Nephrol Dial Transplant (2002) 17: 1333–1335

Nephrology
Dialysis
Transplantation

Case Report

Familial juvenile hyperuricaemic nephropathy in a Caucasian family associated with inborn malformations

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Familial juvenile hyperuricaemic nephropathy (FJHN; OMIM 162000) is considered a rare cause of end-stage renal disease (ESRD). FJHN is characterized by hyperuricaemia and gout after adolescence and the slow development of renal insufficiency, leading to ESRD in adulthood. The disorder is characterized by a renal under-secretion of urate, which may be detected already during early childhood [1]. The histological lesions in affected subjects are characterized by unspecific tubulo-interstitial nephropathy. FJHN is inherited in an autosomal dominant pattern with a high penetrance. Recently, the gene(s) for FJHN was localized to a candidate interval at the short arm of chromosome 16 [2,3].

Case

We report a Caucasian four-generation family with FJHN without consanguinity between spouses and a clustering of various malformations (Figure 1). Tests of renal function, serum uric acid levels, and fractional uric acid excretion (FEua) were done in all 18 living consanguineous family members (Table 1) and seven spouses (data not shown). The serum and urine concentrations of uric acid or creatinine (Sua, Uua, Scr, Ucr, respectively) were determined by using an auto-analyser (Cobas Integra 700) while the patients were not on a purine-restricted diet. FEua was calculated in per cent as $(Uua \times Scr \times 100\%)/(Sua \times Ucr)$. The diagnosis of FJHN was based on a history of hyperuricaemia or gout and/or the finding of an FEua below 6.6% in men, below 7.0% in women, and below 8.2% in children [1].

The index case (III:6) was referred to our hospital with gout and a renal insufficiency (Scr 2.2 mg/dl, creatinine clearance 70 ml/min). His FEua was grossly reduced (2.9%). The family history revealed a clustering of ESRD. His grandmother (I:2) died of ESRD at the age of 40 years; his mother (II:5) and one of his aunts (II:9) suffered from gouty arthritis, both died with renal failure at the age of 44 and 29 years, respectively. Three alive aunts have gout and ESRD (II:2, II:8, II:11), one cousin (III:14) has gout and ESRD. Two cousins (III:1, III:4) have hyperuricaemia, a low FEua, and renal function is impaired in one of them (III:4). The siblings of the index case have no evidence of gout, low FEua, or renal insufficiency. As pregnancy is known to lower Sua, the studies on renal uric acid handling in one of his sisters (III:8) may have been influenced by the concurrent pregnancy (second trimester). Despite that shortcoming we believe from her past history, that she is not affected by FJHN. This patient died postpartum because of endocarditis in another hospital and no further studies are available.

Seven affected patients underwent renal ultrasound studies, renal cysts were revealed in the native kidneys of subject II:2 (diameter <1 cm; investigation 1999), subject II:11 (investigation 1989), subject III:4 (two cysts, diameter 1.5 and 2.4 cm, respectively; investigation 1999), and subject III:6 (two cysts, diameter <1 cm; investigation 2002), no renal cysts could be demonstrated in subjects II:8, III:1, and III:14.

In the described family various somatic malformations were observed. The index case (III:6) suffered from severe congenital pulmonary stenosis and underwent cardiac surgery at the age of 9 years. His mother (II:5), who suffered from gouty arthritis and ESRD, had grade III aortic valve stenosis, necessitating valve replacement. His sister (III:8), who was to the best of our knowledge not affected by FJHN, had congenital aortic valve stenosis and pulmonary stenosis and underwent balloon dilatation during early infancy. Cardiac ultrasound studies revealed no valvular disease in other subjects with FJHN (II:2, II:8, III:1, III:4, III:14) and in two healthy siblings (III:9, III:10) of the index case. During childhood a cousin (III:1) of the index case had idiopathic portal vein thrombosis with consecutive esophageal varices and repeated variceal bleedings. Cytogenetic studies in the index case were unremarkable, renal biopsy was rejected by him.

