Focal segmental glomerulosclerosis in children with idiopathic nephrotic syndrome. A report of the Southwest Pediatric Nephrology Study Group

Focal segmental glomerulosclerosis in children with idiopathic nephrotic syndrome. A report of the Southwest Pediatric Nephrology Study Group. Clinicopathologic correlations were examined in 75 children with focal segmental glomerulosclerosis (FSGS) associated with idiopathic nephrotic syndrome. The biopsy specimens of all patients were examined by electron microscopy (69 patients) or immunofluorescence microscopy (67 patients) in addition to light microscopy. Fifty-three patients (group A) had FSGS diagnosed on their first biopsy; 22 patients (group B) had one to three previous biopsies showing minimal glomerular changes or mesangial hypercellularity prior to the demonstration of FSGS on a subsequent biopsy. Considerable homogeneity between the diagnostic biopsy features in the two groups was evident. Diffuse mesangial hypercellularity and IgM deposition were found in a similar percentage of each group, but these features did not correlate with each other. To date, the mean duration of follow-up for the entire group has been 57 months (range, 7 to 217 months): 21% have developed ESRD, 23% have a decreased GFR but not ESRD, 37% have persistent proteinuria only, 11% are in remission, and 8% have been lost to follow-up. No morphologic or clinical features have been predictive of outcome during this relatively short period of followup. The frequency of chronic renal failure and ESRD has been similar in groups A and B. These data suggest that the clinical outcome in children with FSGS is poor in many patients, whether the diagnosis is established on an initial or subsequent renal biopsy specimen.

Glomerulocérose focale et segmentaire chez des enfants atteints de syndrome néphrotique idiopathique. Un rapport du Southwest Pediatric Nephrology Study Group. Des correlations anatomo-cliniques ont été examinées chez 75 enfants atteints de glomerulocérose focale et segmentaire (FSGS) associée à un syndrome néphrotique. Les spécimens de biopsie de tous les patients ont été examinés en microscopie électronique (69 malades) ou en microscopie avec immunofluorescence (67 malades) et en plus de la microscopie optique. Cinquante-trois malades (groupe A) avaient une FSGS diagnostiquée à la première biopsie; 22 malades (groupe B) avaient eu une à trois biopsies antérieures indiquant des lésions glomérulaires mineures ou une hypercellularité mésangiale avant la démonstration de la FSGS par une biopsie ultérieure. Une homogénéité considérable entre les caractéristiques de la biopsie diagnostique était évidente dans les deux groupes. Une hypercellularité mésangiale diffuse et des dépôts d'IgM ont été trouvés en proportion identique dans chaque groupe, mais ces caractéristiques n'étaient pas corrélées entre elles. À ce jour, la durée moyenne du suivi du groupe entier a été de 57 mois (extrêmes 7 à 217 mois): 21% ont développé une ESRD, 23% ont une GFR diminuée mais pas d'ESRD, 37% ont une protéinurie persistante seulement, 11% sont en rémission, et 8% ont été perdus de vue. Aucune caractéristique morphologique ou clinique n'a permis de prédire le devenir pendant cette période de suivi relativement courte. La fréquence d'une insuffisance rénale chronique et d'une ESRD était identique dans les groupes A et B. Ces données suggèrent que le devenir clinique de malades atteints de FSGS est sombre chez beaucoup de malades, que le diagnostic soit établi sur un fragment de biopsie rénale initiale ou ultérieure.

