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.\textsuperscript{[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\textsuperscript{2}). The calculated glomerular filtration rate (cGFR) was obtained from the Schwartz formula:\textsuperscript{[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' most recent 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),\textsuperscript{[3]} 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.

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