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Original article

Age and ethnicity affect the risk and outcome of focal segmental glomerulosclerosis

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Abstract. In patients with proteinuria, African-American (AA) ethnicity is reported to be a risk factor for focal segmental glomerulosclereosis (FSGS) and its progression to end-stage renal disease (ESRD). We reviewed our single-center experience to determine the probability of FSGS and its progression to ESRD based on ethnicity and age at presentation in children with proteinuria with or without nephrotic syndrome. Proteinuria without systemic disease or acute glomerulonephritis was the presenting feature in 17% (236/1,403) of children in the renal patient database of Texas Children's Hospital, Baylor College of Medicine. Histopathological diagnoses were established in 107 of 236 patients (45%). FSGS was identified in 65 patients, accounting for 28% of all patients with proteinuria and 61% of patients who underwent renal biopsy. FSGS was more prevalent in AA (45%) than in non-AA patients (22%) (P=0.001), and AA patients with FSGS were older at presentation (12.7±4.4 years) than non-AA patients (5.6±4.6 years) (P<0.001). Among patients who underwent renal biopsy, increasing age at presentation increased the probability of having FSGS in AA but not non-AA patients (P=0.04). Five-year actuarial renal survival of FSGS was worse in AA (8%) than in non-AA patients (31%) (P=0.01). These data suggest an increased risk and worse outcome of FSGS in AA compared with non-AA children.

Key words: Focal segmental glomerulosclerosis – Proteinuria – Race

Introduction

Proteinuria with or without the nephrotic syndrome is one of the most-common reasons for referral of a child to a pediatric nephrologist. Clinical presentation alone often does not differentiate relatively benign causes of proteinuria, such as minimal change nephrotic syndrome (MCNS), from potentially more-morbid causes, such as focal segmental glomerulosclerosis (FSGS). Both may present at any age, with steroid-responsive or -resistant disease, and with or without nephrotic-range proteinuria. The reported percentage of children with nephrotic syndrome attributable to FSGS ranges widely from 6% to 70% [1–9]. The reported frequency of end-stage renal disease (ESRD) due to FSGS also ranges widely from 13% to 78% in studies with up to 20 years of follow-up [1, 5, 10–19]. The large differences between studies may indicate that FSGS does not have a uniform risk and prognosis in all children who present with proteinuria. FSGS has been reported to be the histopathological lesion in 19% of adolescents with nephrotic syndrome [4], 25% of children with steroid-resistant nephrotic syndrome [8], and up to 50% of children with persistent, non-nephrotic proteinuria [20–22]. In adult studies, African-Americans (AA) have been reported to be at greater risk for FSGS than whites [23–26]. The only previous pediatric study comparing AA and whites [5], originating from an urban center in the northeastern United States, found a greater risk of FSGS in AA and Hispanic children compared with whites, but did not systematically address the effect of age on this increased risk.

We reviewed our single-center experience from a different region of the United States, with a patient population both rural and urban, to determine the probability of FSGS and its outcome based on ethnicity in children with proteinuria. To further characterize these patients, we specifically examined whether age at presentation might modify the probability of having FSGS or of progressing to ESRD.

Patients and methods

The renal patient database of the Pediatric Renal Section, Baylor College of Medicine and Texas Children's Hospital was reviewed to identify patients who were referred for evaluation of proteinur-

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ia. This database was established in September 1995 and consists of 1,403 patients. Patient data were entered retrospectively from the renal section files for the 10 years prior to September 1995. After September 1995, all new patients referred to our institution were entered prospectively into the database. Patients with proteinuria due to identifiable systemic diseases (e.g., systemic lupus erythematosus, diabetes mellitus, sickle cell disease) or with proteinuria associated with evidence of active glomerulonephritis were excluded.