Focal segmental glomerulosclerosis (FSGS) is the renal histopathologic lesion observed in approximately 10% of children with idiopathic nephrotic syndrome (INS) [1-3]. Although it is well accepted that the presence of FSGS denotes a high risk of steroid resistance in children with NS, the uncertain outcome of such patients has prompted a number of studies to evaluate the prognostic value of specific pathologic and clinical features. Pathologic indicators of poor outcome that have been suggested include mesangial hypercellularity [3-5], the relative percentage of global versus segmental sclerotic lesions [6-9], and the presence of segmental hyalinosis [10], FSGS on an initial versus subsequent biopsy [11, 12], and either tubulo-interstitial [8, 13] or vascular disease [14]. Clinical and laboratory features that have been proposed include hypertension [9, 12], increased levels of serum cholesterol or other lipids [14, 15], and the presence of nephrotic syndrome [12, 16] or hematuria [5, 17, 18]. However, the data remain inconclusive despite the fact that

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Fig. 1. Light micrograph of a focal segmental lesion. This diagnostic biopsy specimen (group B) was taken 10 years after the onset of symptoms. (Trichrome ×500)

Fig. 2. Light micrograph of a focal segmental lesion with an intracapillary foam cell (arrow). The biopsy specimen (group A) was taken 2.5 months after the onset of symptoms. (Trichrome ×500) The inset shows a foam cell at a higher magnification. (×1250)

long-term follow-up studies have confirmed the wide variation in the frequency of progression to chronic renal failure in patients with FSGS [5, 7, 12, 15, 18–25].

Apart from the studies of Habib and Kleinknecht [20] and Gubler et al [22], most of the previous reports of FSGS in children have come from single institutions with relatively small patient populations and have included a number of children whose biopsy specimens were given only light microscopic evaluation (a fact which precludes the ability to eliminate other glomerulopathies associated with focal sclerosis, for example, IgA nephropathy [26]). In an attempt to further elucidate the characteristics of FSGS in children in the United States, members of the Southwest Pediatric Nephrology Study Group (SPNSG) have compiled data on children with this disorder. Our study includes (1) the requirement of both light microscopy (LM) and either immunofluorescence (IF) or electron microscopy (EM) for entry of patients, (2) compilation of the largest number of children with FSGS from the United States, and (3) heterogeneous racial characteristics of the patient population. The aims of this retrospective study were (1) to compare pathologic features of the biopsy specimens from patients in whom the lesion of FSGS was identified in an initial versus a subsequent renal biopsy, (2) to describe the clinical course of the disease in a large group of children in the United States, and (3) to identify clinico-pathologic correlations which might aid in predicting clinical outcome.

Methods

Patient population

Patients under 18 years of age were accepted into the study if they had documented evidence of nephrotic syndrome (defined according to our previously published criteria [27]) and had a renal biopsy studied by LM and either IF or EM, in which the diagnosis of FSGS was established by SPNSG pathologists. FSGS was defined as segmental capillary loop collapse and increased mesangial matrix (Fig. 1) sometimes associated with intracapillary foam cells (Fig. 2) in one or more glomerular tufts [4]. Clinical or laboratory evidence of systemic disease (post-infectious glomerulonephritis, systemic lupus erythematosus, Henoch-Schönlein purpura, IgA nephropathy, diabetes mel-

Clinical and laboratory studies

After FSGS was confirmed, the clinical records of each patient accepted into the study were reviewed by physicians at the participating centers. Complete information for all clinical variables, however, was not available for every patient. Hypertension, proteinuria, and hematuria were defined as in previous studies [27], and glomerular filtration rate (GFR) was assessed by measurement of endogenous creatinine clearance or estimated by the serum creatinine-length equation of Schwartz et al [28]. A decreased GFR was defined as less than 90 ml/min/1.73 m².

Response of NS to steroid therapy was defined as the loss of proteinuria as assessed by dipstick. Steroid-dependent responses were included. Owing to the retrospective nature of the study, no attempt to standardize prednisone dosage schedules, duration of therapy, or the use of adjuvant therapy was carried out. The consequent variation in treatment regimens made it difficult to reach conclusions about specific responses to therapy.

