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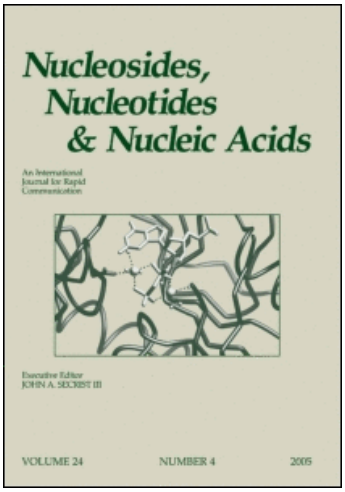

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Familial Nephropathy Associated with Hyperuricemia in Spain: Our Experience with 3 Families Harbouring a UMOD Mutation

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FAMILIAL NEPHROPATHY ASSOCIATED WITH HYPERURICEMIA IN SPAIN: OUR EXPERIENCE WITH THREE FAMILIES HARBOURING A UMOD MUTATION

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□ *Since 1993 we have studied 5 Spanish families with familial nephropathy associated with hyperuricemia (FJHN). Among these families, 24 patients have been identified. All patients had some combination of hyperuricemia, gout, renal insufficiency, arterial hypertension, and reduced kidney size. The clinical presentation in the different families and in the members of the same family was heterogeneous. Allopurinol treatment did not appear to influence renal disease. From a clinical perspective, this syndrome is a distinctive interstitial nephropathy, inherited as an autosomal dominant trait, that progresses to renal failure and is not halted nor prevented by allopurinol therapy. In 2003, genetic linkage analysis in 3 of the 5 families showed linkage of FJHN to 16p 11.2. One family was not analyzed and one family did not show linkage to this region confirming the genetic heterogeneity of this syndrome. A mutation in UMOD gene was found in these 3 families as the cause of the FJHN. The mutations cluster in exon 4 and exon 5 and were point mutation that results in an amino acid change in the uromodulin or Tamm Horsfall protein. This fact allowed in 2004, the presymptomatic genetic diagnosis of an 8-years-old boy belonging to one of these 3 Spanish families. We conclude that in families with a history of renal failure and/or gout in which FJHN is suspected, UMOD mutation screening may enable a definite diagnosis. When a mutation is found, family members can be tested for a UMOD mutation and pre-symptomatic diagnosis may allow counseling to prevent or halt the progression to renal insufficiency.*

Keywords Uromodulin; Renal insufficiency; Uric acid

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INTRODUCTION

Autosomal dominant medullary cystic kidney disease (MCKD) type 1 (Mendelian Inheritance in Man [MIM] 174000) and type 2 (MIM 603860), autosomal dominant glomerulocystic kidney disease (GCKD), and familial juvenile hyperuricemic nephropathy (FJHN, MIM 162000) are a group of hereditary renal diseases that share several clinical features: (a) an autosomal dominant pattern of transmission; (b) hyperuricemia and/or gout; and (c) progressive renal damage that may cause end stage renal disease (ESRD). The genes responsible for these conditions have been identified in recent years. Moreover, the abnormal genes in MCKD2, FJHN and GCKD have been linked to similar genetic loci,[1–6] leading to the hypothesis that these diseases actually may represent allelic mutations of the same disease. In fact, the term MCKD/FJHN/GCKD has been proposed to designate this pathological complex. Thus, to precisely characterize whether this complex is or is not the same disease it appears that genetic diagnosis is essential to definitively identify individuals suffering from one or another condition. In this study, we review three issues concerning FJHN: (a) our experience based on three families genetically diagnosed as having FJHN; (b) the pathophysiology of uromodulin; and (c) debatable questions such as the most appropriate designation of FJHN and whether allopurinol prevents renal deterioration.

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FJHN Experience at La Paz University Hospital

Since 1986, 5 Spanish families have been diagnosed as having FJHN. Members affected in these families were identified on the basis of a combination of the following characteristics: (a) hyperuricemia or gout usually preceding renal failure; (b) chronic renal failure; (c) ultrasound showing small or normal size kidneys with or without medullary cysts; and (d) an autosomal dominant inheritance pattern. One of these 5 families (Family H) did not want further studies and a second family (Family L) did not show genetic linkage to chromosome 16p. This renders 3 families with 12 living affected members as the basis of our experience with FJHN. A brief report of Family M illustrates the typical clinical picture and evolution of FJHN. The propositus (Subject II-1), a 34-year-old man, came to our attention in October 1986 because he suffered tophaceous gout since age 20. Arterial hypertension and renal insufficiency were diagnosed on the basis of increased blood pressure (184/116 mmHg) and a serum creatinine concentration of 2.4 mg/dL (creatinine clearance of 48.5 mL/min/1.73 m^2), respectively. His two younger brothers were also affected, as was his mother aged 53-years. She knew that “she had a renal problem” since age 24 (for the last 30-years).