The records of all renal biopsies from 1985 to the present were also reviewed to identify those that were performed as part of the evaluation of proteinuria. Although no absolute criteria were used to determine when a renal biopsy should be performed, all patients with nephrotic syndrome who were steroid resistant, and the majority of patients who were steroid dependent or frequent relapsers, underwent biopsy prior to treatment with cytotoxic agents or with cyclosporine. When a renal biopsy was performed, diagnostic categories were assigned based on standard histopathological criteria [27]. Histopathological diagnosis included MCNS, FSGS, membranous nephropathy, IgA nephropathy, and congenital nephrotic syndrome. Mesangial hypercellularity and IgM deposition in the glomerulus in the absence of other histopathological features were classified as MCNS.

Relative frequencies of diagnoses are expressed as percentages of the total patient population with proteinuria and of subpopulations defined by age at presentation or ethnicity. Mean age at presentation, age at ESRD, and length of follow-up are expressed as the mean±SD. Length of follow-up for patients with FSGS was calculated by two methods. Total follow-up was calculated for all patients through the date of last evaluation. Follow-up through onset of ESRD was calculated by using the date of ESRD diagnosis as the last date of evaluation for those patients with FSGS who had progressed to ESRD. This latter method provides a more-accurate representation of duration of follow-up by excluding the time that patients have been followed after they have started dialysis or have undergone renal transplantation. Comparisons between ethnic groups were performed by two-tailed *t*-tests. The relative frequency of FSGS in different ethnic groups was compared using chi-squared analysis. The effect of age at presentation on the probability of FSGS stratified by ethnicity was determined by logistic regression analysis. Actuarial renal survival of FSGS was determined by Kaplan-Meier analysis and the comparison of the survival distribution between ethnic groups was performed using the Breslow test.

Results

From the renal patient database, 236 patients who were referred for evaluation of proteinuria were identified. The most-common ethnicity was white (*n*=91, 39%), followed by Hispanic (*n*=67, 28%), AA (*n*=53, 22%), and other (*n*=25, 11%). The ethnic distribution among patients with proteinuria did not differ from the distribution from all patients in the renal patient database, or from all pediatric patients evaluated at our institution for any reason in the previous calendar year. Histopathological diagnoses based on renal biopsy were established in 107 of 236 patients (45%). AA patients were more likely to have undergone renal biopsy (64%) than non-AA patients (40%) ($P<0.01$). Idiopathic FSGS was identified in 65 patients, accounting for 28% of all patients with proteinuria and 61% of patients who underwent renal biopsy (Table 1). Among all patients (*n*=236), FSGS was more prevalent in AA (45%) than in non-AA patients (22%) ($P=0.001$). Among patients who underwent renal biopsy (*n*=107), FSGS tended to be more prevalent in AA (71%) than in non-AA patients (56%), but did not reach statistical significance.

Table 1. Histopathological diagnoses stratified by ethnicity

	AA	Non-AA	*n* (%)
Membranous nephropathy	2	4	6 (5%)
IgA nephropathy	1	1	2 (2%)
FSGS	24	41	65 (61%)
MCNS	7	27	34 (32%)
	34 (32%)	73 (68%)	107 (100%)

FSGS, Focal segmental glomerulosclerosis; MCNS, minimal change nephrotic syndrome; AA, African-American

Table 2. Clinical characteristics of patients with FSGS

	AA	Non-AA	
% of all patients	45% (24/53)	22% (41/183)	$P=0.001$
% of biopsied patients	71% (24/34)	56% (41/73)	NS
% ESRD	38% (9/24)	27% (11/41)	NS
% ESRD (age >5 years)	40% (9/22)	6% (1/16)	$P=0.02$
Age at presentation (years, mean±SD)	12.7±4.4	5.6±4.6	$P<0.001$
Total follow-up (months, mean±SD)	75±57	82±43	NS
Follow-up through onset of ESRD (months, mean±SD)	42±58	49±41	NS
Treatment			
No treatment	9%	11%	NS
Oral prednisone	91%	89%	NS
Cyclophosphamide/ chlorambucil	14%	32%	NS
Cyclosporine	68%	62%	NS

ESRD, End-stage renal disease

Similar clinical characteristics were found in the white and Hispanic patients when compared with AA patients. The percentage of FSGS among all patients was 15% (14/91) for whites, 28% (19/67) for Hispanics, and 45% (24/53) for AA patients. In patients with FSGS, the age at presentation was 5.3±4.2 years for whites and 5.6±5.0 years for Hispanics compared with 12.7±4.4 years for AA patients ($P<0.01$). In patients who progressed to ESRD, the time to ESRD for whites was 40.0±33 months and 40.3±33 months for Hispancis compared with 26±15 months for AA patients.