Pathology studies

Renal tissue samples were prepared in the individual institutions using methods described in our previous studies [27, 29]. Renal biopsy specimens from 134 patients with INS and suspected FSGS were reviewed by pathologists from the participating institutions, following which a mean of four selected slides were re-examined by two principal SPNSG pathologists to confirm the presence of a diagnostic lesion. Questionable cases were submitted to all group pathologists for a consensus opinion. Seventy-five patients were accepted into this study, representing 7.1% of the 1053 biopsies performed on patients with NS during the period of study. Once a case was accepted, all previous and subsequent renal biopsy specimens from that patient were reviewed. Fourteen patients had followup biopsies after the diagnostic biopsy. The total number of biopsies for the group as a whole was 116. For diagnostic biopsy specimens, the
Table 1. Comparison of initial clinical and laboratory features in patients with focal segmental glomerulosclerosis diagnosed on first or subsequent biopsy

| Age
days | Duration of clinical disease before diagnostic biopsy
months | Quantitative proteinuria
(g/24 hr) | Microscopic hematuria
% | Serum albumin
(g/dl) | Serum Cr mg/dl | T BP
% |
<table>
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<tbody>
<tr>
<td>FSGS diagnosed on first biopsy (Group A) N = 53</td>
<td>8.7 ± 4.6</td>
<td>12.7 ± 19.5</td>
<td>4.2 ± 4.2</td>
<td>60</td>
<td>2.2 ± 1.0</td>
<td>0.7 ± 0.4</td>
</tr>
<tr>
<td>FSGS diagnosed on subsequent biopsy (Group B) N = 22</td>
<td>10.2 ± 4.6</td>
<td>59.5 ± 48.3</td>
<td>6.3 ± 3.5</td>
<td>53</td>
<td>1.5 ± 0.9</td>
<td>0.7 ± 0.3</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>0.002</td>
<td>NS</td>
<td>NS</td>
<td>0.01</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: FSGS, focal segmental glomerulosclerosis; Cr, creatinine; BP, blood pressure.

a Mean values ± 1 sd are represented.

b The age given was age at the time of the diagnostic biopsy.

Statistical methods

Correlations were sought between clinical and pathologic features. Statistical methods utilized included Student’s t tests for comparison of means, Spearman correlation testing for the ordinal variables, and χ² contingency table analysis or Fisher’s exact probability test for the association of categorical variables. Statistical significance was defined as a P value equal to or less than 0.05. Results are given in the text and tables as mean ± 1 sd.

Results

Seventy-five children (mean age, 7.7 years at the time of clinical presentation of renal disease) were accepted into the study (Fig. 3). All 18 cases of FSGS in children less than 3 years of age occurred in boys, whereas beyond that age the frequency in the two sexes was similar. Thirty-two patients were white; thirty, black; eleven, hispanic; one, Indian; and one, of unknown racial background. The patients were separated into two groups: In 53 patients (group A) the diagnosis of FSGS was made on the initial renal biopsy; in the other 22 (group B) the diagnostic biopsy was preceded by one to three biopsy specimens showing only minimal change disease or mesangial hypercellularity.

Clinical presentation

Nephrotic syndrome was present initially in 57 of 73 patients (78%). Sixteen of the patients presented with only asymptomatic proteinuria, but all developed the nephrotic syndrome at some time during their clinical course. Hypertension was noted in 36% of the patients, and although microscopic hematuria was present in 57%, an episode of gross hematuria was observed in only one patient. Estimated GFR was decreased in 30 of the 62 patients (48%) for whom this information was available. Other than a slightly lower serum albumin concentration in group B, clinical and laboratory features at presentation (Table 1) did not differ between groups A and B.
specimens, respectively. In no case was IgA dominant or IgM. Staining for IgG and IgA was present in 14 and 7 biopsy specimens with C3 (P = 0.35). Renal biopsy specimens without visceral epithelial caps had focal sclerotic lesions which were attached to Bowman’s capsule by synchiae or dense adhesions.

