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Clinical characterization of a family with a mutation in the uromodulin (Tamm-Horsfall glycoprotein) gene

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Clinical characterization of a family with a mutation in the uromodulin (Tamm-Horsfall glycoprotein) gene.

Background. We have recently identified a mutation in the uromodulin gene in a large family affected with hyperuricemia, gout, and renal failure. The purpose of this investigation is to provide a comprehensive characterization of the clinical findings of this syndrome in family members who had a mutation in the uromodulin gene.

Methods. An extended family suffering from hyperuricemia and gout was identified by a local practitioner. After consent was obtained, patients provided a directed clinical history and blood and urine specimens for chemical and genetic testing. All family members were tested for the presence of uromodulin gene mutations by direct DNA sequence analysis. The clinical and biochemical characteristics of family members carrying the affected mutation were then investigated.

Results. Thirty-nine family members were found to have an exon 5 uromodulin gene mutation (g.1966 1922 del), and 29 unaffected family members were identified. The cardinal clinical features in individuals with the uromodulin mutation included hyperuricemia, decreased fractional excretion of uric acid, and chronic interstitial renal disease leading to end-stage renal disease (ESRD) in the fifth through seventh decade. Women did not always develop hyperuricemia or gout, but still developed progressive chronic renal failure.

Conclusion. Mutation of the uromodulin gene resulted in hyperuricemia, reduced fractional excretion of uric acid, and renal failure. Genetic testing will be required to definitively identify individuals suffering from this condition. We are interested in studying other families that may suffer from this condition and would appreciate any such referrals.

Key words: uromodulin-associated kidney disease, juvenile hyperuricemic nephropathy, uric acid, genetic, medullary cystic kidney, uromodulin, Tamm-Horsfall glycoprotein.

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Uromodulin, also known as Tamm-Horsfall (TH) glycoprotein [1], is the most abundant urinary protein in healthy individuals. Uromodulin has been postulated to be responsible for maintaining the integrity of the loop of Henle [2], preventing urinary tract infection [3], and binding cytokines such as interleukin-1 (IL-1) [4] and tumor necrosis factor (TNF) [5]. However, despite being the most common urinary protein in healthy individuals, the exact function of uromodulin is unclear. In addition, there have been no previous reports of pathologic changes in this protein resulting in human disease. We have recently reported mutations occurring in the uromodulin gene in four families [6]. These families developed gout, hyperuricemia, and renal failure. This investigation provides an extensive characterization of the clinical changes resulting from the uromodulin mutation in the largest kindred, containing 39 affected family members.

The constellation of findings seen in these families is consistent with two heritable illnesses transmitted as autosomal-dominant traits: familial juvenile hyperuricemic nephropathy (FJHN) and medullary cystic kidney disease type 2 (MCKD 2). FJHN, also known as familial juvenile gouty nephropathy [Mendelian Inheritance in Man (MIM) 162000] [7], is an uncommon disorder characterized by reduced fractional excretion of uric acid and development of chronic renal failure. MCKD 2 (MIM 603860) [8] is another uncommon genetic renal disease characterized by defects in urinary concentration, hyperuricemia, and the development of ESRD. The genes responsible for these two conditions have been linked to similar genetic loci [9–12], and it has been postulated that these diseases actually represent allelic mutations of the same gene [13].

Previously, it was impossible to determine the penetrance or full clinical characteristics of these syndromes

due to small family sizes and lack of a certain diagnostic test. The family involved in this report represents one of the largest families ever reported suffering from FJHN, MCKD 2, or related disorders. Ascertainment of the mutation now allows for the first time a comprehensive genotype-phenotype correlation permitting a more complete clinical characterization of the range of clinical findings associated with this syndrome and provides increased information about the function of uromodulin.