The mean age at presentation for all patients with FSGS was 8.2±5.7 years. AA patients with FSGS were older at presentation (12.7±4.4 years) than non-AA patients (5.6±4.6 years) ($P<0.001$) (Table 2). Logistic regression analysis showed that the effect of age at presentation on the probability of FSGS differed by ethnicity for all patients ($P=0.001$) and for those who underwent renal biopsy ($P=0.04$) (Fig. 1). Among AA patients, the probability of FSGS on renal biopsy was 0.5 at approximately 6 years of age, and increased to 0.8 by 14 years of age. In contrast, in non-AA patients the probability of having FSGS was 0.50 at 13 years of age, and decreased slightly with age.

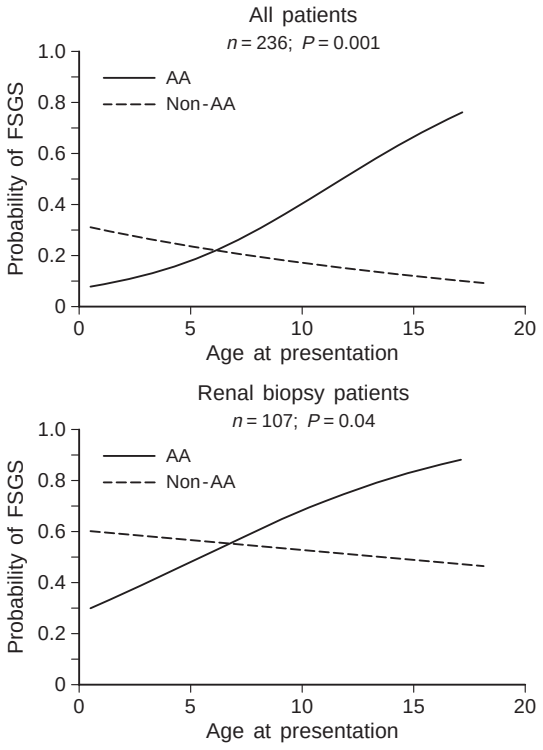

Fig. 1. Logistic regression model for probability of focal segmental glomerulosclerosis (*FSGS*) by age in African-American (*AA*) and non-AA patients. For all patients, $P=[1+\exp(0.76+0.08*AP+1.85*Race-0.3*AP*Race)]^{-1}$ and for biopsied patients, $P=[1+\exp(-0.4+0.03*AP+1.36*Race-0.2*AP*Race)]^{-1}$, where *P*=probability of FSGS, AP=age at presentation, and Race=1 (AA) or 0 (non-AA)

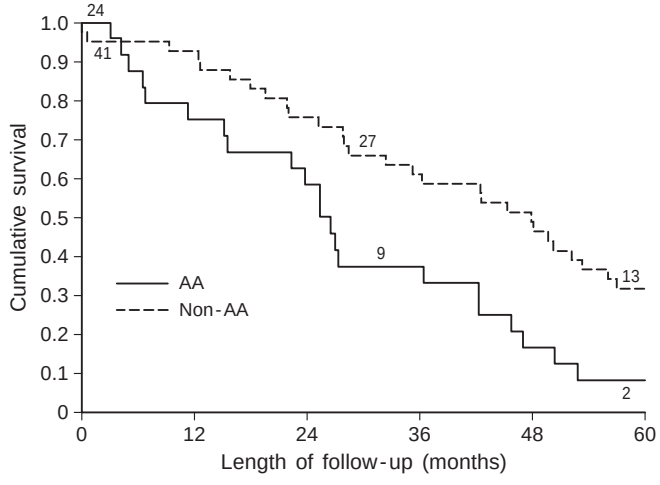

Fig. 2. Actuarial renal survival of FSGS for AA versus non-AA patients expressed as proportion of patients who have not progressed to end-stage renal disease for duration of available follow-up

