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Focal segmental glomerulosclerosis in a kidney transplant population: hereditary and sporadic forms

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Abstract Between 1985 and 1993, 16 of 1000 kidney transplant patients in Göteborg had biopsy-verified primary focal segmental glomerulosclerosis (FSGS), and among them they received 23 transplants. Their age range was 19–67 years (median 39 years). Patients were followed for 3–10 years (median 6.5 years). Eight patients were members of seven separate families in which at least one other member had FSGS, while eight cases were sporadic. The patients with hereditary FSGS were younger at onset of symptoms than sporadic cases (median 12.5 vs 26 years, $P = 0.041$) but not at the time of renal failure. Only one versus five had received immunotherapy. After transplantation, recurrence of FSGS occurred in five grafts, all in sporadic cases, and two of these were lost. In conclusion, it appears that there are at least two forms of FSGS, one hereditary and one sporadic form. The hereditary form does not seem to recur after transplantation, whereas the risk in sporadic cases is very high.

Key words Kidney transplantation, focal segmental glomerulosclerosis · Glomerulosclerosis, kidney transplantation · Hereditary glomerulosclerosis, kidney transplantation

Introduction

Primary focal segmental glomerulosclerosis (FSGS) is one of the best known renal diagnoses with a definitive impact on the outcome of transplantation because of its tendency to recur in the renal allograft [2, 17]. Recurrence rates of 20 %–50 % have been reported [1, 6, 16]. When recurrence occurs, the risk with a new transplant is even higher [1, 9]. Young age, a rapid progression of the original disease, and demonstrated mesangial expansion in the native kidney are other reported risk factors [2, 6]; recurrence is unpredictable in the individual case. The problems with risk evaluation may be related to diagnostic difficulties. Focal glomerulosclerosis may be seen in a variety of conditions, and the primary form of chronic glomerulonephritis (CGN) is not always easy to identify [5, 9]. An accumulation of cases in certain families has been reported, suggesting a separate entity, yet without histopathologic or clinical characteristics [4, 14, 15, 19]. We have identified all FSGS patients in a cohort of transplant patients and analyzed their family history and other background data, as well as the outcome of transplantation.

Materials and methods

Patients

Sahlgrenska University Hospital in Göteborg, serves 3.5 million (40 %) of Sweden's 8.7 million inhabitants, when in need of kidney transplantation; the only exceptions to this rule are children from the Northern region who are referred to the Huddinge Hospital in Stockholm. Between January 1985 and January 1993, a total of 1000 patients received 1095 kidney transplants in Göteborg, 874 of which were primary transplants. All patients' records were retrospectively investigated and, if needed, missing information from

before and after transplantation was obtained from the local nephrology units. Biopsies of the native kidney were performed in 345 cases. The pathologists' protocols of all but eight of these were obtained. This enabled us to evaluate the original kidney disease. Details of this study have previously been published [15]. Of the 1000 patients, 185 (18.5 %) had biopsy-proven CGN. In addition, 201 (20.1 %) had unknown renal disease including non biopsy-verified CGN. Sixteen patients, 8.6 % of the biopsy-verified CGN group, had FSGS. In each case, the diagnosis was made by one of Sweden's experienced renal pathologists: A. Bergstrand ($n = 1$), S-O. Bohman ($n = 4$), S. Enestrom ($n = 3$), or C. Svalander ($n = 8$), based on light microscopy and immune fluorescence ($n = 11$), light microscopy and electron microscopy ($n = 1$), or light microscopy alone ($n = 4$). The combination of clinical and histopathologic features did not suggest Alport's disease in any case. One of the patients underwent a retransplantation while 15 received there first graft in the time period studied. No patient had FSGS secondary to drug abuse or HIV. All patients were of Scandinavian origin. No child with FSGS from our area of recruitment received a kidney transplant at the Huddinge Hospital in this time period.

