

Case Report

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Outcome of kidney transplantation in familial juvenile hyperuricaemic nephropathy

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Introduction

Familial juvenile hyperuricaemic nephropathy (FJHN) and medullary cystic kidney disease (MCKD) are rare autosomal-dominant disorders, both characterized by early hyperuricaemia due to reduced urinary excretion of urate and the development of chronic interstitial nephropathy, most often leading to end-stage renal failure (ESRF) in adulthood. Although a history of gout is more frequently reported in FJHN and cortico-medullary renal cysts more frequently found in MCKD, both phenotypes overlap [1]. Two loci for MCKD (*MCKD1* and *MCKD2*) were localized to chromosome 1q21 and 16p12, respectively [2,3]. A locus for FJHN was mapped to chromosome 16p11.2, in a region overlapping with the MCKD2 locus, raising the hypothesis that FJHN and MCKD2 were two facets of the same disease [4]. This was demonstrated by the identification of mutations in the *UMOD* gene encoding uromodulin (or Tamm-Horsfall protein) in three families with FJHN and one with MCKD2 [5]. Several groups soon confirmed the role of the *UMOD* gene as the cause of FJHN, with a cluster of mutations in exons 4 and 5 (reviewed in [1]).

The cause of the onset and progression of chronic interstitial nephritis in *UMOD*-related disorders remains a moot point. Uromodulin is a kidney-specific protein produced in the thick ascending limb (TAL) of the loop of Henle and excreted in the urine [1]. Mutant uromodulin has been shown to accumulate in the endoplasmic reticulum of TAL cells, with only wild-type uromodulin found in the urine of affected

patients [6,7]. Intratubular accumulated uromodulin is thought to induce cell death and interstitial fibrosis, through unidentified mechanisms. If this is true, the transplantation of a normal kidney producing only wild-type uromodulin should cure the disease, without fear of recurrence.

The earliest manifestation of the disease is a decreased fractional urinary excretion of urate (FE_{ur}), expressed as a function of age and sex. The most likely explanation for this abnormality is an increased reabsorption of urate in the proximal tubule along with sodium, the latter thought to be a compensation for the decreased sodium uptake in the TAL related to the uromodulin defect [1]. This abnormality should be reversed after kidney transplantation.

There is so far no data in the literature on the results of kidney transplantation in this condition. This prompts us to report on the outcome of kidney transplantation in six patients with FJHN due to a documented mutation in the *UMOD* gene, with emphasis on the post-transplant renal handling of uric acid.

Cases

Six patients belonging to three Belgian families with a mutation in the *UMOD* gene were transplanted in our centre between 1991 and 2003. Their pedigrees and clinical characteristics are summarized in Figure 1 and Table 1, respectively. The mutations are: 658>A with substitution of arginine by serine in Family 1; 281>A with substitution of aspartate by alanine in Family 2, and 754>G, with substitution of cysteine by glycine in Family 3. All are missense mutations in the exon 4.

Individuals IV.4, IV.7, IV.14 and IV.16 belong to Family 1, a large family from Southern Belgium previously reported [4]. Individual IV.4 was found to have renal failure at age 32 (Scr 4.4 mg/dl, CrCl 24 ml/min), at the time he suffered a first gout attack. Urinary excretion of urate was not determined. Haemodialysis (HD) treatment was required at