When the frequency of pathologic features in the entire group was compared between diagnostic and nondiagnostic biopsy specimens, it was found that hyalinosis was noted in 50% of the specimens exhibiting FSGS but was also seen in 2 of 22 biopsy specimens without demonstrable focal sclerosis. In these two biopsy specimens the hyalinosis occurred near the vascular pole and was not associated with segmental sclerosis. Mild arteriolar wall thickening was seen in ten diagnostic biopsy specimens (13%) but not in nondiagnostic ones.

IF studies revealed one or more immunoreactants in 51 of 67 patients evaluated. Glomerular IgM, seen in 34 of 56 biopsy specimens studied (61%), had a pattern of distribution that was diffuse mesangial in 14, focal segmental in 18, and nonspecified in two biopsy specimens. C3 accompanied IgM in 23 biopsy specimens and was present alone or with an immunoreactant other than IgM in eight. Twenty-five patients with diffuse mesangial hypercellularity (DMH) were studied for the presence of IgM; only five showed diffuse mesangial IgM staining. Thus, there was a poor association between diffuse IgM staining and DMH. The presence of hyalinosis by LM was associated with C3 (P = 0.03), most often focal, segmental, but not with IgM. Staining for IgG and IgA was present in 14 and 7 biopsy specimens, respectively. In no case was IgA dominant or codominant. No significant differences were seen in IF findings between groups A and B.

EM studies were performed on 69 biopsy specimens, but only 22 (32%) had segmental sclerotic lesions in the glomeruli available for EM. Sixty-two biopsy specimens (90%) had some degree of glomerular endothelial cell swelling. All biopsy specimens had effacement of visceral epithelial cell podocytes, but this change was diffuse in only 36 (53%). Fifty-five biopsy specimens (79%) had visceral epithelial cell swelling or vacuolization. Sixteen diagnostic biopsy specimens (21%) contained electron dense material, which was observed in regions of hyalinosis in ten, discrete within the mesangial matrix and suggestive of “immune-type” deposits in five, and in both areas in one biopsy specimen. The lamina rara interna of the glomerular basement membrane was focally widened in 60 specimens (87%). Ultrastructural findings of diagnostic biopsy specimens were not different between groups A and B.

Follow-up biopsies. Fourteen follow-up biopsies (eight in group A, six in group B) were performed at a mean of 37.5 months after the diagnostic biopsy. Of the 14 biopsy specimens, hyalinosis was first identified in the follow-up biopsy in six patients, whereas in three others it was present in the diagnostic biopsy but not in the follow-up biopsy. The percentage of segmentally sclerotic glomeruli showed no consistent trend in follow-up biopsy specimens, but in 9 of the 14 cases, the percentage of globally sclerotic glomeruli increased substantially from a mean of 7% in diagnostic biopsies to 51% in follow-up biopsies (P = 0.02). Tubulointerstitial disease, which was present to some degree in the diagnostic biopsies of all 14 patients, was the same or increased in severity in all but one follow-up biopsy. DMH, which had been present in nine diagnostic biopsies from this group, was present in five follow-up biopsies. In two of these, the severity was decreased, in two, the same, and in one, increased.

Clinical course and outcome. For the total group, the mean duration of follow-up was 57 months (range, 7 to 217 months) from the onset of symptoms. The latest evaluation revealed that 21% have endstage renal disease (ESRD), 23% have decreased GFR but not ESRD, 37% have persistent proteinuria, 11% have remission of INS, and 8% have been lost to followup. Analysis
of only those patients with greater than 2 years followup (49 patients) revealed data which are not different from those described for the whole group. To date, 7 of the 16 patients who developed ESRD have received renal transplants. Five of these patients have subsequently died, one returned to dialysis after rejection, and one has been nephrotic (10 g proteinuria/day). Of five transplanted kidneys which have been examined morphologically, only one demonstrated recurrent FSGS. Of the remaining nine patients who progressed to ESRD, eight have been maintained on dialysis, and one has died.