Transplantation procedures

Living donor transplantation is the preferred treatment in our program and was performed in 25 % of the total cohort and in 39 % of our population with FSGS. During the entire study period, maintenance immunosuppression after transplantation was based on cyclosporin A and prednisolone, most often in combination with azathioprine. Antithymocyte globulin (ATG) was used as induction therapy only in patients with panel reactive antibodies and in cases of delayed onset of graft function while cyclosporin was withheld. The standard antirejection treatment consisted of bolus doses of methylprednisolone for 4 consecutive days, in resistant cases followed by a second course, ATG, or OKT3. Allograft biopsies were performed on wide indications both in the short and long-term follow-up and were analyzed by the same pathologist (C. S.) with both light microscopy and immunofluorescence and, when needed, electron microscopy. The histopathological classification of glomerular diseases was performed according to the recommendations of the WHO collaborating center [3].

Follow-up

Our report is based on data available in the records in April 1996. No patient has been lost to follow-up, except those who died. The median follow-up period is 6.5 (3–10) years.

Patients with a family history of renal disease ($n = 8$) and several family members were thoroughly interviewed about their pedigrees on the telephone or during personal visits. Medical records of family members with kidney disease were obtained, including any biopsy protocols.

Statistical analysis

The χ^2-test and the Mann-Whitney test were used to compare groups of patients with respect to categorical and numeric values, respectively.

Results

Eight patients had at least one other family member with biopsy-proven FSGS and sometimes other members with a history of glomerulonephritis or unspecified uremia. The eight patients belonged to seven separate families originating from all parts of Sweden. Of the eight patients in the sporadic group, six had no family history of renal disease. One has no knowledge of his origin since he was adopted, and the father of one other died of undefined uremia at the age of 62.

The families

Family A

The index patient was born in 1948 and developed mild proteinuria at the age of 15. He was never nephrotic. Hypertension presented after 10 years. In 1982, a kidney biopsy showed FSGS. In 1985, the patient received a kidney transplant from his mother after a short period in dialysis. His brother has biopsy-proven FSGS. Their grandfather is known to have died of uremia in 1924 at the age of 36 years.

Family B

The index patient, born in 1945, had proteinuria since childhood. In 1984, serum creatinine was elevated and a kidney biopsy showed FSGS. At the age of 45 hemodialysis was started and 1 year later he underwent a cadaveric kidney transplantation. His mother, born in 1916, developed uremia at about the age of 70. A kidney biopsy obtained in 1983 showed FSGS.

Family C

The index patient, born in 1960, was noted to have proteinuria in 1978. With a maximum protein loss of 5 g/24 h and hypertension, kidney function slowly declined and he started hemodialysis in 1985. One year later he received a kidney from his older sister. He has two younger sisters, both with biopsy-proven FSGS, but not yet uremic. No one in the older generation is known to have had kidney disease.

Family D

Born in 1950, our patient developed proteinuria with a maximum of 3 g/24 h at the age of 20. At the age of 40 he started hemodialysis, and shortly afterwards a kidney transplantation was performed with his only sister as a

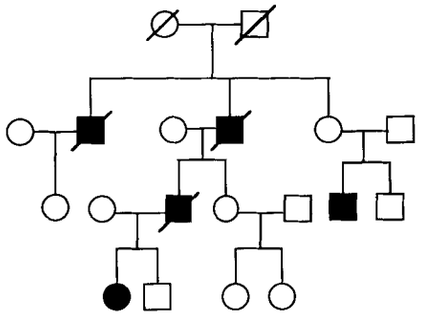

Fig. 1 Pedigree of family G in which four members in three generations have biopsy-verified focal segmental glomerulosclerosis. One died of terminal renal failure with unspecified chronic glomerulonephritis. *Black symbols* indicate patients with histologically proven chronic glomerulonephritis. / denotes death or renal death

donor. A maternal uncle had biopsy-proven FSGS, but no other person in this family has kidney disease.

Family E

In this family a man and his mother have biopsy-proven FSGS. The son was born in 1967. In 1971 microscopic hematuria was discovered, and in 1986 a kidney biopsy revealed FSGS in an advanced stage. Peritoneal dialysis was started in 1989 and 2 years later a cadaveric kidney transplantation was performed. The mother, born in 1943, is not yet uremic. She has not agreed to further investigation of her pedigree.

Family F

In this family there is also a mother and son with biopsy-proven FSGS. The mother was born in 1946. She has had known proteinuria since the age of 8, about 4 g/24 h. In 1987 a kidney biopsy showed FSGS. Two years later, a pre-emptive transplantation was performed, the kidney donated by her sister. The patient's son was born in 1967. He had proteinuria since childhood, maximum 2 g/24 h. FSGS was biopsy-verified in 1975. Peritoneal dialysis was started in 1990. He received a cadaveric transplant in 1991.

