclerosis (FSGS) in group I patients

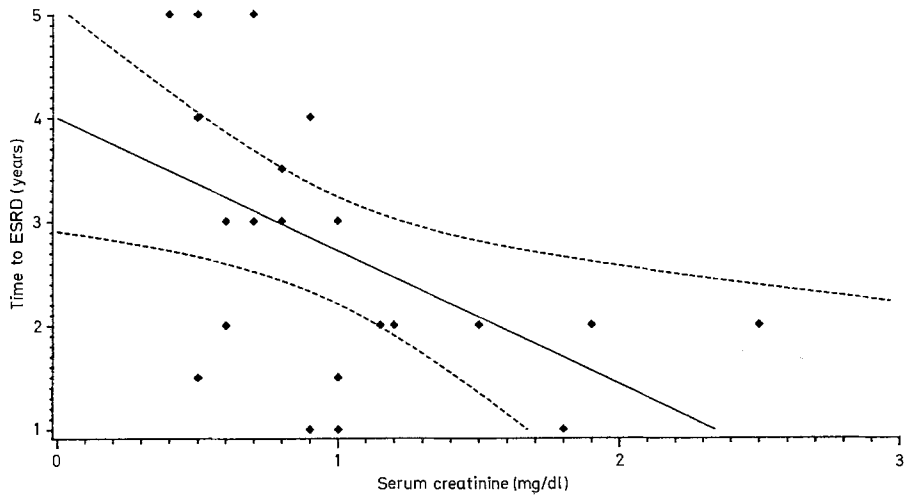

Fig. 2. Predicting end-stage renal disease (*ESRD*) in primary FSGS; relationship with serum creatinine. Time to ESRD = 4.0 – 1.28 creatinine; $r = -0.52$, $P = 0.013$

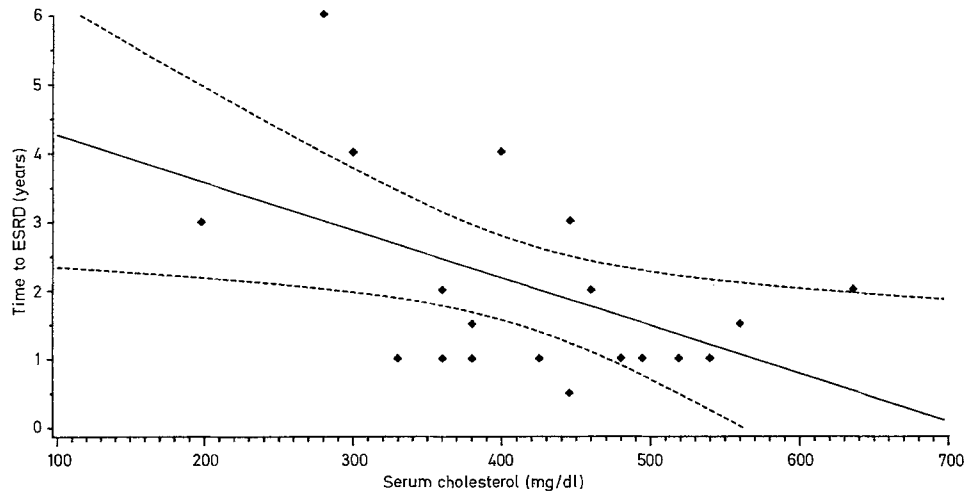

Fig. 3. Predicting ESRD in secondary FSGS; relationship with serum cholesterol. Time to ESRD = 4.97 – 0.007 cholesterol; $r = -0.51$, $P = 0.021$

Twenty-two of 29 primary FSGS patients (75%) and 20 of 28 secondary FSGS patients (71%) progressed to ESRD (Table 2). Life table analysis of group I children showed that 50 % would reach ESRD within 3 years of the histological diagnosis of FSGS, and at 6 years 95% of these patients would develop ESRD (Fig. 1). A similar analysis was not performed for group II patients because of the small sample size. Since both primary and secondary group I patients progressed rapidly to ESRD we reviewed clinical and laboratory data at presentation (i.e., serum cholesterol, serum creatinine, serum albumin, proteinuria and hypertension) to assess whether a correlation exists

with the time for progression to ESRD which could be predictive. Multiple regression analysis revealed an inverse correlation between serum creatinine in primary FSGS patients and the time for progression to ESRD. The higher the serum creatinine at the onset of NS the more rapid the progression to ESRD ($P < 0.01$, $r = 0.519$). This is depicted graphically in Fig. 2. There also exists an inverse correlation between serum cholesterol in secondary FSGS patients and time for progression to ESRD. The higher the serum cholesterol at onset of NS the more rapid the progression to ESRD ($P < 0.02$, $r = 0.511$). This is depicted graphically in Fig. 3. The individual serum cholesterol values in secondary FSGS patients did not differ from onset of NS to histological diagnosis of FSGS.

Discussion

The incidence of FSGS among our black and Hispanic children with NS is 32%, higher than that observed among our white children (20%) and those previously reported by Habib (12%) [3] and Cameron and Glassock (7%) [11]. Among predominantly white patients with FSGS, the frequency of progression to ESRD ranges from 21%–37% [3, 12, 13]. The frequency among our white patients falls within this range (33%), but the equivalent value (78%) for our black and Hispanic patients is much higher. In studies of FSGS where the population consists predominantly of white children, actuarial analysis of the 50% kidney survival ranges from 10 to 17 years [2, 3]. In our study, 50% of black and Hispanic children will reach ESRD within 3 years, and at 6 years we project a kidney mortality of 95%. These high rates of renal attrition suggest that a more virulent form of FSGS may occur in non-white patients.