Group B patients were followed significantly longer than group A patients (Table 2), but the mean period of followup after the diagnostic biopsy (group A, 32.8 months; group B, 37.9 months) was not significantly different. The percentage of patients with decreased GFR and ESRD was found to be similar in groups A and B. Group A patients progressing to ESRD developed symptoms at a mean age of 7.3 years and ESRD occurred after a mean followup of 67 months. Group B patients who progressed to ESRD were younger at the onset of disease (mean age, 2.9 years) and ESRD tended to occur after longer followup (mean, 114 months).

To examine the possibility that group A patients might do worse over a longer period of time, we also compared 18 group A patients and 12 group B patients who had followup periods of more than 4 years. Mean followup did not differ for these two subgroups (group A, 88 months; group B, 123 months; \( P > 0.2 \)) and the outcome was not significantly different: Nine patients (50%) in group A and seven patients (58%) in group B had decreased GFR while six (33%) group A patients and three (23%) group B patients developed ESRD.

**Clinical features as outcome indicators**

Hypertension at onset did not show a significant correlation with decreased GFR at followup, although 57% of patients with hypertension at onset developed decreased GFR compared to 35% who were normotensive initially (\( P = 0.29 \)). Hypertension at the latest evaluation was present significantly more frequently in group B than in group A patients (Table 2); in those followed more than 4 years, hypertension was still more common in group B (78%) than group A (29%) (\( P < 0.002 \)).

Neither the presence of hematuria nor the severity of proteinuria at onset was a significant factor predicting outcome. Hematuria was present initially in 75% of patients who later developed ESRD and in 52% of patients who did not (\( P = 0.25 \)). Of the 16 patients who presented with only asymptomatic proteinuria, eight developed decreased GFR and three of these progressed to ESRD.

**Response to treatment—relationship to subsequent outcome**

Prednisone was prescribed for 56 patients (38 in group A, 18 in group B). Nine patients (24%) in group A and seven (39%) in group B responded to steroid therapy at some time (\( P = 0.34 \)). Response to therapy given prior to the initial biopsy was significantly different between the two groups; only 15% (4 of 26) of group A patients who were given pre-biopsy steroids responded, whereas 60% (6 of 10) of group B patients responded (\( P = 0.014 \)). The postdiagnostic biopsy response, however, was not different; 26% (9 of 35) of group A patients and 19% (3 of 16) of group B patients responded (\( P = 0.73 \)).

Response to corticosteroids did not predict outcome. Sixteen of 56 patients who received corticosteroids responded. The outcome for these 16 patients was no different from that of the group as a whole. Six patients developed decreased GFR (two had ESRD), eight had persistent proteinuria, and two were asymptomatic at latest follow-up.

**Clinico-pathologic correlations**

DMH tended to be observed more frequently in biopsy specimens taken early in the clinical course of the disease, and often was not present in follow-up specimens. The sex distribution of patients with DMH was similar to that of the group as a whole (20 males; 9 females). Four children with DMH were less than 2 years of age at presentation. Three of these children had normal renal function without proteinuria after 10 to 28 months of followup. The fourth child had moderately decreased GFR (30 to 60 ml/min/1.73 m²) after 115 months of disease. The relationship of DMH to the time of biopsy and renal function at follow-up is shown in Table 3. Fifteen of the 16 patients who progressed to ESRD had no or only mild DMH, and no patient developing ESRD had severe DMH. There was no significant

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**Table 2. Comparison of latest clinical and laboratory features in patients with focal segmental glomerulosclerosis diagnosed on first or subsequent biopsy**