TABLE 1 Mutations Characterized in 3 Spanish Families[10]

Family	Exon	Mutation	Amino Acid Change	Confirmed by
A	4	488 G > A	N128S	ASO hybridation analysis
M	4	869 G > A	C255Y	ASO hybridation analysis
T	5	1003 T >G	C300G	Restriction Endonuclease

Affected subjects showed diminished size of the kidneys and increased renal vascular resistance. Renal pathology showed sclerotic glomeruli, interstitial fibrosis, and tubular atrophy. What happened to these 4 patients over the last 20 years? The mother had stable renal function until she turned 70 years. She is now on dialysis. Her 2 elder sons needed renal transplants despite allopurinol therapy for the last 10 years. The third sibling had mild renal insufficiency (serum creatinine less than 2.0 mg/dL) for the last 20 years, that progressed very slowly and has not been on allopurinol. This family, together with a second family, totalling 14 patients was reported in 1993 and we postulated that hyperuricemia was not of pathogenic relevance, but rather was a consequence of the genetic disease affecting the kidneys.[7] Ten years later, our collaboration with European research groups led to linkage analysis of the FJHN critical region on chromosome 16p11.2.[8,9] These studies led to the identification of a precise UMOD mutation in the affected members of families M, T, and A (Table 1). To our knowledge, the exon 5 mutation described in our Family T is the first ever reported.[10]

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The Pathophysiology of Uromodulin

Uromodulin, also known as Tamm-Horsfall protein, is a specific kidney protein produced by the tubular cells of the thick ascending limb (TAL) of the loop of Henle. Based on its gelling structure and localization it has been hypothesized that uromodulin major function is to maintain water impermeability at the TAL and to facilitate chloride absorption.[12] Uromodulin mutations affect folding of the protein rather than its synthesis. This would affect the transport of uromodulin to the plasma membrane along the secretory pathway. Accordingly, unfolded proteins are retained in the endoplasmic reticulum and ultimately degraded in the cytosol. This is reflected by an immunostaining pattern significantly different from normal kidneys. Normal kidneys show a distinct apical membrane reactivity whereas in kidneys harbouring uromodulin mutations the staining pattern is intense, diffusely intracellular and heterogeneous within tubular cells.[13] The accumulation of uromodulin in the tubular cells due to misfolding may cause a diminished impermeability of the TAL to water and chloride absorption

leading to a markedly diminished urinary concentrating ability and volume depletion. Volume contraction enhances proximal tubular reabsorption, leading to increased serum urate concentration and diminished urinary uric acid excretion.

Debatable Issues

The fact that the genetic disturbances in three different diseases (MCKD2, FJHN, and GCKD) have been linked to uromodulin mutation, has markedly modified our concept of this disease-complex. In addition, differences of opinion have emerged concerning the response of these disorders to allopurinol therapy. Our studies add information on these issues.

Which is the most appropriate designation of FJHN? Bleyer et al.[13] studied an extensive family with 39 members showing an exon 5 uromodulin gene mutation. From their study it may be concluded that some patients are: (a) not juvenile; (b) normouricemic; and (c) renal insufficiency was not present in all affected members. Thus, the latter 3 words of its actual designation FJHN—juvenile, hyperuricemic and nephropathy—could not be strictly applied to the all the patients of this extensive family. In accord with other authors,[12,14] we propose that the disorder presenting with hyperuricemia and/or gout and renal insufficiency, with additional affected family members, and with a uromodulin gene mutation be designated uromodulin storage disease.

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Does allopurinol prevents renal deterioration? This question has generated much debate.[7,15–20] We have approached this question by following 12 patients, genetically diagnosed as having a uromodulin mutation. Six patients with gout received allopurinol. Six patients without symptoms did not receive hypouricemic treatment. All 12 patients were followed up for 1–6 years. Mean baseline serum urate was similar in both groups (7.5 and 7.2 mg/dL), but only decreased in patients treated with allopurinol (mean, 4.6 mg/dL). Mean baseline serum creatinine was 2.0 and 1.4 mg/dL in both groups. Over time serum creatinine increased similarly in both groups: In allopurinol-treated patients from 2.0 to 4.5 mg/dL and in non-allopurinol treated subjects from 1.4 to 2.1 mg/dL. This experience is in accord with that of Bleyer et al.[14] These authors stated that "declining [in] renal function occurred over time even in patients with normal serum uric acid levels and in those who were taking allopurinol. Despite treatment with allopurinol, four male patients had declines in estimated creatinine clearance of greater than 3 mL/min/year on determinations made 5 years apart."[14] In summary: We have diagnosed 3 families with uromodulin mutations, being one of them having the first reported exon 5 mutation. Uromodulin storage at the TAL explains the clinical findings of the disease, and thus we propose the name of uromodulin storage disease,

for which allopurinol therapy does not seem to be useful to prevent renal insufficiency.

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