Risk profiles of progression in primary focal segmental glomerulosclerosis

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Background: Focal segmental glomerulosclerosis (FSGS) is a component of childhood nephrotic syndrome occurring in 10%-20% of all cases. Over time, 25%-50% of children with FSGS develop kidney failure disease. We followed a cohort of children with FSGS in order to delineate the risk profile of progression to kidney failure (KF).

Methods: We evaluated patient data collected from 1977 to 2002 at a regional mid-Atlantic nephrology center in the United States. KF was defined primarily for those patients whose serum creatinine (SCr) value doubled compared with the SCr value from a previous visit. Patients who received dialysis or a kidney transplant were also defined as having KF. We analyzed patient data for those who had at least two visits with SCr values recorded. Various baseline characteristics of patients who had developed KF and those with no kidney failure (NKF) were compared. Hazard ratios and correlation were used to further investigate potential risk factors of the kidney failure. We also compared the inverse SCr trend for KF and NKF patients using weighted linear regression.

Results: Thirty-four of 43 FSGS patients had adequate follow-up data. About 60% of the patients developed KF over the study period. The average age of the KF patients at diagnosis of FSGS was 9 years, and that of NKF patients 12 years (P=0.05). FSGS patients with KF had a significantly higher mean diastolic blood pressure (DBP) at baseline, compared to those with NKF (P<0.0001). Other baseline characteristics including race, body mass index (BMI), systolic blood pressure, total cholesterol, urinary protein/creatinine ratio and calculated glomerular filtration rate (cGFR) were not significantly different. Baseline DBP was a significant risk factor in progression to KF (HR: 1.03; 95%CI: 1.01-1.06). Inverse SCr values were significantly decreased over time in KF patients (P=0.01).

Conclusions: The data of this study indicate that children diagnosed with FSGS who are younger than 10 years and have elevated baseline DBP are more likely to develop kidney failure. The non-significant hazard ratios for other baseline characteristics including gender, race, and BMI are not instrumental risk factors. These results may help understand what may affect progression towards kidney failure in children with FSGS.

Key words: blood pressure; focal segmental glomerulosclerosis; gender; predictors of progression; risk profile

Introduction

Focal segmental glomerulosclerosis (FSGS) is the second most common pathological diagnosis of primary childhood nephrotic syndrome.[1] In previous reports on children with FSGS, characteristics at presentation including age, gender, ethnicity, and obesity have been suggested as risk factors for developing end-stage kidney failure (KF).[2-4] However, follow-up periods are limited and conclusions about outcomes over time could not be extrapolated. To improve these findings, we conducted a cohort study to examine these and other variables including systolic blood pressure (SBP), diastolic blood pressure (DBP), serum total cholesterol, severity of proteinuria, and glomerular filtration rate in a longitudinal setting. In our previous study on FSGS in children with nephrotic syndrome,[5] we noted a high incidence of elevated DBP. We hypothesized that elevated DBP may be an unrecognized risk predictor in progression to end-stage KF.
**Methods**

**Patients**
We tested our hypothesis using a database that included patient records from 25 years of clinical practice. Clinical and laboratory data were collected at the point of care and recorded on standard forms used throughout the follow-up period (July 1977-June 2002) for 43 biopsy-proven FSGS patients. The patients were not on anti-hypertensive medications at presentation. Details describing inclusion and exclusion criteria and treatment protocol for our study were previously reported.\(^5\) We accessed these forms to retrieve the variables of interest. Patients with a doubling of serum creatinine (SCr) value at a follow-up visit and/or those who had dialysis or kidney transplantation were classified as having KF. We compared baseline characteristics of patients with KF to those with no kidney failure (NKF).

Informed consent authorization from study participants (and their parents) was waived because we performed analyses using pre-existing, de-identified data. The Institutional Review Board exempted this research project from review according to US Federal Regulation 45 CFR 46.101 (b) (2) (i) (ii).

**Variable definitions**
Our primary outcome was KF. If a patient was coded as having both a doubling of SCr value and dialysis or a transplant at their follow-up visit, the earlier date of these events was recorded as the event date. Body mass index (BMI) was obtained by applying the standard formula: weight (kg) divided by the square of the height (m\(^2\)). The calculated glomerular filtration rate (cGFR) was obtained from the Schwartz formula:\(^6\) K multiplied by the length (cm) and divided by SCr (mg/dl), with a K of 0.41.