METHODS

Clinical studies

A large family in western North Carolina was identified by a local family practitioner (A.W.) and referred for evaluation to Wake Forest University Medical Center. The proband underwent diagnostic laboratory studies (see below), and family screenings were then held in July 1996, October 1999, and March 2001. In addition, individual visits were made to the homes of family members. For each individual, a detailed clinical history, serum uric acid, and serum creatinine were obtained. For many participants, 24-hour urine collections were performed to determine the fractional excretion of uric acid (mean fractional excretion of uric acid in healthy adult United Kingdom males is 8.1 ± 3.2% and 12.8 ± 2.9% for females) [14]. Serum uric acid levels were also determined and hyperuricemia was based on the appropriate normal values for the patient's age and gender [15, 16]. The creatinine measurements were performed by the Jaffe, alkaline picrate, kinetic method [17]. The uric acid measurements were performed on the ADVIA 1650 Chemistry System. The uric acid determination method is based on the Fossati enzymatic reaction using uricase with a Trinder-like end point [18]. Descriptive characteristics were calculated for each patient. Estimates of creatinine clearance, as determined by the Cockroft-Gault formula [19], were made using the patient's weight or ideal body weight, whichever was less. Urine osmolality was determined by freezing point depression after an overnight fast.

Statistical analysis included multiple linear regression with estimates of creatinine clearance as the dependent variable, and age and gender as independent variables. Other models were also created using age, gender, use of allopurinol, and serum uric acid levels as dependent variables. The Wilcoxon rank-sum test was used to compare urine osmolality values.

Genetic studies

Peripheral venous blood samples were obtained by standard venipuncture and genomic DNA isolated using the QIAmp blood kit (Qiagen, Valencia, CA, USA). To determine if patients carried a mutation of the uromodulin gene, all coding regions of exons 1-12, including intron-exon junctions, were sequenced. Using oligonucleotide primers, polymerase chain reaction (PCR) amplification of the uromodulin gene was performed [6]. Amplified DNA was purified with the QIAquick PCR Purification Kit (Quiagen) and was sequenced using the BigDye Terminator Cycle Sequencing Kit on an ABI 3700 DNA Analyzer (Applied Biosystems, Foster City, CA, USA) by the Genomics and Proteomics Core Laboratories of the University of Pittsburgh. Sequence analysis was performed with Sequencher 4.1 software (GeneCodes, Ann Arbor, MI, USA).

RESULTS

Over a 5-year period, genetic samples were obtained on 10 controls (spouses of affected family members), and 68 other family members.

Uromodulin sequence analysis

Direct genomic sequence analysis of the uromodulin gene identified a 27 base pair deletion in exon 5 in 39 family members. This deletion mutation (g.1966_1922 del) results in the in-frame deletion of amino acids 177-185 (p. H177_R185 del). Thirty-nine individuals were found to have one mutated uromodulin allele and one wild-type allele, consistent with autosomal-dominant transmission. Twenty-nine individuals were found to have two normal uromodulin genes. Segregation of the uromodulin gene mutation through this family was consistent with autosomal-dominant transmission of the affected phenotype.

Index case

The proband was identified in early 1995. He suffered from enuresis until his early teenage years. He first suffered from gout at the age of 17 years. The patient was noncompliant with allopurinol, and over time, numerous large tophi developed. At age 39 years, the serum creatinine was 2.8 mg/dL. A kidney biopsy specimen revealed tubular atrophy and interstitial fibrosis. A computed axial tomography scan of the abdomen revealed a 3.7 cm simple cyst in the lower pole of the left kidney but no evidence of medullary cysts. At age 44 years, the patient was placed on peritoneal dialysis. The proband's daughter was screened at age 20 years. At that time, the serum uric acid was 7.8 mg/dL, the fractional excretion of uric acid 3.1%, and the creatinine clearance on a 24-hour collection was 81 mL/min. Three years later, the serum uric acid was 9.4 mg/dL with a fractional excretion of uric acid of 4.1%, and the estimated creatinine clearance was 85 mL/min. A computed axial tomography scan of the abdomen revealed no medullary cysts in the kidney.