<table>
<thead>
<tr>
<th></th>
<th>Age(^a) years</th>
<th>Duration(^a) of follow-up months</th>
<th>↑ BP (^b) %</th>
<th>Hematuria (^b) %</th>
<th>GFR(^a) ml/min/1.73 m²</th>
<th>↓ GFR(^a) %</th>
<th>ESRD (^a) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSGS diagnosed on first biopsy (Group A)</td>
<td>11.6 ± 5.5</td>
<td>45 ± 39</td>
<td>22</td>
<td>17</td>
<td>123 ± 99</td>
<td>39.2</td>
<td>22</td>
</tr>
<tr>
<td>FSGS diagnosed on subsequent biopsy (Group B)</td>
<td>14.3 ± 5.6</td>
<td>101 ± 62</td>
<td>56</td>
<td>20</td>
<td>114 ± 44</td>
<td>61.9</td>
<td>23</td>
</tr>
</tbody>
</table>

\( P \) NS 0.003 0.02 NS NS NS NS

Abbreviations: ESRD, endstage renal disease; FSGS, focal segmental glomerulosclerosis; GFR, glomerular filtration rate; BP, blood pressure.

\(^a\) Mean values ± 1 SD are represented.

\(^b\) The values include patients with ESRD.

\(^c\) The data presented are from the time of clinical presentation.
difference between outcomes for children with DMH who were less than 6 years of age versus those older than 6 years.

Glomerular hyalinosis tended to be more frequent in the initial biopsy specimens of patients who subsequently developed renal failure, although this was not statistically significant. However, when follow-up biopsies were included in this analysis, hyalinosis was present significantly more often in specimens of patients with renal failure (72%) than in those of patients with a normal GFR (48%; P = 0.05). Biopsy specimens were taken from patients with glomerular capillary foam cells (GFC) a mean of only 19 months after the onset of symptoms while those without GFCs were symptomatic for 35 months before biopsy (P = 0.04). This correlation is compatible with the observation that GFCs tended to be more common in group A biopsy specimens, although this was not statistically significant.

The presence of tubular atrophy or interstitial fibrosis was associated with a longer duration of clinical disease prior to biopsy (28 months vs. 8 months, P = 0.06). A similar relationship existed for the presence of interstitial foam cells (IFC) [65 months for patients with IFC vs. 19 months for patients with no IFC (P = 0.05)]. Tubulointerstitial disease (TID) was seen more frequently in the biopsy specimens of patients who subsequently developed chronic renal failure, but this association did not reach statistical significance, even when the analysis was limited to specimens exhibiting moderate to severe TID.

Nine of the 14 patients who had followup biopsies developed decreased GFR. Eight of these nine had markedly increased percentages of globally sclerotic glomeruli on the followup biopsy, compared to patients who maintained a normal GFR (P = 0.02). The mean duration from diagnostic biopsy to followup biopsy was similar for both groups, but the groups are quite small, making statistical evaluations suspect.

Hypertension was present in 17 of 52 (33%) patients at followup. No correlation was found between hypertension and the percentage of glomeruli with either segmental or global sclerosis. Only two of ten patients with documented arterial or arteriolar sclerosis had hypertension at followup.

**Discussion**

The present study confirms the poor prognosis of FSGS and INS reported previously in children with relatively homogeneous racial characteristics. However, in our multicenter evaluation of a heterogeneous group of children with FSGS, we have not been able to identify any clinical or pathologic features of prognostic significance in this condition. More specifically, we found that children in whom FSGS is documented on initial renal biopsy appear to have a similar lesion and prognosis to those with FSGS identified on a later biopsy.

The patient population in the present study was derived initially from children with documented nephrotic syndrome in whom FSGS was observed in a renal biopsy. By definition we have therefore excluded a number of patients who had focal sclerotic lesions but no evidence of nephrotic syndrome. It should be noted that during a 10-year period from 1972 to 1981, our group performed a total of 2929 renal biopsies. Of these, 1053 were in children with nephrotic syndrome. Hence, the 75 patients who showed the lesion of FSGS represented 7.1% of the total number of children with NS. However, since most of the children with INS in our centers are not biopsied, this apparent frequency rate probably overestimates the incidence of FSGS in children with INS.