The Health Care Financing Review Administration (HCFA) [8] reports that at the age of 10 years a racial difference begins to emerge, non-whites forming a higher percentage of patients who reach ESRD. In early childhood, progression to ESRD is primarily due to congenial lesions which are presumed to be equally distributed between races. In later childhood, glomerulonephritis, primarily FSGS, is the predominant cause of ESRD [9]. Despite similar mean age at onset, duration of follow-up, and therapy, more black and Hispanic children in our series reached ESRD than did white children. This finding along with the mean age of our population at ESRD (11.5 years) may explain the emerging racial difference noted by Eggers et al. [8].

Since McGovern's original observation in 1964 [14] numerous studies [12, 15–19] have reinforced that MCD in some patients evolves to FSGS. Conversion of MCD to FSGS occurred in both groups of patients in our study. We feel the non-evolution reported in some studies [20–22] is not reflective of different patient populations, but rather the varying aggressiveness in performing subsequent biopsies at different institutions. Cameron and Glassock [11, 23] maintain that the prognosis of secondary FSGS is benign unlike the poor outcome seen in patients originally diagnosed with FSGS. Our study notes that once the lesion of FSGS is diagnosed, the age of the patients, the number of patients who progress to ESRD, and the time for progression to ESRD are similar, regardless of whether the disease is diagnosed as primary or secondary. The Southwest Pediatric Nephrology Study Group reported an outcome similar to ours [12].

Previous attempts at correlating clinical signs with outcome have not been successful [12]. We attempted to identify those clinical signs that were associated with a likelihood of progression to ESRD in our black and Hispanic children. A particularly interesting finding in secondary FSGS patients was that an elevated serum cholesterol at onset of NS appeared to lead to a poor outcome. With multiple regression analysis we were able to derive a formula that predicts the time for progression to ESRD using cholesterol as a variable. Is the hypercholesterolemia seen in NS a factor in the progression to ESRD? If so, would cholesterol-lowering agents slow or prevent this progression [24]? Future studies are necessary to clarify the role of hypercholesterolemia in NS.

In summary, we have observed a high incidence of FSGS and ESRD, and a rapid devolution of kidney function among our black and Hispanic children compared with previous studies of primarily white children. Earlier South African studies also reported a high incidence of FSGS among their black patients [25–28], and the latest study from Johannesburg observed FSGS to be the most common lesion among their black children with idiopathic NS [29]. The reason for this increased incidence and virulence is not known. Our treatment regimen is similar and at times more aggressive than other institutions, therefore it is unlikely that inadequate therapy is responsible for the poor outcome. A poor outcome can usually be traced to noncompliance, however, our review revealed that failure to comply was not an issue. Thus it appears that genetic and/or environmental factors may be prime contributors to the incidence observed. The pathogenesis of NS remains unclear, however, a variety of lymphokines including interleukin-2 have been implicated [30–33]. Recently it has been demonstrated that levels of interleukin-2 in healthy black and white populations are different [34].

We suggest that a national survey of children diagnosed with FSGS and NS should be undertaken. Evaluation of racial background, lymphokine profiles, and patterns of hypercholesterolemia might clarify the pathogenesis of FSGS and determine whether FSGS is more virulent in certain subsets of children.

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Literature abstract

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Screening of urinary tract abnormalities among day and nightwetting children

Marjo R. Järvelin, Niilo-Pekka Huttunen, Juhani Seppänen, Ulpu Seppänen, and Irma Moilanen

In order to detect possible urinary tract abnormalities among wetters, assessments of previous history completed by ultrasonography of the urinary tract and uroflowmetry were obtained for 145 wetting children and a random sample of 156 sex-matched non-wetting children drawn from a population of 3375 seven-year-olds. Ultrasonography revealed abnormalities, including both morphological ones and cases with incomplete bladder emptying, in 5 out of 73 nightwetters (6.8%, 95% confidence limit, CL, 1.1–12.6), 10 out of 72 day and day and nightwetters (hereafter daywetters) (13.9%, CL 5.9–21.9) and 4 controls (2.6%, CL 0.1–5.0), the figure for the daywetters differing significantly from that for the controls (p <0.01). A fractioned voiding curve was recognized in 1 nightwetter (1.4%, CL –1.3–4.0), 7 daywetters (9.7%, CL 2.9–16.6) and 7 controls (4.5%, CL 1.2–7.7) the difference between the nightwetters and daywetters being significant (p <0.05). Depending on the previous history and abnormal findings in ultrasonography or uroflowmetry, examinations were continued with intravenous pyelography, voiding cystography, cystoscopy and/or by cystometry. Finally, marked structural or functional disorders of the urinary tract were detected in 11 out of 72 daywetters (15.3%, CL 7.0–23.6), 1 out of 73 pure nightwetters and 1 out of 156 control children. It is concluded that imaging of the urinary tract is not necessary for pure nightwetters, while ultrasonography or uroflowmetry and more sophisticated radiological or urological methods should be focused on those children with daytime wetting and clinical symptoms of voiding disturbances.