**Statistical analysis**
Baseline differences between the KF and NKF groups were tested using Students’ \( t \) test and Fisher’s exact test for continuous and categorical measures. We estimated hazard ratios for kidney failure, with baseline univariate predictors, using the Cox proportional hazard regression. The Spearman’s rank-order correlation coefficient was used to determine linear associations of DBP with other continuous measures at baseline.

We plotted the average inverse SCr values for KF and NKF patients to inspect the five-year trend. The data displayed were selected from the patients’ nearest visit (within 3 months) to each year from their baseline visit. Weighted linear regression was used to determine the difference in slopes. Because DBP levels less than 80 mmHg are considered to be normal, we compared overall averages for KF and NKF patients using dichotomous cutoffs of less than or equal to 75 and 80 mmHg. All significance tests were based on an error rate of 0.05. All statistical analyses were performed using SAS 9.1.3 software package (Cary, North Carolina).

**Results**
Of the 43 patients previously studied (reported earlier),\(^5\) 9 were excluded from the analysis because there were baseline data only \((n=5)\) or no record of a follow-up measure on serum creatinine \((n=4)\). In the remaining 34 patients, 20 developed KF and 14 had no kidney failure. Of the 20 patients with KF, 17 had a doubling of SCr value at a follow-up visit and 3 had dialysis during the follow-up even though they never had a SCr doubled value. In our cohort, 75% of the patients who developed KF had aggressive disease progression since the event occurred within three years of their baseline visit. The average follow-up time for the patients with KF was 2 years, with a maximum time to failure around 7.5 years. The average follow-up time for the patients with NKF was 3.5 years, with a maximum of 11 years.

**Baseline characteristics**
The patients with KF at presentation of biopsy-proven FSGS had an average age of 9 years and the patients with NKF had an average age of 12 years. The difference in age was borderline significant \((P=0.05)\). The patients with KF were primarily males, but the distribution of their gender compared to the patients with NKF was not significantly different. The average baseline SBP was not different between the KF and NKF patients, but the average baseline DBP (85.4 and 71.6 mmHg respectively) was significantly different \((P<0.001)\). The other baseline characteristics including race, BMI, weight group, serum creatinine, total cholesterol, urine protein/creatinine and glomerular filtration rate were not statistically different (Table).

**Predictors**
Hazard ratios were used to further examine potential baseline predictors for risk of KF. Although some point estimates such as race and urine protein/creatinine ratio indicated a possible increased risk of KF, most confidence intervals were not significant. The hazard ratio for DBP at baseline had a significant confidence interval \((HR: 1.03; 95\% CI: 1.01-1.06)\). For a 10 unit increase in DBP the risk for kidney failure increased by an average of 34% and could increase up to 80%. Other baseline measures such as BMI and cGFR with a hazard ratio of 1.0 revealed no evidence of increased risk of KF.
Correlation
Among the variables correlated with DBP, no linear relationship was found for age, BMI, cholesterol, proteinuria, and cGFR. As expected, SBP was highly correlated with DBP ($r=0.46$, $P=0.01$). Besides, SCr had a positive, significant linear association with DBP ($r=0.36$, $P=0.04$).

Trend
Fig. 1 shows the average inverse (1/SCr) values over 5 years at baseline in KF and NKF patients. Using the inverse of serum creatinine over time as a clinical indication of renal function, we found a decline in values over time for the patients with KF and an upward trend for the patients with NKF. The two weighted regression slopes were statistically different ($P=0.01$).

Fig. 2 shows the mean DBP over time for both KF and NKF patients. The patients with KF had a higher average DBP at baseline ($t=0$) and appeared to be higher for the first year visit. However, the trend varied in other years and it is unclear whether the patients maintained a lower average DBP. We found most (85%) of the patients with NKF had an average follow-up DBP value less than or equal to 80 mmHg, versus only 65% of the KF patients.