Morphologic studies, which showed no differences in pathologic features between biopsy specimens of patients who did and did not develop a decreased GFR, suggested that mesangial hypercellularity, visceral epithelial caps, synechiae, hilar prominence, and tubulointerstitial disease were part of the spectrum of FSGS and not correlated with clinical severity of disease. However, an increase in the percentage of globally sclerotic glomeruli from diagnostic to followup specimens correlated with the development of decreased GFR (P = 0.02). This finding agrees with the observations of Velosa, Donadio, and Holley [9] and Saint-Hillier et al [18]. The number of patients with followup biopsies who did not have a decreased GFR was so small, however, that this correlation may not be valid. When followup and diagnostic biopsies were considered together, hyalinosis also correlated with decreased GFR (P = 0.05).

Diffuse mesangial hypercellularity has been cited as an indicator of a poor prognosis by Gubler et al [22]. We were unable to confirm this observation, as were Brown et al [14] and White, Glasgow, and Mills [30]. In fact, while patients with moderate to severe DMH comprised only 20% of the patients in our study, 38% of the patients in remission came from this group, and no patient who developed ESRD had marked DMH (Table 3). In our study, DMH was less frequent in patients with clinical disease of long duration, suggesting that the mesangial hypercellularity was an early response. These findings agree with those of Newman et al [23] who reported a similar decrease in cellularity in FSGS with time, although some authors [5, 22] have reported the persistence of DMH in repeat biopsies. Diffuse glomerular IgM in the presence of DMH has also been cited as predicting a poorer prognosis in patients with INS [31].

**Table 3. Latest clinical status of 75 children with focal segmental glomerulosclerosis—relationship to degree of diffuse mesangial hypercellularity**

<table>
<thead>
<tr>
<th>Degree of DMH</th>
<th>Number of patients</th>
<th>Age at onset years</th>
<th>Clinical onset to biopsy months</th>
<th>Clinical onset to followup months</th>
<th>Complete remission</th>
<th>Isolated proteinuria</th>
<th>↓ GFR</th>
<th>ESRD</th>
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<tr>
<td>None (0)</td>
<td>46</td>
<td>7.4</td>
<td>26.4</td>
<td>58.8</td>
<td>8</td>
<td>44</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Mild (1+)</td>
<td>15</td>
<td>6.1</td>
<td>31.1</td>
<td>70.8</td>
<td>14</td>
<td>28</td>
<td>22</td>
<td>36</td>
</tr>
<tr>
<td>Moderate (2+)</td>
<td>10</td>
<td>7.3</td>
<td>9.0</td>
<td>48.0</td>
<td>20</td>
<td>40</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>Severe (3+)</td>
<td>4</td>
<td>6.9</td>
<td>7.0</td>
<td>42.0</td>
<td>25</td>
<td>50</td>
<td>25</td>
<td>0</td>
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</table>

Abbreviations: DMH, diffuse mesangial hypercellularity; ESRD, endstage renal disease; GFR, glomerular filtration rate.

* The group represents patients for whom clinical data were available.

The patient population in the present study was derived initially from children with documented nephrotic syndrome in whom FSGS was observed in a renal biopsy. By definition we have therefore excluded a number of patients who had focal sclerotic lesions but no evidence of nephrotic syndrome. It should be noted that during a 10-year period from 1972 to 1981, our group performed a total of 2929 renal biopsies. Of these, 1053 were in children with nephrotic syndrome. Hence, the 75 patients who showed the lesion of FSGS represented 7.1% of the total number of children with NS. However, since most of the children with INS in our centers are not biopsied, this apparent frequency rate probably overestimates the incidence of FSGS in children with INS.

