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Original Article

Prediction of kidney survival in children with primary focal segmental glomerulosclerosis (a two-center study)

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Abstract

BACKGROUND: Focal segmental glomerulosclerosis (FSGS) is one of the most common glomerulopathies in children leading to end stage renal disease (ESRD). Different values of median renal survival have been reported among different ethnicities and races. Many factors are assumed to be responsible for ESRD in these patients. In this study, we tried to determine median renal survival (MRS) and also some clinical and histopathological features predisposing FSGS patients to ESRD in two referral hospitals in Tehran.

METHODS: The study involved 103 FSGS patients (61 males and 42 females) with a mean age of 7.08 ± 0.68 years. The diagnosis was made based on kidney biopsies. All kidney biopsies were studied by light and immunofluorescent microscopes. Ocular grids (counting squares) were used as the standard method to calculate the percentage of cortical interstitial fibrosis (CIF). The percentage of glomerular sclerosis was presented as renal injury score. Glomerular filtration rate (GFR)≤50 ml/min was considered as renal death or the end point. Patients were followed for 1 to 15 years, until occurrence of renal death.

RESULTS: The MRS was 9.04 ± 1.8 yrs. The renal survival reached 72%, 47% and 17% after 5, 10 and 15 years, respectively. Univariate analysis showed significant reverse correlation (P<0.05) between renal survival and the following variables: hypertension, anemia, GFR at the time of first admission and also renal injury score >50%, peritubular fibrosis, periglomerular fibrosis, tubular atrophy and CIF≥20%. However, multivariate analysis revealed only a reverse correlation between renal survival with CIF≥20% and also hypertension (P<0.0001 and P<0.05, respectively).

CONCLUSIONS: In our patients, FSGS showed a rapid course towards ESRD compared with patients of western countries. Perhaps some ethnic and genetic factors such as angiotensin converting enzyme genotypes (ACE-DD) can be considered as a cause of this rapid progression. Also, we carried this study only on children and adolescents which might change the MRS results.

KEY WORDS: Focal segmental glomerulosclerosis, children, renal survival, end stage renal disease.

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Idiopathic nephrotic syndrome presents with edema, severe proteinuria, decrease in serum albumin level and increase in serum lipids. The non-specific histopathological changes under light microscopy include minimal change, focal segmental glomerulosclerosis (FSGS) and diffuse mesangial proliferation [1]. The prevalence of FSGS has dramatically increased during recent years. However, there is an incidence of 7%-20% among the children with primary nephrotic syndrome [2].

FSGS is one of the most common causes of end-stage renal disease (ESRD) in children. Many factors are assumed to be responsible for ESRD in these patients. Furthermore, it may relapse in the transplanted kidney causing

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transplantation failure [3]. Hence, given the remarkable importance of FSGS and shortage of studies on such patients in Iran, we set out to determine renal survival in FSGS children, as well as some of the factors which predispose them to ESRD.

Methods

This analytical descriptive cross-sectional study involved 103 patients (61 males and 42 females) admitted to Ali-Asghar and Dr Ahari Children's Hospitals in Tehran from 1984 to 1999. Diagnosis of FSGS was made based on kidney biopsies. The patients were aged from 6 months to 15 years (mean age: 7.08 ± 0.68 years) and were observed for 1-15 years after diagnosis until renal death. The endpoint for the study (renal death) was considered as the glomerular filtration rate (GFR) equal to or less than 50 ml/min. The same treatment protocols were applied for all patients at both centers. The demographic, clinical and histopathological data were recorded in a separate sheet for each patient. All paraffin embedded sections (kidney biopsies) were cut and stained. Trichrome and PAS staining were chosen to assess fibrosis and sclerosis. Each slide was examined three times (twice by a nephrologist and once by a nephropathologist) under the light microscope using ×10 objective lens and ocular grids. Different histopathological characteristics and findings of FSGS including glomerular sclerosis, cortical interstitial fibrosis, mesangial proliferation, periglomerular and peritubular fibrosis, interstitial oedema and tubular atrophy were assessed. Specimens showing different results were examined for the forth time by the nephropathologist. Immunofluorescent data were extracted from the patients' files. The specifications of the microscope were as follows: photomicroscope-3 with immunofluorescence appendices equipped with two ocular grids (counting square), Zeiss-Germany.

