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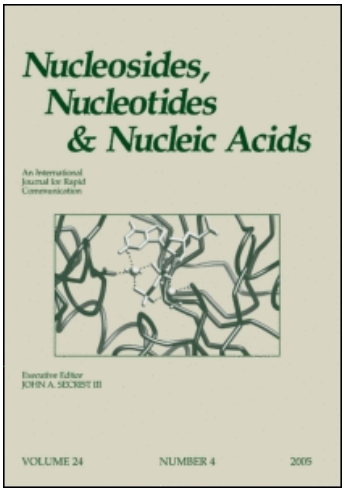

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Familial Juvenile Hyperuricaemic Nephropathy is not Such a Rare Genetic Metabolic Purine Disease in Britain

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FAMILIAL JUVENILE HYPERURICAEMIC NEPHROPATHY IS NOT SUCH A RARE GENETIC METABOLIC PURINE DISEASE IN BRITAIN

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□ *Renal disease is rare today in classic adult gout, and gout is rare in renal disease—especially in the young. Here we summarise studies in 158 patients from 31 kindreds diagnosed with familial juvenile hyperuricaemic nephropathy FJHN from a total of 230 kindred members studied in Great Britain. Some patients have been followed for up to 30 years, and allopurinol has ameliorated the progression of the renal disease in all 113 surviving members provided:*

1. *They have been diagnosed and treated* sufficiently early.
2. Compliance *with allopurinol treatment and diet has been as important as early recognition.*
3. *Hypertension has been rigorously controlled.*
4. *The use of oral contraceptives has been avoided, as has pregnancy in any female with a Glomelar Filtration Rate GFR < 70 ml/min.*

The question arising is: Why is FJHN the most prevalent genetic purine disorder diagnosed in Britain? Is it a lack of awareness *which needs to be improved Europe-wide?*

Keywords Adolescent gout; Familial renal disease

INTRODUCTION

FJHN is a dominantly inherited disorder affecting females and males equally, characterized by hyperuricaemia, gout, and/or potentially fatal

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renal disease if unrecognized and untreated.[1] In Britain, FJHN originally was considered "familial renal disease, cause unknown," due to rapid progression to death in the third or fourth decades in earlier generations.[1] Unusually, children, and young women as well as men are affected equally. The problem lies in a universally low fractional clearance of uric acid (FE_{ur} = fractional clearance of uric acid relative to creatinine clearance x100) for age and sex and is present from birth. The net result is usually an elevated plasma uric acid, which precedes the onset of severe renal disease.[1] By contrast, in healthy subjects the FE_{ur} is high in children of either sex, but falls at puberty more in males than in females (Table 1).

Renal cysts are not a feature of British FJHN kindreds, though they have been noted in some other kindreds with autosomal dominant medullary cystic kidney disease (MCKD), also associated with gout in men and women.[1]

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FAMILY STUDIES

The recognition of FJHN in Britain in the early 1970s stemmed from the unusual development of gout in two young women from separate kindreds, whose relatives were being treated for "familial renal disease, cause unknown." Not only were the propositi female, there was a history of progressive renal disease, leading to death in the 30s, in earlier generations affecting men and women in both families.[1] Additional family members have been recognized, studied and treated since then, and 29 other kindreds diagnosed. The diagnostic criteria has been a reduced FE_{ur} for age/sex (Table 1). The methods used have been given in detail in previous publications.[1] Mutation analysis[2] has been performed in 25 of 31 GB kindreds from which DNA was available.

RESULTS

One hundred fifty-eight affected individuals were found by metabolic screening among the 230 subjects from the 31 kindreds tested over a 30-year

TABLE 1 Fractional urate clearance (FE_{ur}) in controls and FJHN

	CONTROL FE_{ur}	FJHN FE_{ur}
CHILD	13.2 ± 3.5%	5.9 ± 1.6%
ADULT (f)	12.8 ± 2.9%	5.1 ± 1.5%
ADULT (m)	8.1 ± 3.2%	5.1 ± 1.6%

period, The pattern of presentation followed that reported in the first 3 kindreds, summarized below:

a) The propositus in K1, a female, presented with gout at 29. Severe renal disease, considered gouty nephropathy, was found. She progressed rapidly to dialysis, failed transplantation and died at 36.[1] Her 2 children, both affected, but diagnosed/treated early with allopurinol have shown only a slow fall in GFR to around 50 ml/min over 15 years. This family is one of 6 among the 25 studied so far found to have a defect in the uromodulin gene on chromosome 16. The 3 grandchildren are disease free (Figure 1).
b) The propositus of K2, also female, developed gout in a big toe at 9.[1] She was found to have severe renal disease, progressed to dialysis, and died aged 39, after 3 failed transplants. Family screening revealed FJHN in a twin sister and cousins, one of the latter progressing rapidly to dialysis following a failed pregnancy. The mother and an aunt in the previous generation had also progressed to dialysis early and died in their 40s.
c) The father in the third kindred had died aged 43 of chronic renal failure. A son, aged 40, had an elevated plasma creatinine (291 μmol/l) and developed an attack of gout; a brother had been on dialysis from the age of 42. Other family members were also affected.[1]