Disorders in uric acid metabolism

Hyperuricemia secondary to a reduced fractional excretion of uric acid was a cardinal manifestation of this

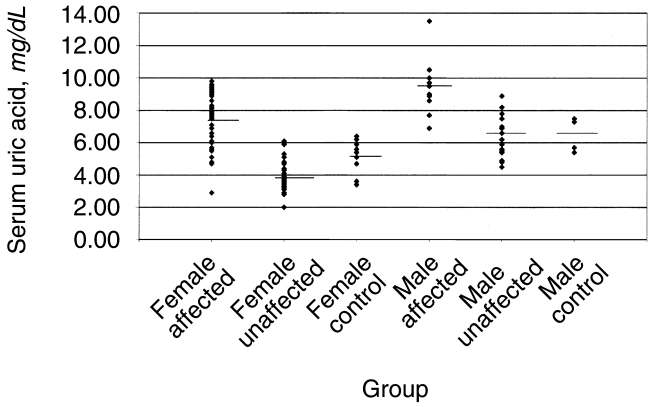

Fig. 1. Serum uric acid values according to group.

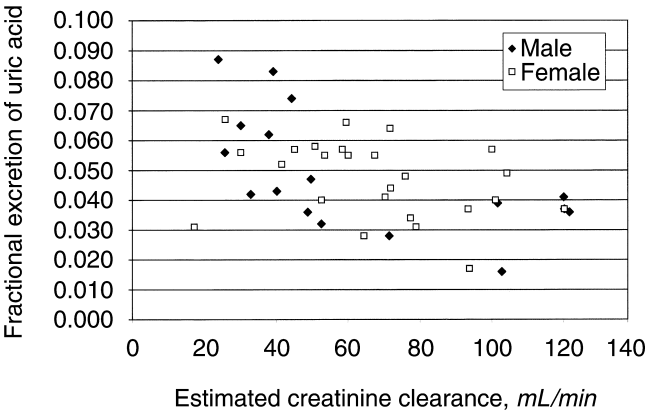

Fig. 2. Fractional excretion of uric acid according to renal function in affected individuals.

Table 1. Patients with the uromodulin mutation who were not hyperuricemic

Patient number	Age *years*	Estimated creatinine clearance *mL/min*	Serum uric acid *mg/dL*	Upper normal serum uric acid *mg/dL*	Fractional excretion of uric acid %
1	17.2	91	4.8	6.26	5.1
2	36.8	92	2.9	6.26	—
2	40.3	54	4.7	6.26	5.5
3	44.9	104	5.5	6.26	4.9
3	49.6	56	5.7	6.26	—
4	24.3	71	7.1	6.26	6.4
4	28.6	76	5.1	6.26	4.8
4	28.9	58	5.6	6.26	—
5	62.7	24	6.0	6.26	—

disorder. Figure 1 shows the distribution of serum uric acid levels in men and women older than age 16 years who were not on allopurinol. There were 109 determinations in 66 patients older than 16 years of age. The mean serum uric acid level for affected women was 7.49 ± 1.71 mg/dL, compared to 4.24 ± 1.09 mg/dL in control and unaffected women ($P < 0.001$). The mean serum uric acid level for affected men was 9.43 ± 1.78 mg/dL vs. 6.44 ± 1.23 mg/dL in unaffected and control men ($P < 0.001$). The youngest patient studied at age 6 years had an elevated serum uric acid level of 8.3 mg/dL (normal for this age group <6.1 mg/dL) [15] and a reduced fractional excretion of uric acid of 5.7% (normal >15%) [20]. However, hyperuricemia was not a constant finding in this condition, especially in women. There were five women with a serum uric acid measurement less than or equal to 6 mg/dL. Table 1 shows the characteristics of these patients at different ages. These five patients usually had depressed fractional excretions of uric acid despite normal serum uric acid values. On repeat testing, the serum uric acid value appeared to stay relatively consistent, except for one patient who had one high serum uric acid measurement followed by two normal values. The estimated creatinine clearance declined in four of five of these patients with follow-up measurements. The overlap of serum uric acid values between unaffected and affected female individuals was the result of normal serum uric acid values in the five affected women. In contrast, the serum uric acid values were all elevated in male patients, with the lowest value of 6.9 mg/dL. However, there was significant overlap between unaffected individuals and affected individuals due to higher serum uric acid values in some of the unaffected individuals.