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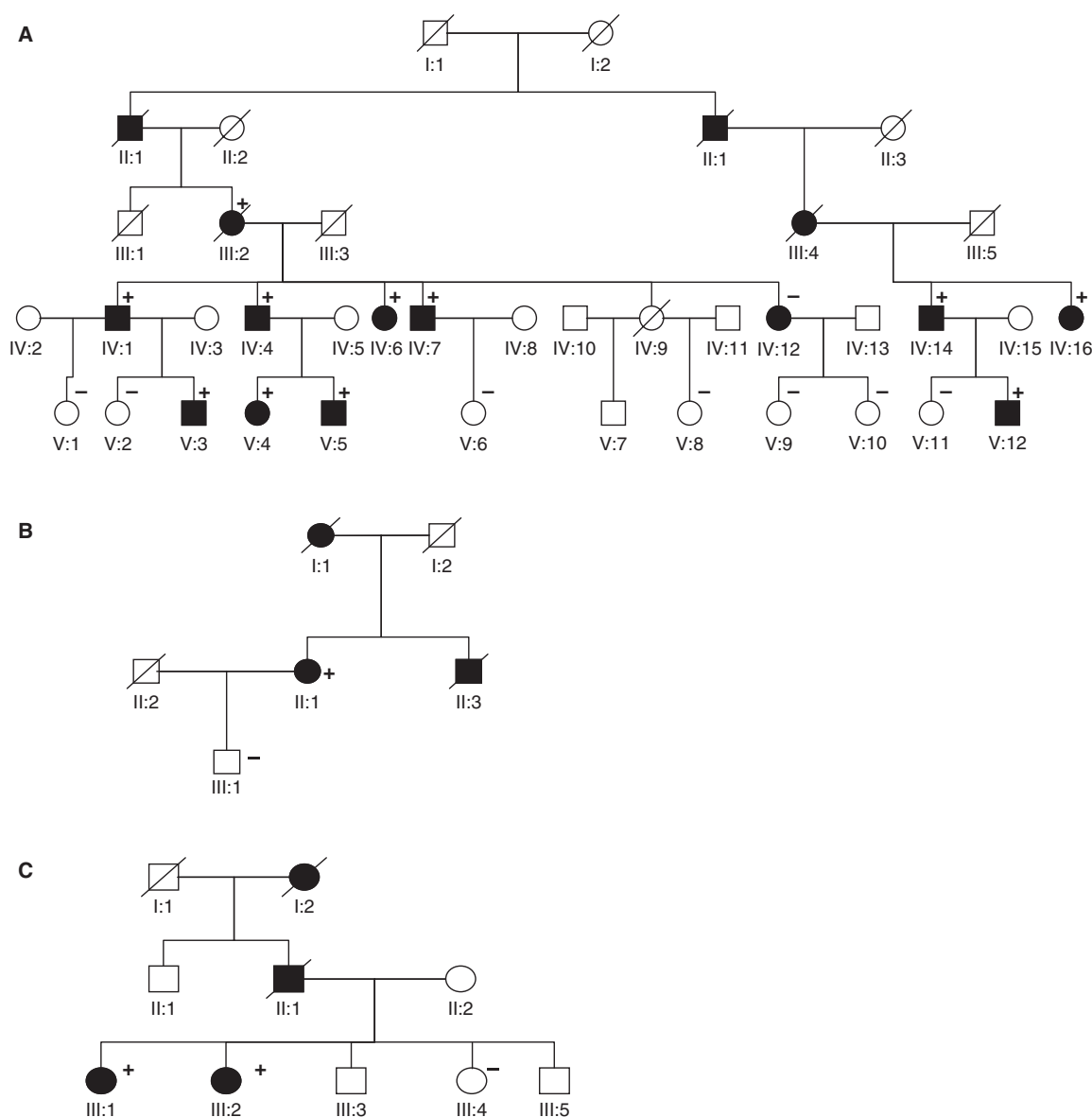


Fig. 1. Pedigrees of families 1 (A), 2 (B) and 3 (C). Ref.: Circles: females; squares: males; black symbols: clinically affected individuals; +: identified mutation in the UMOD gene; -: lack of mutation in the UMOD gene.

age 36. One year later he received a cadaver kidney transplant. Immunosuppressive regimen included ciclosporin A (CSA), mycophenolate mofetil (MMF) and prednisolone. At discharge Scr was 2.3 mg/dl. Currently, 6 years after transplantation (Tx), renal function remains stable. Hyperuricaemia was constantly found after Tx and required allopurinol treatment. The only available measurement of FEur is 5.6% six years after transplantation. There is a long history of alcohol abuse.

