Familial juvenile hyperuricaemic nephropathy

Sir,

In their letter to the Editor, Drs Bleyer and Hart\(^1\) raised several aspects concerning familial juvenile hyperuricaemic nephropathy (FJHN). First, they state that in QJM letter of February 2003,\(^2\) we wrote that ‘...an unresolved aspect of FJHN is the gene defect’, despite their having reported a mutation in the uromodulin gene (UMOD, the gene encoding the Tamm-Horsfall/uromodulin protein) in three kindreds as a cause of FJHN in December 2002.\(^3\) Our letter to QJM\(^2\) was sent on 12 November 2002. At that time, we could not be aware that a month later, Hart et al.\(^3\) would publish such a relevant contribution to the knowledge of the gene defect in FJHN, but we still apologize for our oversight in not mentioning them.

Second, Drs Bleyer and Hart’s experience agrees with the observation that allopurinol does not halt or diminish renal deterioration, in contrast to that of Fairbanks et al.\(^4\) Our experience with 12 patients belonging to three families also indicates that allopurinol does not exert a nephroprotective effect in FJHN.\(^5\)

Third, the authors state that ‘...it would be most useful to know if uromodulin mutations are responsible for FJHN in the families reported by Puig’.\(^6\) We are grateful for the opportunity to communicate that we have diagnosed five Spanish families as ‘having familial nephropathy associated with hyperuricemia’.\(^6\) This term was chosen because we questioned the pathogenic relevance of increased serum urate levels in FJHN.\(^7\) Of these five families,\(^6\) one refused genetic testing, one did not have a UMOD mutation, and three contributed to the confirmation by Turner et al.\(^8\) of the UMOD mutation as the cause of FJHN.

Whether the UMOD mutation is a unique characteristic and pathogenic feature of FJHN is uncertain. Recently, Dahan et al.\(^9\) reported a cluster of UMOD mutations in 11 FJHN families (10 missense and one in-frame deletion). By examining urine samples and renal biopsies, these authors concluded that UMOD mutations led to aberrant expression and accumulation of the protein within the intracellular epithelia of the thick ascending limb of the loop of Henle. This could affect urate transport through a decrease in sodium chloride reabsorption, and the latter would induce a state of volume contraction, thereby enhancing proximal urate reabsorption and causing hyperuricaemia. UMOD mutations have also been described in families with the autosomal-dominant form of medullary cystic kidney disease (MCKD2).\(^3,10\) and in families with the disease complex MCKD/FJHN.\(^11\) However, several other families that apparently have the clinical characteristics of FJHN have not shown UMOD mutations, lending support to the possibility of genetic heterogeneity in FJHN. In fact, a hepatocyte nuclear factor-1\(\beta\) gene mutation has been described as associated with diabetes and FJHN.\(^12\) Thus, we believe that an adequate and precise phenotype–genotype classification of patients showing hyperuricaemia, decreased urinary uric acid excretion, young-onset gout, kidney cystic disease and renal impairment is necessary to increase our knowledge on these familial nephropathies, before we can establish a precise diagnosis for individual patients.

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References


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