Patients III:1 and III:4 were treated with allopurinol 300 mg/day without improvement of FEua. FEua

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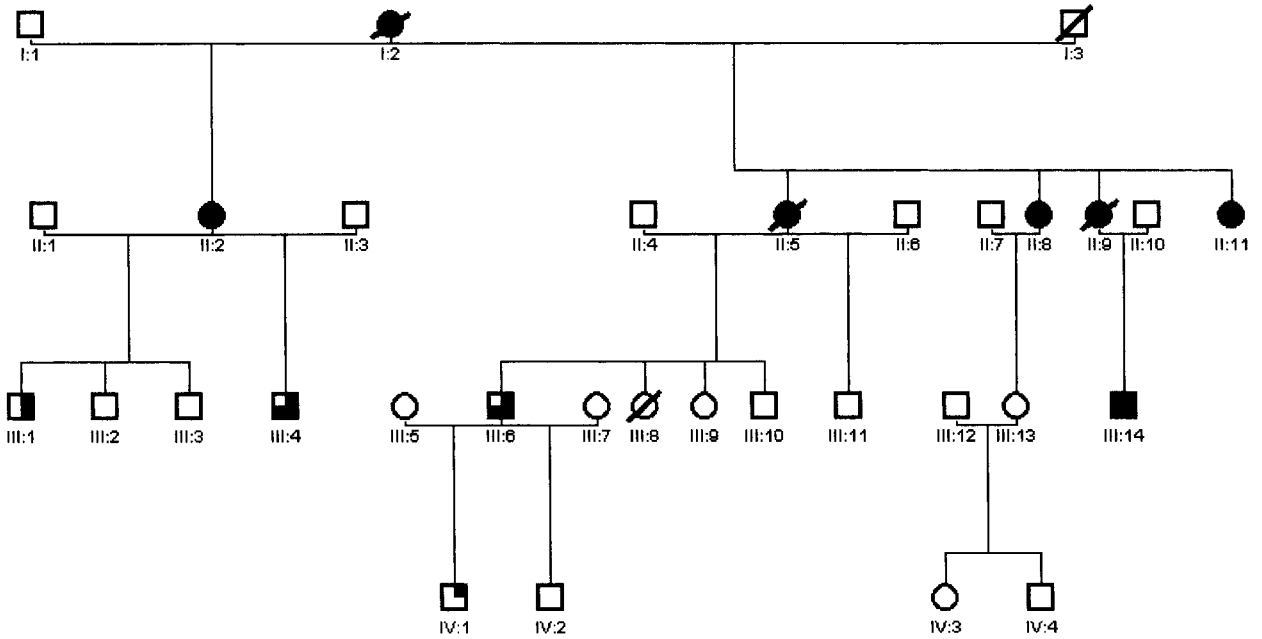

Fig. 1. Pedigree of a Caucasian family with FJHN. Squares indicate males, and circles indicate females. Unblackened symbols indicate unaffected individuals, and blackened symbols indicate affected individuals with ESRD. Blackened right upper quadrant denotes individuals with reduced FEua, blackened right lower quadrant denotes individuals with gout. Blackened left lower quadrant denotes individuals with renal insufficiency. Deceased individuals are shown by diagonal bars across the square or circle.