The prevalence of ESRD due to FSGS was 29% (20/65) with a total follow-up period of 80±49 months, and follow-up through onset of ESRD of 48±44 months. The prevalence of ESRD was 38% (9/24) in AA and 27% (11/41) in non-AA patients (*P*=NS) (Table 2). In patients presenting over 5 years of age, the prevalence of ESRD was 41% (9/22) in AA and 6% (1/16) in non-AA patients (*P*=0.02). Among patients who progressed to ESRD (*n*=20), age at presentation was greater in AA (14.3±3.2 years) than in non-AA patients (3.5±3.9 years) (*P*<0.001). The time from presentation to ESRD tended to be shorter in AA (26.3±15.9 months) than non-AA patients (41.4±31.7 months), but did not reach statistical significance. The 5-year actuarial renal survival of FSGS was worse in AA than in non-AA patients (*P*=0.01) (Fig. 2). Estimated 5-year renal survival was 8% in AA compared with 31% in non-AA patients. The types of treatment received for each patient were identified in 91% (59/65) of FSGS patients (Table 2). The frequency of high-dose oral prednisone, cyclosporine, 8–12 weeks of oral cyclophosphamide, and no treatment did not differ between AA and non-AA patients.

Discussion

This study reviews the experience of a single pediatric referral center with children presenting with proteinuria. The large referral base and similar ethnic distribution to the total patient population at this institution suggest a representative sampling of the demographics and diagnoses of proteinuria in the southwestern United States. Regional differences may be important in comparing studies that address the prevalence of renal diseases based on ethnicity. One of the largest studies of nephrotic syndrome in children originates from South Africa, where the prevalence of FSGS was 28% in blacks, 21% in Indians, and 44% in colored patients [9]. However, black South African children may be quite different from AA children due to differing genetic backgrounds. A previous study in children in the United States compared the risk and outcome of FSGS for AA and Hispanics together compared with whites, because they found that AA and Hispanic children were “almost identical” [5]. This finding contrasts directly with our data showing that Hispanics were more similar to whites than to AA children. The imprecise nature of categorization by ethnicity may account in part for the differences in the clinical presentation and course of FSGS in Hispanics between the previous and current study. The previous study that reported similar clinical profiles in the Hispanic and AA children originates from the northeastern United States where many of the patients classified as Hispanic may have been of Caribbean descent. The current study originates from a region where all the patients classified as Hispanic are of Mexican or Central American descent. This difference in geographical origin among patients labelled as Hispanic may explain why in our study Hispanics were similar to whites, whereas in the other study Hispanics were similar to AA children.

The current study demonstrates that the probability of FSGS in children is affected by the interaction of both ethnicity and age. AA children were more likely to have FSGS and were older at presentation than non-AA patients. In addition, the probability of having FSGS increased with age in AA, but not in non-AA patients.

This finding is consistent with previous reports showing that FSGS in adults is more common in AA patients than whites [23–25, 28]. The increased prevalence of FSGS in AA adults would be expected to become detectable in pediatric patients during adolescence, the period of transition from child to adult age ranges. Our analysis shows that the divergence in the probability of FSGS between AA and non-AA patients begins at approximately 7 years of age and increases throughout the remaining pediatric age range into adulthood.

The current study also found that among patients with biopsy-proven FSGS, AA patients had overall worse renal survival and tended towards a shorter time from presentation to ESRD than non-AA patients. However, it cannot be concluded that ethnicity alone accounts for the difference in renal outcome. Although AA and non-AA patients received similar types of immunosuppressive therapy, the current study does not address possible systematic ethnic differences in severity of disease at presentation, dosages and duration of treatment, or patient adherence to treatment regimens. The results are consistent with previous reports of the effect of ethnicity on the risk of progression to ESRD from other diseases with renal sequelae. It is well established that AA patients are at greater risk for ESRD compared with whites from hypertension and diabetes [29–33]. The increased relative risk of hypertension-induced ESRD in AA patients was found to be most striking in young adults [29], and persisted when adjusted for age, prevalence of hypertension, hypertension severity, and socioeconomic status [30, 31].