The percentage of glomerular sclerosis was presented as renal injury score more or less than 30%, using the equation below:

$$RIS[6] = \frac{SSG + GS}{TG} \times 100$$

Where
RIS = Renal injury score
SSG = Segmental sclerosed glomeruli
GS = global sclerosed
TG = Total glomeruli

Cortical interstitial fibrosis was expressed by percentage less or more than 20% as the cut-off point, using the following equation:

$$PCIF[6] = \frac{ACI}{TCIA} \times 100$$

Where
PCIF = Percentage of cortical interstitial fibrosis
ACI = Area of cortical interstitial fibrosis
TCIA = Total cortical interstitial area

The data were analyzed by SPSS (version 10).The median renal survival was estimated by Kaplan Meier method. The Cox Regression method was used to determine univariate correlation between each variable and renal survival, followed by calculation of the multivariate correlation between the variables and renal survival. A P value of less than 0.05 was considered significant.

Results

The study included 61 male and 42 female patients. The mean age of patients was 7.08 ± 0.68 years. Table 1 shows more demographic data. Complete remission, i.e. normal range of proteinuria and subsiding of all signs and symptoms was only observed in 19.6% of the patients on prednisolon therapy. The Median renal survival was 9.04 ± 1.8 years. The Renal survival after 5, 10 and 15 years from the diagnosis, was 72%, 47% and 17%, respectively (figure 1). We had 3 patients with established history of familial FSGS, all of whom reached the endpoint in less than one year. About 25% of our patients had hypertension at the time of diagnosis. Moreover, 5, 10 and 15-year renal survival in normotensive patients were 85%, 60% and 25%, respectively. These values dropped to 70%, 30% and 12%, respectively, in hypertensive patients. The difference between the two groups was significant (P<0.05) .Also,

multivariate analysis showed strong correlation between hypertension at the time of diagnosis and progression to ESRD among our patients (P<0.05). We divided the patients into two groups according to the percentage of CIF more or less than 20%. In those with CIF of 20% or more, renal survival rates were 50%, 22% and 12% after 5, 10 and 15 years, respectively. In patients with less than 20% CIF, renal survival rate increased to 90%, 75% and 45%, respectively. The difference between these groups was also significant (P<0.0001).

The results of histopathologic study under light and immunofluorescent microscopes are shown in tables 2 and 3. Univariate analysis showed that renal survival had a significant correlation with the following variables: hypertension, GFR at the time of the first admission, anaemia, renal injury score more than 50%, CIF more than 20%, periglomerular and peritubular fibrosis and tubular atrophy. We applied backward cox regression multivariate analysis and concluded that only hypertension and CIF of more than 20% were independent determinants of renal survival (figure 2 and 3).

Table 1. This table shows the percentage of some clinical findings among the patients.

Clinical findings	Positive	Negative
Growth impairment	39.3%	60.7%
Peripheral edema	96%	4%
Macroscopic hematuria	23.3%	76.7%
Hypertension	25.3%	74.7%
Pallor	27.2%	71.8%

Table 2. This table shows some prominent histopathological findings among the FSGS patients.

Histopathological findings	Positive	Negative
Mesangial proliferation	35.4%	64.6%
Periglomerular fibrosis	58.3%	41.7%
Peritubular fibrosis	55.2%	44.8%
Interestitial edema	26.3%	73.7%
Tubular atrophy	53.1%	46.9%
Tip lesion	14%	86%

Table 3. This table shows some immunofluorescent findings among The FSGS patients.

Immunofluorescent findings	Positive	Negative
IgM Alone	48.7%	51.3%
IgM plus IgA and or IgG	87.8%	12.2%
All components of complement	46.5%	53.5%
C3 Alone	11%	89%

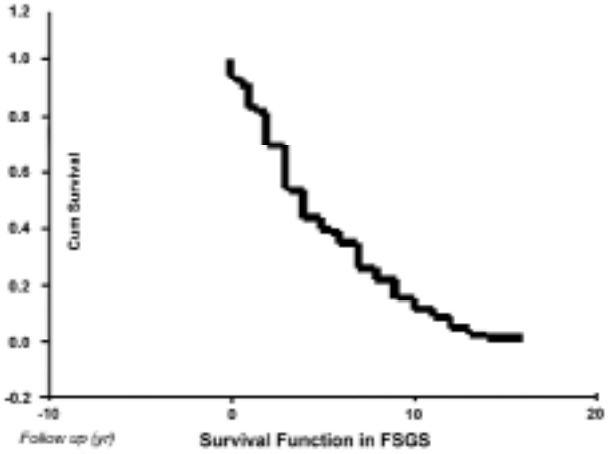

Figure 1. Median renal survival in Iranian children with FSGS. Median renal survival was 9.04 ± 1.8 years.