Morphologic studies, which showed no differences in pathologic features between biopsy specimens of patients who did and did not develop a decreased GFR, suggested that mesangial hypercellularity, visceral epithelial caps, synechiae, hilar prominence, and tubulointerstitial disease were part of the spectrum of FSGS and not correlated with clinical severity of disease. However, an increase in the percentage of globally sclerotic glomeruli from diagnostic to followup specimens correlated with the development of decreased GFR (P = 0.02). This finding agrees with the observations of Velosa, Donadio, and Holley [9] and Saint-Hillier et al [18]. The number of patients with followup biopsies who did not have a decreased GFR was so small, however, that this correlation may not be valid. When followup and diagnostic biopsies were considered together, hyalinosis also correlated with decreased GFR (P = 0.05).

Diffuse mesangial hypercellularity has been cited as an indicator of a poor prognosis by Gubler et al [22]. We were unable to confirm this observation, as were Brown et al [14] and White, Glasgow, and Mills [30]. In fact, while patients with moderate to severe DMH comprised only 20% of the patients in our study, 38% of the patients in remission came from this group, and no patient who developed ESRD had marked DMH (Table 3). In our study, DMH was less frequent in patients with clinical disease of long duration, suggesting that the mesangial hypercellularity was an early response. These findings agree with those of Newman et al [23] who reported a similar decrease in cellularity in FSGS with time, although some authors [5, 22] have reported the persistence of DMH in repeat biopsies. Diffuse glomerular IgM in the presence of DMH has also been cited as predicting a poorer prognosis in patients with INS [31].
but we found no relationship between the presence of IgM and DMH. Furthermore, there was no correlation between the presence of IgM and the progression to renal failure. We have no explanation for some of the differences between our patients and those in the literature, although genetic factors [32] may be important in understanding these differences. Our patients represented a homogeneous population with a high proportion of black and Hispanic children compared to the more homogeneous English and French populations reported previously [12, 22].

It has also been suggested that the presence of vascular changes [7, 14] is indicative of a poor prognosis and a tendency to develop hypertension. We looked specifically at this relationship and found no correlation. Platelet thrombi and arteriolar and arteriolar thickening, which have been cited by others [33, 34] as evidence for a primary vascular lesion, were too infrequent and randomly distributed to be helpful.

The suggestion that children in whom FSGS is documented on an initial renal biopsy have the worse prognosis [11, 12] was not substantiated by the results obtained in this study. Follow-up renal function was similar in groups A and B, and although group B patients were followed longer from the time of clinical presentation, the time from diagnostic biopsy to last follow-up visit was the same for both groups. In addition, there was no difference in renal function when patients in groups A and B were followed for more than 2 or 4 years, so the frequency of renal failure in group B was not a reflection of the longer follow-up period. However, group B children did take twice as long from onset of symptoms to develop ESRD and were significantly younger at onset of INS.

The only clinical difference between groups A and B patients was the more frequent occurrence of hypertension at follow-up in group B, even when only groups A and B patients with an equal duration of clinical disease were compared. It is possible that the increased frequency of hypertension in group B was related to the dosage or duration of corticosteroid therapy, but the clinical data were not adequate to test this hypothesis. An alternate possibility is that hypertension itself was involved in the development of focal sclerotic lesions in the group B patients.

In summary, this study shows: (1) children in the southwestern United States are no more likely to develop chronic renal failure if the diagnostic lesion of FSGS is demonstrated on an initial rather than a subsequent renal biopsy, (2) a greater percentage of children with a nondiagnostic first biopsy (group B) have hypertension at follow-up; (3) an increase in the percentage of globally sclerotic glomeruli in the follow-up biopsy correlates with the development of chronic renal failure; (4) neither DMH nor the presence of IgM in a diffuse mesangial pattern predict a poorer outcome. Although additional follow-up of these patients will be necessary to confirm our current observations, it would seem reasonable to conclude that FSGS in association with INS portends a poor prognosis in a high percentage of patients irrespective of whether the lesion was identified on the first or subsequent biopsy specimen of the patient—but that specific outcome indicators for individual patients remain elusive at the present time.

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Focal segmental glomerulosclerosis in children

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