Discussion
Collection of data from patients over 25 years has offered a unique opportunity to evaluate the validity of clinical markers for kidney failure disease in a longitudinal setting. A recent and ongoing NIH funded interventional clinical trial is designed to treat FSGS children with a combination of new medications http://clinicaltrials.gov/ct2/show/NCT00135811. In addition, this trial will use urinary molecular markers

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Table. Baseline characteristics of patients with focal segmental glomerulosclerosis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Kidney failure ($n=20$)</th>
<th>No kidney failure ($n=14$)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>9.3 (3.9)</td>
<td>12.1 (4.7)</td>
<td>1.01 (0.92, 1.12)</td>
</tr>
<tr>
<td>Gender, $n$ (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13 (65.0)</td>
<td>4 (28.6)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Female</td>
<td>7 (35.0)</td>
<td>10 (71.4)</td>
<td>0.76 (0.30, 1.92)</td>
</tr>
<tr>
<td>Race, $n$ (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-black</td>
<td>6 (30.0)</td>
<td>5 (35.7)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Black</td>
<td>14 (70.0)</td>
<td>9 (64.3)</td>
<td>1.33 (0.50, 3.52)</td>
</tr>
<tr>
<td>BMI,* mean (SD)</td>
<td>24.1 (9.8)</td>
<td>24.4 (7.2)</td>
<td>1.00 (0.95, 1.04)</td>
</tr>
<tr>
<td>Weight,* $n$ (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>8 (42.1)</td>
<td>7 (50.0)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Overweight</td>
<td>4 (21.1)</td>
<td>3 (21.4)</td>
<td>1.37 (0.42, 4.53)</td>
</tr>
<tr>
<td>Obese BMI</td>
<td>7 (36.8)</td>
<td>4 (28.6)</td>
<td>1.24 (0.45, 3.39)</td>
</tr>
<tr>
<td>Systolic blood pressure,* mean (SD) mmHg</td>
<td>129.6 (16.4)</td>
<td>131.1 (26.3)</td>
<td>1.01 (0.99, 1.03)</td>
</tr>
<tr>
<td>Diastolic blood pressure,* mean (SD) mmHg</td>
<td>85.4 (14.0)</td>
<td>71.6 (11.6)</td>
<td>1.03 (1.01, 1.06)</td>
</tr>
<tr>
<td>Serum creatinine, mean (SD) mg/dl</td>
<td>2.6 (4.4)</td>
<td>1.1 (0.5)</td>
<td>1.10 (0.99, 1.21)</td>
</tr>
<tr>
<td>Total cholesterol,* mean (SD) mg/dl</td>
<td>259.2 (64.4)</td>
<td>258.5 (13.4)</td>
<td>1.01 (1.00, 1.02)</td>
</tr>
<tr>
<td>Urine protein/creatinine,* mean (SD) mg/mg</td>
<td>1.6 (1.7)</td>
<td>1.4 (2.2)</td>
<td>1.20 (0.89, 1.61)</td>
</tr>
<tr>
<td>Glomerular filtration rate,* mean (SD) ml/min/1.73 m$^2$</td>
<td>72.3 (46.9)</td>
<td>67.4 (27.2)</td>
<td>1.00 (0.99, 1.01)</td>
</tr>
</tbody>
</table>

*: missing data: $n=1$ for BMI, weight, and glomerular filtration rate; $n=2$ for diastolic and systolic blood pressure; $n=21$ for total cholesterol; $n=9$ for urine protein/creatinine.
of greater precision and specificity to identify kidney disease progression. This long-term study is in the early stages of implementation and is expected to continue to follow up patients over many years. However, until this study is completed, identifying patients with higher risk of progression to kidney failure is still dependent on clinical markers, such as gender, age at time of presentation, BMI, obesity, blood pressure and cholesterol. These conventional risk factors of higher likelihood of progression to end-stage kidney disease have been evaluated previously in a cross-sectional setting. Thus we compare the findings with ours.

Compared to other studies, more males developed kidney failure disease than females in this study. However this is not a key driver of risk when compared to the patients with NKF because gender proportions were not statistically different. As shown by the epidemiology of this disease, more blacks developed kidney failure. Again, the proportions in our categories of race were essentially the same for the KF and NKF patients. This result suggests that race does not play a role as a risk factor in kidney failure from FSGS.

Apart from gender and race, obesity has been implicated in hyperperfusion-induced kidney damage and development of FSGS in adults. Reports in pediatrics by Adelman et al have shown that severe obesity with BMI in the range of 46±11 is associated with FSGS and kidney failure. The BMI values of our patients, irrespective of kidney failure, were much lower than that reported by Adelman et al. In our study of FSGS children, BMI is not a risk factor for disease progression. Even when we grouped BMI percentiles into normal, overweight and obese, we found no associated risk.