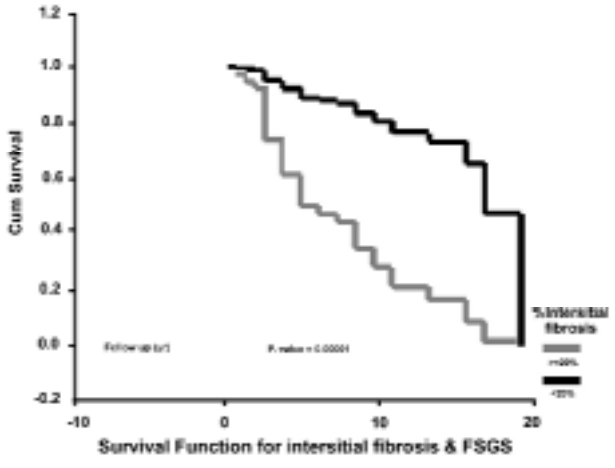

Figure 2. Relationship between renal survival and interstitial fibrosis. This figure shows a significant difference between renal survival of patients with CIF≥20% and renal survival of patients with CIF<20%.

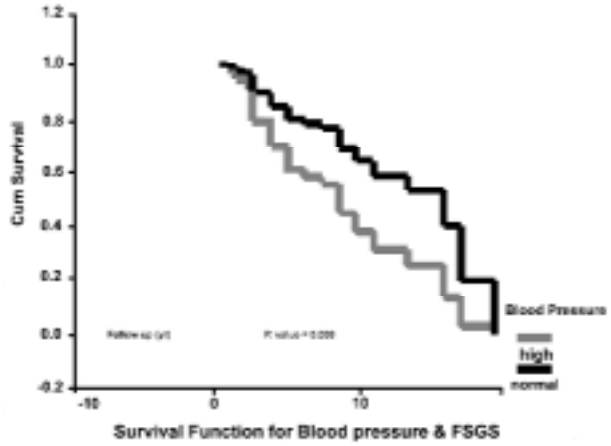

Figure 3. Relationship between blood pressure and renal survival. The patients with hypertension had a rapid course to ESRD compared with normotensive patients.

Discussion

Different renal survival values are reported in various studies. Kobert et al reported the minimum time to ESRD as short as 9 months [2]. Patients with familial FSGS took a more rapid course to ESRD [4]. We had 3 patients reaching ESRD in less than one year and all of them had a history of familial FSGS. Collapsing histopathology and tuberculosis in two different studies were proved to accelerate the rate to ESRD [5,6]. However, we could not find those findings in our patients. Chitali et al reported that the median renal survival (MRS) in 111 FSGS patients was about 16.4 years and also the 5, 10 and 15-year renal survival rate were 80%, 65% and 55%, respectively [7]. According to another study on 177 patients, 5-year renal survival rate was about 50% among Hispanic race. Furthermore, Black and Hispanic children reached ESRD much faster than the whites [8]. The difference between values of MRS in our study and these two surveys may be related to ethnicities and genetics and also the number of samples of the same race that survey was carried on.

Kidney survival in our study was less than that of western studies, especially among the white Americans and Europeans. However, compared with similar studies, kidney survival was longer among our patients than in Blacks and Hispanics.

Progression to ESRD in our patients had strong correlation with hypertension at the time of diagnosis. However, the same correlation was not shown in some studies [2,9,10]. This could be related to the number of cases entered in the survey and also different antihypertensive regimes, although we were not able to find the exact antihypertensive protocols in other studies. On the other hand, angiotensin converting enzyme genotype (ACE.DD) may shorten the progression time to ESRD [11]. Perhaps some patients have had certain genotypes that along with hypertension shortened the time to ESRD.

This study showed that interstitial fibrosis of more than 20% had a more rapid course to ESRD. The same result has been achieved in Chitali et al study [7]. Indeed, in the course of the primary disease, sclerosis and fibrosis leads to hyperfiltration and thus causes a vicious cycle leading to further sclerosis. Our study revealed that the hypertensive patients and those with CIF more than 20% may require a more aggressive treatment and vigorous intensive follow up visits.

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