Table 1. Baseline characteristics of a Caucasian family with FJHN

Pedigree position	Year of birth	Date of investigation	Serum creatinine (mg/dl)	Serum uric acid (mg/dl)	FE uric acid (%)	Remarks
II:2	1944	August 1989	8.0	7.8		Gout; HD commenced 1989; RTx 1990; graft failed 1992
	1992	June 1999	9.1	6.6		On HD; small renal cysts
II:8	1952	June 1999	0.8	6.2	5.2	Gout; RTX 1986; cyclosporine; no renal cysts
II:11	1956	August 1989	3.5	9.7		Gout; HD commenced 1991; RTx 1996; renal cysts
		August 1999	1.7	7.8	4.8	With renal transplant; cyclosporine
III:1	1966	November 1996	1.3	7.8		Gout
		June 1999	1.1	6.6	3.0	Allopurinol 150 mg/day; no renal cysts
		July 2000	1.4	5.8	2.5	Allopurinol 150 mg/dl
		January 2001	1.1	2.6	7.6	Allopurinol 150 mg/day + benzbromarone 100 mg/day
III:2	1969	July 1999	0.8	3.1	9.6	
III:3	1972	February 2001	0.7	2.9	7.6	
III:4	1978	May 1997	1.8	9.8		Gout; two renal cysts
		June 1999	1.7	8.3	3.8	Allopurinol 300 mg/day
		July 1999	1.8	7.8	3.8	Allopurinol 300 mg/day
III:6	1974	May 1999	2.2	7.6	2.9	Gout; allopurinol 150 mg/day; no renal cysts
		July 1999	1.9	6.2	7.7	Allopurinol 150 mg/day + benzbromarone 100 mg/day
		January 2001	2.0	5.4	2.7	Allopurinol 150 mg/day
		January 2002	3.0	7.7	3.6	Allopurinol 150 mg/day; two renal cysts
III:8	1976	May 1999	0.7	2.5	16.4	Pregnant second trimester; died postpartum (endocarditis)
III:9	1968	June 1999	0.6	2.0	13.4	
III:10	1972	June 1999	1.1	4.9	7.6	
III:11	1970	June 1999	0.8	4.8	10.6	
III:13	1972	January 2001	0.8	3.3	9.0	
III:14	1966	November 1984	2.0	9.7		Gout; no renal cysts
		August 1999	9.1	5.5		Gout; HD commenced 1995
IV:1	1993	January 2001	0.7	4.2	6.6	Asymptomatic
IV:2	1995	January 2001	0.5	3.1	11.0	
IV:3	1994	September 2001	0.7	3.9	8.7	
IV:4	1996	September 2001	0.5	2.9	9.0	

Data on all consanguineous family members are shown: HD and RTx denote haemodialysis and renal transplantation, respectively.

increased from 2.5 to 7.6% in subject III:1 after benzbromarone was added (100 mg/day). The index case (III:6) was given allopurinol (150 mg/day) and benzbromarone (100 mg/day), his FEua rose initially from 2.9 to 7.7%. A careful history revealed that the consecutive decline of the FEua (Table 1) was probably due to poor compliance. With the combination therapy of allopurinol and benzbromarone uric acid normalized in all treated patients and none experienced further gout attacks.

Three patients were successfully kidney grafted at the age of 46 (II:2), 34 (II:8), and 40 years (II:11). Patient II:2 returned to haemodialysis (HD) 2 years post-transplant, the two other patients have functioning grafts 16 and 6 years post-transplant, respectively. The low FEua observed in the two subjects with functioning renal transplants (II:8, II:11) is most probably due to the cyclosporine therapy. One patient (III:14) is on HD since 29 years of age and awaits renal transplantation.

Discussion

We presented a large Caucasian family with FJHN. The diagnosis of FJHN was based on a history of hyperuricaemia or gout and/or the finding of a reduced FEua. Recently, a possible link between FJHN and autosomal dominant medullary cystic kidney disease type 2 (MCKD 2) has been postulated [4]. Ultrasound studies revealed renal cysts in four out of seven patients studied. Although it may well be that these cysts represent an unspecific sequel of renal insufficiency, MCKD 2 cannot be excluded on clinical and biochemical grounds. It has been suggested that the combination of an uricosuric agent with allopurinol might be effective in FJHN and increase FEua [5,6]. This notion is supported by the observations made by us. The combination therapy with allopurinol and benzbromarone increased the FEua to a near normal range and therefore may possibly help to avoid ESRD in FJHN. It appeared in line with previous reports that patients with FJHN can be successfully treated with renal transplantation.

Hitherto unreported is a clustering of cardiac malformations in a FJHN family. In the general population congenital heart disease, with the commonest form being ventricular septal defect, occurs in approximately 1% of liveborn children [7]. It cannot be excluded that the observed association between cardiac malformations occurred by chance, as one subject with congenital aortic valve stenosis and pulmonary stenosis (III:8) did not have FJHN. Nevertheless, the occurrence of congenital heart disease in two patients (II:5, III:6) with FJHN may aid the search for the FJHN gene locus. Congenital valve defects have been located to many other chromosomes beside the sex chromosomes (e.g. chromosomes 1, 4, 5, 7, 8, 10, 20, and 22) but to the best of our knowledge not to chromosome 16, which carries a candidate region for FJHN. To further elucidate that issue we suggest that in patients with congenital valvular heart disease and a family history of hyperuricaemia and/or ESRD determination of FEua may be worthwhile.

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