Family G

The patient was born in 1951. In 1974, proteinuria was discovered and slowly increased from 3 g/24 h to 9 g/24 h in 1980,when a kidney biopsy revealed FSGS. By the age of 35, the patient had developed uremia and a pre-emptive transplantation was performed, the kidney donated by his sister. The patient's father also had biopsy-verified FSGS and received a kidney transplant in 1971. This man's brother, born in 1925, had CGN and died of uremia at the age of 37. Our patient's cousin has recently undergone a renal biopsy due to proteinuria and is also diagnosed as having FSGS. Finally, the patient's daughter, now 15 years old, has proteinuria 2.2 g/24 h with normal kidney function, no edema, and no hypertension. A biopsy has revealed an early stage of FSGS. Figure 1 shows this family's pedigree.

Clinical course before transplantation

Table 1 shows demographic data for the patients with a family history and for the sporadic cases. The clinical picture of FSGS before transplantation differed. The onset of symptoms was earlier in the hereditary group whereas the age at time of renal failure was similar, i.e., progression was slower in patients with a family history. Proteinuria tended to be less. The clinical course before transplantation was, therefore, judged less serious than in patients with sporadic FSGS, as also indicated by the lower incidence of immunotherapy.

HLA antigens

No single HLA antigen was shared by all patients in either the hereditary or the sporadic group, but five of eight hereditary cases had B15 and six of eight sporadic cases had A1. DR 8 was present in only one patient from the sporadic group, and DR 4 was present in two hereditary and one sporadic case.

Outcome of transplantation

The outcome of the transplantations is presented in Table 2. Total patient survival was 13 out of 16; two heredi-

Table 1 Demographic data on patients with FSGS prior to transplantation

	Hereditary	Sporadic	*P* value
Males/females	7/1	5/3	
Age at onset of symptoms in years, median (range)	12.5 (4–23)	26 (7–59)	0.041
Maximal proteinuria (g/24 h), median (range)	4.5 (2–11)	7.0 (4–20)	NS
Immunotherapy	1	5	0.013
Age at end-stage renal failure, median (range)	36 (22–45)	39 (9–62)	NS

Table 2 Transplant conditions and outcome of transplantation in 16 patients with FSGS (*CD* cadaveric donor, *LD* living donor)

	Hereditary	Sporadic	*P* value
Number of patients	8	8	
Number of grafts in the study period	11	12	
CD/LD	6/5	8/4	
Patient death	2	1	
Graft loss, total number	7	6	
Cause			
Rejection	5	2	
Recurrence	0	2	
Technical	1	1	
Death	1	1	
Grafts with recurrence	0	5	0.01
With antirejection treatment 1st year	8	6	

tary and one sporadic case died. The index patient in family A died due to cardiac arrest 5 years after the loss of his second kidney transplant. In family E, the patient developed a highly malignant T-cell lymphoma 3 years after transplantation and died 2 months later. The patient from the sporadic group lost his first kidney transplant almost 2 years after transplantation due to recurrence of FSGS. One year after his second, uneventful transplantation, he died of colon carcinoma at the age of 47.

As also shown in Table 2, the total number of graft losses was equal in the two groups. Recurrence occurred with five kidneys transplanted into four patients, all sporadic cases. They had a known renal disease of between 2 and 4 years, and time in dialysis before transplantation ranged from 0 to 2 years. Two grafts were from living donors.

Recurrence was suspected clinically in all cases due to heavy proteinuria, 7.7–10 g/l. The signs of recurrence occurred within 2 weeks after transplantation in four grafts. In two of these, there was also delayed onset of kidney function and generalized edema, including ascites. In the fifth case, recurrence, the collapsing form, occurred after 6 years. This patient had lost two grafts in her childhood due to early recurrence and preferred many years of hemodialysis to a third transplantation, which was performed once cyclosporin became available.

In the early phase of recurrence, transplant biopsies could not confirm the diagnosis, but follow-up biopsies obtained 3–6 months later in all but one patient verified FSGS. The unconfirmed case was a patient who had lost his first graft due to biopsy-verified recurrence. The biopsy of his second transplant was obtained only 2.5 months after transplantation and no sclerotic glomerular lesions were found, but in glomeruli studied by electron microscopy there was fusion of epithelial foot processes.