His brother (subject IV.7) was aged 8 when he suffered a first gout attack. Renal failure (Scr 1.5 mg/dl, CrCl 63 ml/min) was documented 12 years later. FEur was 4.6%. HD was started at age 28. A cadaver kidney transplantation was performed 13 months later, under an immunosuppressive treatment including CSA, azathioprine (AZA)

and prednisolone. Scr never decreased below 2 mg/dl. A *de novo* membranous nephropathy was documented 3 years after Tx. Currently, 12 years after Tx, Scr is 5.8 mg/dl and the patient is on the waiting-list for a second kidney transplantation. Hyperuricaemia was constant after Tx. FEur was measured at 14% and 11% 3 and 6 years after Tx, respectively.

Individual IV.14 was aged 24 when he suffered his first gout attack. Four years later he was found to have renal failure (CrCl 43 ml/min). FEur was 4.3%. ESRF was reached at age 42. Four months later he received a cadaver kidney transplant. Immunosuppressive regimen included tacrolimus (TAC) and prednisolone. Renal function immediately normalized after Tx. Diuretic therapy was started because of hypertension. Sur varied between 5 and 7.7 mg/dl. FEur was 7.5, 7.3, 9.4 and 8.3% at 1, 2, 4

Table 1. Clinical characteristics of the six patients before and after renal transplantation

Subject (sex)	History				Follow-up after Tx			
	Gout/age at onset	FEur/Ccr (%/ml/min)	Age at ESRF	Age at Tx	Months	Scr (mg/dl)	Sur (mg/dl)	FEur (%)
F1.IV.4	+/32	ND	36	37	18	2.3	7.5	ND
(M)					60	2.6	7.4	ND
					72	2.2	6.4	5.6
F1.IV.7	+/8	4.6/63	28	29	24	3.2	6.9	ND
(M)					36	3.4	8.2	14.5
					72	4.4	8.8	11
					96	4.9	9.1	ND
					132	5.8	7.3	ND
F1.IV.14	+/24	4.3/43	42	42	12	1.6	7.7	7.5
(M)					24	1.5	6.3	7.3
					48	1.6	7	9.4
					60	1.3	5	8.3
F1.IV.16	+/18	ND	41	41	6	0.7	4.6	11.4
(F)					18	0.7	5.4	ND
					24	0.7	4.6	ND
					60	0.6	4.9	7.2
					96	0.6	5	9.1
F2.II.1	-	ND	59	60	12	1.1	6.5	16
(F)					24	1.1	7	10.8
					60	1.2	7	10.7
					120	1.7	7.2	9.4
F3.III.2	+/22	5/50	37	37	3	0.8	3.8	12
(F)					12	0.9	6.5	7.3
					18	1	7.1	7.5
					24	0.9	6.8	7.5
					30	1.1	6.4	ND

Ref: M: male; F: female; ND: not determined; +: yes; -: no; age is expressed in years; bold type indicates hyperuricaemia and reduced FEur for age, sex and renal function according to Calabrese *et al.* [12].

and 5 years after Tx. Currently, 6 years after Tx, renal function remains excellent.

His sister (individual IV.16) developed her first gout attack at age 18. Renal failure (CrCl 63 ml/min) was found at age 31. HD was started 10 years later. FEur was not measured before Tx. A cadaver kidney transplantation was performed at age 41 under a CSA-based immunosuppressive regimen. Renal function normalized immediately. After Tx Scr levels were constantly normal; FEur was normal 6 months after Tx and slightly decreased thereafter. Currently, 8 years after Tx, renal function remains excellent.

Individual II.1 of Family 2 is a woman who was found to have renal failure (Scr 2.5 mg/dl, CrCl 33 ml/min) at age 54. It is of note that Sur never exceeded 7.4 mg/dl and that the patient had no gout. HD treatment was started at age 59. One year later she was transplanted with a cadaveric graft kidney under an immunosuppressive regimen including CSA, MMF and prednisolone. Currently, 10 years after Tx, Scr is 1.7 mg/dl. Chronic rejection was documented. After Tx, Sur was constantly found slightly elevated, while FEur were always normal.