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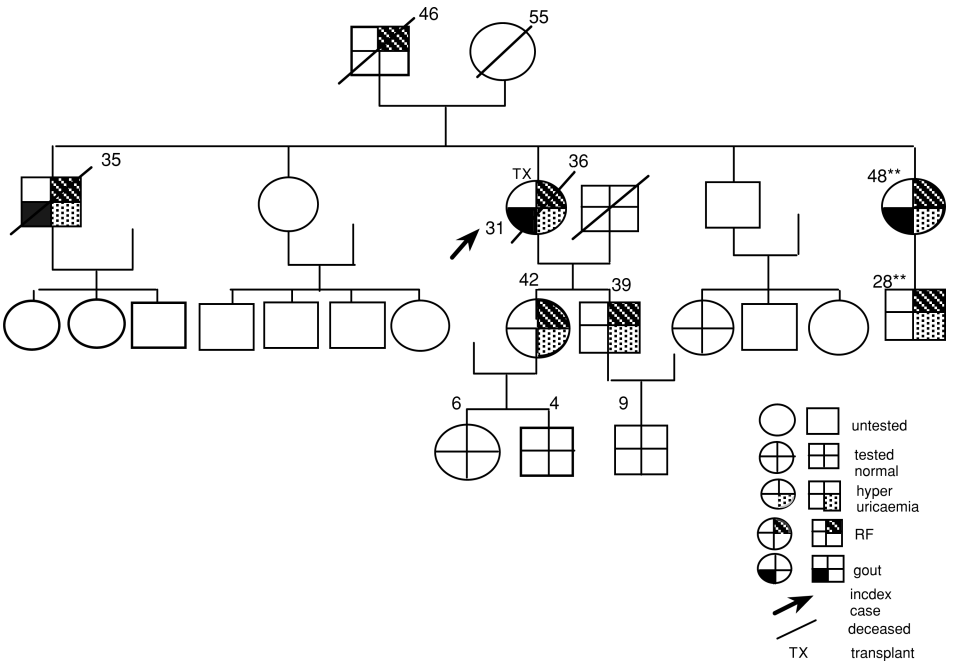

FIGURE 1 Kindred GB 1.

Here we review results in a total of 230 subjects from 31 families, including the above. The diagnostic feature characteristic of FJHN (a reduced FE_{ur} which does not show any age and sex differences) was present in 28 further families. Females (72) and males (86) were affected equally, a total of 158 members being affected. Mean age at death of the propositi in 11 of the families (found when renal failure was severe) was 36 years.

All surviving members in the 31 kindreds found with the characteristic hallmark of FJHN have been treated with allopurinol at a dose appropriate to their renal disease.[1] In 113 members recognized sufficiently early (before plasma creatinine had risen above 200 μmol/l) allopurinol has ameliorated progression of the renal disease in all good compliers.[1] In one, inadequate control of hypertension led to a fall in renal function; in another, stable for 15 years, pregnancy precipitated rapid progression to haemodialysis.

To date, linkage to the locus on Chromosome 16 has been confirmed in only 6 of our 25 kindreds studied for the uromodulin gene mutation.[3] A mutated gene has been found also on chromosome 17 (the gene coding for hepatocyte nuclear factor 1 beta) in a single kindred,[1] and there is linkage to an unknown gene on chromosome 1 in another.[4]

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DISCUSSION

Gout is rare in women and prior to the recognition of FJHN, had been reported only in middle-aged women on diuretic therapy (i.e., diuretic induced gout.)[1] Likewise renal failure today is rare in "classic" gout (i.e., gout affecting middle-aged men). By contrast gout in FJHN is a *direct consequence* of the hyperuricaemia resulting from the reduced $FE_{ur,}$men women and children being affected equally.

The present study underlines the importance both of early diagnosis in FJHN and treatment with allopurinol. All members of the 31 families found to be affected by metabolic testing, and with a creatinine of <200 μmol/l at diagnosis, have been given allopurinol, which has ameliorated the progression of the renal disease.[1] Some few patients have been poor compliers and renal function has fallen as a result, underlining the importance of compliance.

Other factors precipitating a rapid drop in renal function in young FJHN women have been hypertension, or its inadequate control, and pregnancy. The experience in our 31 kindreds confirms that blood pressure requires rigorous control and it is always recommended that pregnancy should be avoided in any young woman with a GFR of <70 ml per minute—a precipitous fall to dialysis and/or transplantation being inevitable.

Twenty-five of our kindreds have been screened for mutations in the uromodulin gene on chromosome 16, and mutations found in only 6

families.[1] In contrast the uromodulin mutation has been found in all four Spanish famlilies tested[3] and screening in six Japanese families has found this defect in the gene on chromosome 16 in 5 of them.[2] One of our families has a mutation in the hepatocyte nuclear factor 1 beta on Chr 17 found in few other kindreds[1] another shows linkage to an unknown gene on chromosome 1,[4] different from the other chromosome 1 defects reported. Thus, since most of our families have none of these defects, there must be yet more genes involved.

In summary, FJHN is unusual, since renal disease is rare in gout, as is gout in renal disease. It is clear from the 31 kindreds here that early recognition and treatment with allopurinol has ameliorated the progression of the renal disease in all 113 surviving members; but compliance with treatment and diet must be rigorous. Likewise, hypertension must be strictly controlled the use of oral contraceptives and pregnancy avoided, where the GFR is <70 ml/minute. Finally, awareness of FJHN must be improved to reduce morbidity, mortality as well as health service costs throughout Europe.

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