Direct comparisons between studies that categorize proteinuria and nephrotic syndrome by diagnosis are difficult, since the criteria that are used to determine when a renal biopsy should be performed vary by institution, individual nephrologist, and the standards of care at the time of the study. Because it is not possible to establish definitive diagnoses in patients who have not undergone renal biopsy, the current study focuses primarily on patients with established histopathological diagnoses. Renal biopsy was performed more often in AA than in non-AA patients. This finding might indicate a greater prevalence of treatment-resistant disease in the AA children. Alternatively, a preconception among nephrologists that AA children are less likely to have benign diagnoses may have lowered the threshold to perform a biopsy and thereby establish histopathological diagnoses. However, such a bias would be expected to diminish rather than enhance the observed ethnic differences in the prevalence of FSGS. A higher threshold for performing biopsies in non-AA children would likely lead to less diagnoses of FSGS in treatment-responsive patients. In contrast, a lower threshold for performing biopsies in AA children might result in more-definitive diagnoses of benign conditions such as MCNS. In neither case would such bias have resulted in an erroneous conclusion that AA are at greater risk for FSGS than non-AA children.

The prevalence estimates of FSGS in any study may be imprecise for several reasons. The referral patterns of primary care physicians may differ between centers, such that uncomplicated cases of nephrotic syndrome are not evaluated by a subspecialist. Persistent non-nephrotic proteinuria is not always considered an indication to perform a renal biopsy. FSGS that is steroid responsive is less likely to be identified by renal biopsy. The appearance of MCNS on biopsy may not definitively exclude FSGS due to sampling error within the kidney or to the timing of the biopsy in the course of the disease. It is well established that an initial diagnosis of MCNS may be made either by clinical presentation or histopathological criteria and then revised to FSGS based on subsequent biopsy [5, 34, 35]. For these reasons, the actual prevalence of FSGS is uncertain unless all patients presenting with proteinuria are systematically subjected to renal biopsy on presentation.

In aggregate, these results confirm the previous report that FSGS in children is more probable in AA patients and has a poorer prognosis compared with non-AA patients. In addition, a strong effect of age on the probability of FSGS based on ethnicity was found. These differences in the probability of FSGS and its outcome based on age and ethnicity suggest that FSGS is expressed differently in AA compared with non-AA children. If so, studies that evaluate treatment of FSGS should be stratified by age and ethnicity, since the response to treatment is likely to differ based on these factors.

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Literature abstract

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Protein kinase C in the developing kidney: isoform expression and effects of ceramide and PKC inhibitors

Eva Serlachius, Johan Svennilson, Martin Schalling, and Anita Aperia

Protein kinase C (PKC) is a serine/threonine kinase recognized as a key enzyme in signal transduction mechanisms in various biological processes. During development, PKC is involved in the regulation of growth and differentiation. In mature tissue PKC is important for homeostatic functions. We studied PKC with regard to expression and effects on differentiation, growth and apoptosis in the developing kidney. Using in situ hybridization, we demonstrate *age*-dependent expression of PKCα, PKCδ, PKCξ and PKCλ during fetal and postnatal kidney development. The endogenous sphingolipid product ceramide, as well as specific PKC inhibitors, disturbed nephron formation and induced apoptosis in organ cultures of E13 kidneys. In primary cell cultures of proximal tubule cells, ceramide and the specific PKC inhibitors induced apoptosis. In conclusion, PKCα, PKCδ, PKCξ and PKCλ are expressed in an age-dependent pattern during kidney development. Inhibition of PKC disturbs nephron formation, inhibits growth and induces apoptosis in the developing kidney. The findings suggest that PKC plays an important role in regulating normal kidney growth and differentiation.