Fractional excretion of uric acid

Fractional excretion varied greatly among both affected and unaffected family members. In unaffected women, the fractional excretion of uric acid ranged from 3.1% to 10%. The fractional excretion of uric acid in affected females ranged from 1.7% to 6.7%. For affected males the fractional excretion ranged from 1.6% to 8.7% and for unaffected males from 2.5% to 7.3%. The variation in fractional excretion of uric acid in affected individuals was very much related to renal function and age. Figure 2 shows the fractional excretion of uric acid according to estimated creatinine clearance in 25 collections in women and 16 collections in men. For affected women older than 18 years of age with estimated creatinine clearance greater than 80 mL/min, the fractional excretion ranged from 1.7% to 4.9%. For affected men older than 18 years of age with estimated creatinine clearance greater than 80 mL/min from 1.6% to 4.1%. Reduced fractional excretion of uric acid was a consistent finding in all affected patients with normal renal function. (In general, individuals with a creatinine clearance less than 80 mL/min will start developing an elevated fractional excretion of uric acid [21].) Several unaffected and control patients also had fractional excretions less than 5%, a condition not uncommon in the general population [22].

Eight of 28 women had a history of gout, with onset at

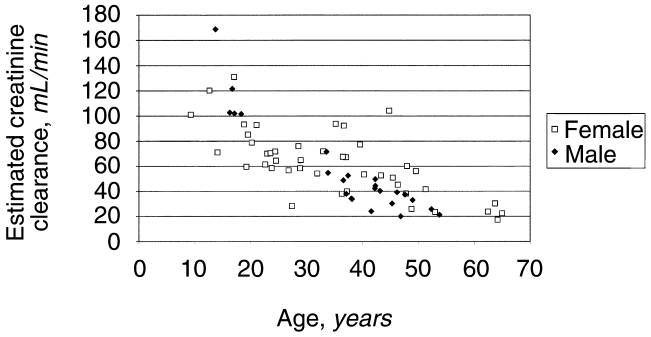

Fig. 3. Estimated creatinine clearance according to age in affected individuals.

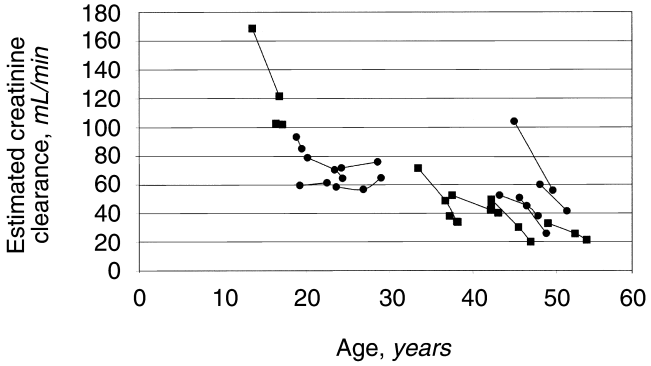

Fig. 4. Estimated creatinine clearance according to age in affected individuals who have multiple measurements of serum creatinine. Symbols are: (●) females and (■) males.

ages 17, 20, 32, 38, 46, 48, 58, and 62 years. Only women with gout were receiving allopurinol. Nine of 11 affected men suffered from gout; one of the unaffected men was less than 18 years at the time of the study, and the other was 33 years old. Gout started between 18 and 25 years in all men except one affected man at age 33 years.

Estimated creatinine clearance

Renal insufficiency was the most consistent finding in the study. The estimated creatinine clearance values for affected patients according to age are presented in Figure 3. Mild renal insufficiency tended to develop before age 20 years. In men, the decline in renal function appeared somewhat faster. Several patients have proceeded to dialysis, including one male at age 44 years. Three women lived to age 60 years without starting dialysis; two of these began dialysis in their late sixties. One female patient had a serum creatinine of 0.7 mg/dL and a normal estimated creatinine clearance of 100 at age 44.9 years. However, at age 49.6 years, the estimated creatinine clearance had decreased to 56.0 mL/min and the serum creatinine increased to 1.3 mg/dL. Of note, this patient had normal serum uric acid levels on both occasions. Figure 4 shows estimated creatinine clearance values for patients in whom multiple measurements were available. In several patients, a rapid decline in renal function is noted that reflects a small change in serum creatinine resulting in a large change in creatinine clearance calculated by the Cockroft-Gault formula.