Often related to weight, unsuccessful control of hypertension has been considered to be a definite risk factor for kidney injury and progression to failure. The finding of higher DBP at baseline in the KF patients is an under-recognized risk factor when considering other published reports. The vital importance of maintaining a normal DBP in children with FSGS is highly encouraged.

As we define our primary event as a measure of SCr, higher SCr concentrations at the time of FSGS presentation would indicate severe kidney damage. Since the majority of our patients were diagnosed early in their disease process, it is likely that the initial SCr value does not suffice as a prognostic index. This conclusion comes from our finding that the risk of kidney failure (SCr doubling) does not depend on the magnitude of SCr at baseline, only on the increased value of SCr over time.

Often, proteinuria in a spot urine sample is elevated to above 2.0 mg/mg in children at onset of nephrotic syndrome or at relapse. It is a long-standing belief that reversal of proteinuria by any therapeutic regimen indicates healing of the kidney lesion. By extension, the severity of proteinuria is considered an index of severity of kidney injury. The results of our study suggest the opposite. Thus a moderate severity of proteinuria has minimal utility in kidney failure risk profile. The finding may be due to marginally good baseline renal functions of our patients, as shown by the mean glomerular filtration rate (Table).

Hazard ratios can confirm the risk of kidney failure in FSGS patients. Because the point estimate for DBP is statistically significant, we recommend that controlling and lowering blood pressure may aid in slowing the progression of kidney failure. Although total serum cholesterol concentrations in KF and NKF patients are not statistically different, the hazard ratio is of some value in monitoring total cholesterol, yet it may not be a strong risk factor as higher DBP levels in children with FSGS.

Since baseline DBP is a predictor for kidney failure risk, other measures correlated with DBP could affect the management of DBP in FSGS patients. We found that most measures were not linearly associated with DBP. It can be argued that efforts to lower BMI or cholesterol in children with FSGS will not necessarily affect changes in DBP. Finding a linear relationship between SCr and DBP values highlights how integral elevated DBP may be, over time, in the progression of kidney failure disease. We believe that focusing on monitoring and managing normal ranges of DBP is an important conclusion from this study.

Over time, inverse serum creatinine has been shown to approximate the rate of decline or treatment-induced improvement in renal functions in patients with chronic kidney disease. Patients with kidney failure, based on decreasing inverse SCr (increasing SCr) have declining renal function. Our results indicate that significant decline of renal function in patients with KF can be anticipated, yet the improvement of inverse SCr for patients with NKF may result from response to the treatment protocol as we described earlier. Another plausible explanation could be related to better management of DBP. Although both KF and NKF patients in our study reduced their average DBP over time, the patients with NKF had maintained an overall lower DBP on average.

There are limitations in our study. Although we collected and analyzed data in a longer period of time than other studies, we recognize our sample size was small. This is primarily because FSGS in children with nephrotic syndrome is a relatively rare condition. Our study design was not as powerful as a randomized clinical trial with a predetermined study sample size.
Having a larger group of patients might lead to finding additional significant factors in the development of kidney failure. We also note that some data of patient follow-up visit were incomplete. This limited our ability to analyze all of the follow-up measures. Additionally, while serum albumin measures were originally collected, we did not have the data available for our analysis. In spite of these potential sources for bias, we add evidence for enhancing treatment protocol for children with FSGS in order to limit progression to kidney failure.

In conclusion, our study showed that patients with presentation of FSGS at less than 10 years of age and those with elevated DBP at baseline, even borderline elevations, should be identified as having a higher risk for progression to kidney failure compared with older FSGS patients and those who are within a normal range of DBP. An important conclusion from our analyses is the necessity to monitor and manage DBP levels for children with FSGS. We also found in our baseline data, BMI, total cholesterol, urinary protein/creatinine ratio, and steadily reduced cGFR were not strong predictors of progression to kidney failure. Our results help to understand what risks are associated with characteristics of children diagnosed with FSGS as they progress to kidney failure. We recommend that future studies involving FSGS patients are designed to analyze various subgroups within treatment protocol in order to obtain additional evidence on effective management of FSGS, ultimately reducing kidney failure rates. Finally, on completion of its follow-up phase, the NIH supported clinical trial will provide recommendations on new therapeutics in FSGS in children and young adults (http://www.fsgs trial.org/).

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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 subjects were waived, because the data analyses were from spread sheets.

Competing interest: None.

Contributors: Chan JCM and Travis L proposed the project and wrote the paper. Chan JCM is the guarantor.

References

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