Individual III.2 of Family 3 is a woman who was found to have CRF (Scr 1.5 mg/dl, CrCl 65 ml/min) at age 22, when she suffered a first gout attack. Two years later, FEur was measured at 5%. A history of hypertension was known since an episode of

preeclampsia at age 20, requiring a triple antihypertensive treatment. HD treatment was started at age 37. Five months later, the patient received a kidney from her husband. Currently, 30 months after Tx, graft function remains excellent under an immunosuppressive regimen including TAC, MMF and prednisolone. She has never taken diuretics. The patient suffered four gout attacks after Tx and hyperuricaemia was repeatedly documented. It is to note that she gained 30 kg since Tx, with a current BMI of 34 kg/m². FEur normalized 3 months after Tx and decreased thereafter. Allopurinol therapy was not given because of a known intolerance.

Discussion

We report on the post-renal transplant outcome of six patients with FJHN, belonging to three families with a missense mutation in the *UMOD* gene. To the best of our knowledge this is the first report on the outcome after Tx in this disorder. Our six patients currently have a functioning kidney graft 2–12 years after Tx. Two of them have a significant graft dysfunction due to chronic rejection or *de novo* membranous nephropathy. Overall, this outcome does not differ from that currently observed in patients transplanted for another nephropathy.

The post-Tx outcome of 10 patients with a FJHN phenotype was briefly mentioned in a paper devoted to allopurinol treatment: only 3/10 patients kept a functioning graft after a follow-up time ranging from 1 to 14 years [8]. The underlying genetic defect accounting for FJHN was however unknown, except in one of them, in whom a mutation in the *HNF-1 β* gene was subsequently identified [9]. Stavrou *et al.* reported on the results of Tx in 19 patients from 6 Cypriot families with MCKD1 disease, an autosomal-dominant disorder with a phenotype resembling MCKD2-FJHN but mapped on chromosome 1q21. Patient and graft survival rates reached 100% and 95% at 5 years, respectively, and were not different from those of 22 patients transplanted for another nephropathy in the same centre [10].

Since the nephropathy related to a *UMOD* mutation is thought to result from intrarenal storage of mutated uromodulin, and since uromodulin is only expressed in the kidney [11], transplantation of a normal kidney is expected to cure the disease. Since the earliest clinical manifestation is a decreased FEur and subsequent hyperuricaemia, we were interested to observe the course of urinary and serum urate levels in our transplanted patients.

Bearing in mind that in normal adults FEur is $8.2\% \pm 1.2\%$ in males and $12.2\% \pm 1.9\%$ in females [12], it appears that lower figures were generally found in our transplanted patients. Nonetheless, in the three patients in whom a pre-Tx FEur was available, the first value measured after Tx was clearly improved from 4.3% to 5% before to 7.3 to 14.5% after Tx (Table 1), witnessing the expected trend to normalization. Why normalization of FEur was not constant and not sustained in most patients is easily explained by several post-Tx factors lowering FEur, the two most common of which are the use of diuretics and that of anticalcineurins [13]. Loop diuretics and thiazides are well-known causes of reduced FEur and subsequent hyperuricaemia, through extracellular volume depletion and compensatory rise of proximal tubular reabsorption of urate [12,13]. CSA also decreases the renal clearance of urate, with resulting hyperuricaemia, through a mechanism not completely understood [13]. This is also true for TAC [14,15].

The values of FEur observed in our FJHN are in agreement with those reported in cohorts of patients transplanted for another nephropathy and treated by anticalcineurins (summarized in [13]). Likewise, the occurrence of hyperuricaemia post-Tx (defined as >7 mg/dl in men and >6 mg/dl in women) and gout in four and one out of our 6 patients, respectively, concur with the 30% to 80% and 10% to 30% prevalence rates, respectively, reported in a large series of transplanted patients given anticalcineurins [13]. Additional contributing factors observed in our patients are alcohol abuse in patient F1.IV.4 and overweight in patient F3.III.2.

In conclusion, kidney transplantation is recommended in patients with an *UMOD*-related nephropathy leading to ESRF. Overall graft outcome does not differ from that currently recorded in other patients. The prevalence rate of reduced FEur and hyperuricaemia is similar to that commonly observed under anticalcineurin-based immunosuppressive regimens in patients transplanted for another nephropathy.

Conflict of interest statement. None declared

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