Declining 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.

Table 2. Urine osmolality obtained after an overnight fast in affected participants

Participant number	Urine osmolality *mOsm/L*	Age *years*	Estimated creatinine clearance *mL/min*[a]
1	531	38	94
2	574	18	103
3	736	15	120
4	560	26	83
5	523	42	54
6	655	35	61
7	574	29	64

[a] Estimated creatinine clearance was determined 18 months prior to urine osmolality determination

Enuresis

Ten of 39 affected patients suffered from enuresis versus three of 32 unaffected and controls ($P = 0.12$ with chi-squared test for statistical significance). Enuresis occurred until the teenage years in several affected individuals.

Urinary concentration

Table 2 provides the results of maximal urinary concentration after an overnight fast in seven affected individuals. These collections were performed approximately 18 months after the estimated creatinine clearance determinations. The mean urine osmolality value was 593 ± 76 mOsm/kg in affected individuals versus 918 ± 239 mOsm/kg in nine unaffected family members ($P = 0.01$). If only the three affected individuals with an estimated creatinine clearance >90 mL/min were included, the mean urine osmolality was 614 ± 108 mOsm/kg versus 918 ± 239 mOsm/kg in the nine unaffected members ($P = 0.067$).

Hypertension

Ten of 13 patients with estimated creatinine clearance less than 50 mL/min suffered from hypertension, seven of 16 with estimated creatinine clearance between 50 and 80 mL/min, and zero of eight with estimated creatinine clearance values greater than 80 mL/min.

Urinary tract infection

Urinary tract infections did not occur in affected men. In 14 affected women, seven had not suffered from urinary tract infections. One had suffered from more than 10 urinary tract infections and had been referred to a urologist for a negative evaluation, and all other affected women had suffered from less than five infections. There were only two instances of hospitalization for urinary tract infection in the 14 women.

Pathology

Kidney biopsy specimens were obtained on two men and one woman. These specimens revealed tubular atrophy and interstitial fibrosis with globally sclerotic glomeruli. No medullary cysts were identified, but the samples were composed predominantly of cortical tissue.

Computed axial tomography scans were obtained on two patients and did not reveal medullary cysts. Magnetic resonance imaging was obtained on one patient at age 45 years and revealed medullary cysts. Several other patients underwent ultrasonographic examination. These examinations characteristically do not reveal medullary cysts, and they did not reveal cysts in these patients.

DISCUSSION

Uromodulin is the most common protein excreted in the urine in healthy individuals. This is the first clinical characterization of a family suffering from a mutation in the uromodulin gene. This mutation results in the deletion of 9 amino acids in the uromodulin protein. This region of the uromodulin protein is highly conserved and this region is postulated to be very important in determining protein structure [23]. Small in-frame deletions are known to be responsible for a number of genetic diseases and are believed to be a major disease mechanism in genetic diseases [24]. Once synthesized, uromodulin monomers aggregate and undergo glycosylation to form a large glycoprotein. It is likely that this deletion in affected family members results in abnormal aggregation, affecting the structure and function of uromodulin.

Hoyer, Sisson and Vernier [25] previously localized uromodulin by ultrastructural immunoperoxidase localization. Uromodulin was restricted to the thick ascending limb and the early distal convoluted tubule and was distributed between adjacent intercellular membranes, in the infolding of intracellular membranes, and on the luminal membranes. These authors postulated that uromodulin formed a gel that helped to restrict water movement along the thick ascending limb. In the current investigation, family members were found to have an increased rate of enuresis and a decreased urinary concentrating ability, although these differences were not statistically different from controls. One would expect defects in urinary concentration if a function of uromodulin was the preservation of the counter-current mechanism.