Two grafts with recurrence were lost after 6 and 20 months, respectively. The other three grafts are still functioning 2.5, 5, and 10 years after transplantation.

No patient with a family history of FSGS had recurrence. One patient who lost his graft due to biopsy-verified chronic rejection had proteinuria 5 g/24 h. No other patient had more than 1 g/24 h. The rate of acute rejection was high in the hereditary group, with treatment given in 8 of 11 transplantations during the 1st year, and five of these grafts were lost. Four were from cadaveric donors. The corresponding numbers in the sporadic group were six treated and two grafts lost, both with cadaveric donors. The figures were not statistically different between the groups.

Discussion

The prevalence of FSGS in our kidney transplant population was 1.6 %, slightly less than the 2.4 % reported in the Irish experience [16]. No more than half the number of transplant patients with presumed CGN have actually had a renal biopsy obtained from native kidneys [13, 15, 16]. The proportion of FSGS in patients with biopsy-verified CGN was 8.6 %, which is similar to that in an Italian series [20]. In a French epidemiological study, 17.4 % of patients with biopsy-verified CGN had FSGS [18], and Neumayer et al. reported that 18.5 % of a transplant population with biopsy-verified CGN had FSGS [13]. However, in the same series, only 14.6 % had IgA nephropathy, perhaps indicating that immunofluorescence had not always been available to distinguish the two entities.

The absence of children with FSGS in our material is remarkable, but true. It may be related to improved treatment of the basic disorder by cyclosporin, other immune modulators, or other agents [9].

There are several reports in the literature suggesting that FSGS can be hereditary [4, 11, 12, 19, 21], the largest experience being the eight families described by Conlon et al. [4]. In our series of transplant patients with FSGS, the hereditary forms were as frequent as the sporadic cases. Furthermore, the family history was

not always known in the sporadic cases, some parents died early, and some patients had no siblings or offspring. Therefore, the actual proportion of hereditary cases may have been even higher. It seems likely that the mode of inheritance is autosomal dominant with a variable penetrance. Conlon et al. consider the trait to be autosomal dominant in two families but, as an alternative, suggest a recessive mode of transmission in the other six [4]. Men appear to be more susceptible than women. There were more men than women in our series, and in all three families where both mother and son were affected, the mothers had a more benign course. This may be a parallel to findings in autosomal dominant polycystic kidney disease, which progresses more slowly in women than in men [8, 15].

The HLA DR 8 antigen has been suggested to be linked with the hereditary form of FSGS [11, 19], whereas DR 4 has been implicated in idiopathic FSGS [7]. We could not confirm any such connection.

Until now, the histopathologic picture had remained indistinguishable between the hereditary and sporadic forms of FSGS [4]. Yet, we found clear clinical differences. Patients with a family history were younger at onset than the sporadic cases and had a slower progression rate. Their disease was judged to be more benign than in the sporadic cases, where a high proportion had received immune therapy before transplantation. Most importantly, so far no patient with a family history of FSGS has had recurrence of the disease after transplantation. Conlon et al. also reported that there was no recurrence after seven transplantations [4]. Therefore, if hereditary cases could be identified, they could be accepted in the transplant program as "normal risk" patients in this respect.

A crucial question is whether living donors should be accepted when there is a hereditary disease with an unknown mode of inheritance. A higher age limit than usual should be set for the donor, but if the predonation investigation is negative, the outlook for the donor is extremely good, and for the recipient living donation remains advantageous.

When hereditary cases are excluded, the recurrence rate in the remaining patients is even higher than previously reported. However, grafts with recurrence often function for several years and transplantation is not contraindicated [9]. The use of living donors has been thought to increase the risk of recurrence, but this view has been challenged lately [10]. In our opinion, living donors can be accepted, provided they have been informed about the specific risks of recurrence and still volunteer. In contrast, a second transplantation from a living donor following recurrence is questionable. Retransplantation with a cadaveric donor could be considered. A prudent protocol would then include pre-emptive plasma exchange [6], also to be reinstituted in the case of recurrence in combination with high levels of cyclosporin.

Further work is needed to elucidate the specific etiologic, morphologic, and clinical features of the various forms of FSGS.

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