Hyperuricemia occurred in 92% of the adult carriers of the uromodulin mutation. Other studies have not been able to identify the penetrance of hyperuricemia in these conditions due to the lack of a definite diagnostic test. Identification of the mutation allows a more accurate determination of the prevalence and significance of hyperuricemia. Further investigations will be required to determine how a uromodulin mutation results in decreased urinary uric acid excretion. Difficulties in studying this will include that renal insufficiency causes defects in urinary concentration and hyperuricemia, and renal insufficiency develops early in the course of this disease.

While hyperuricemia was present in most family members, it was not universally present. Hyperuricemia occurred more frequently and was more severe in male individuals, with almost all affected males suffering from gout in their twenties. Serum uric acid levels were higher in men than in women. A number of female patients had normal serum uric acid levels, and many did not suffer from gout. While hyperuricemia was frequent, the degree of hyperuricemia was not severe. As hyperuricemia is not uncommon in the general population, diagnosis of this condition based on elevated serum uric acid levels was not possible due to the overlap seen.

Renal insufficiency was more common than hyperuricemia, occurring in all but one patient after the age of 20 years. Renal insufficiency occurred in patients with normal serum uric acid levels as well as patients who had been taking allopurinol for long periods of time. This finding suggests that the renal insufficiency was not linked to the hyperuricemia. Previous pathologic studies of MCKD (of which this disease may be an example) have shown deposits of uromodulin in the renal interstitium [26, 27]. It is possible that abnormal aggregation of uromodulin results in interstitial deposition. A mouse model that did not produce uromodulin has recently been found to have normal kidney structure and function (abstract; Bates JM et al, *J Am Soc Nephrol* 13:55A, 2002), suggesting that abnormal aggregation of this protein may be integral in the development of renal failure. Uromodulin also binds to various interleukins such as TNF, and inability to bind to these molecules may lead to interstitial fibrosis. Kidney biopsies in family members were nonspecific. Most kidney biopsies were composed of renal cortex, and renal disease in these patients takes place in the medulla of the kidney, with only secondary changes in the cortex. Several women did not develop ESRD into their sixties.

It has been postulated that uromodulin may be important in the prevention of urinary tract infection because of its ability to bind to type I fimbriated *Escherichia coli* [3]. However, the incidence and severity of urinary tract

infections did not appear increased in affected women or men.

Patients in this family have characteristics of FJHN and MCKD 2, two conditions which have recently been postulated to be the same disease [13]. These conditions both map to a small area of chromosome 16, in the region where the uromodulin mutation was identified. Patients with FJHN suffer from hyperuricemia and a reduced fractional excretion of uric acid, as well as progressive renal insufficiency. Patients with MCKD 2 also develop progressive renal insufficiency. Hyperuricemia is a frequent finding, and medullary cysts are actually an inconstant finding in this condition. While we have identified mutations in uromodulin in four families, including several previously reported as suffering from MCKD 2 or FJHN, all cases of MCKD 2 may not be caused by a uromodulin mutation [28]. Given the difficulties in the terminology of MCKD 2 and FJHN, and given that these illnesses may be the phenotypic expression of different mutations, we believe that uromodulin associated kidney disease may be a preferable term for families in whom a uromodulin mutation is identified.

How does the nephrologist diagnose families with this condition? The most important finding in these families is a strong family history of renal failure with autosomal-dominant inheritance. The renal disease is interstitial in nature with the absence of proteinuria and a bland urinary sediment. This finding rules out conditions such as Alport's or other familial forms of glomerulonephritis. In addition, families also have a history of hyperuricemia and gout, although at first glance it may seem that the gout is a result of renal failure. The development of precocious gout or gout in women is suggestive of this disorder.

Once a family has been identified as suffering from this disorder, genetic testing is currently required to determine if individual family members are affected. Hyperuricemia was not uncommon in unaffected men, and normal serum uric acid levels were found in five women with this condition. Thus, we believe it is not possible at present to obtain a certain diagnosis of this disease prior to the development of renal failure without genetic testing.

The current study identifies a mutation in a common urinary protein resulting in renal disease in a large family. Further studies will both help to characterize the function of uromodulin as well as the nature of this disease. We are interested in studying other families that may suffer from this condition and would appreciate any such referrals.

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