Familial Juvenile Hyperuricemic Nephropathy and Uromodulin Gene Mutation

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Familial Juvenile hyperuricemic nephropathy (FJHN) is a rare autosomal dominant disorder, characterized by early onset of hyperuricemia, gout and progressive kidney disease. Hyperuricemia prior to renal impairment and decreased fractional excretion of uric acid are hallmarks of FJHN. Renal dysfunction gradually appears early in life and results in end-stage renal disease usually between the ages of 20 and 70 years. FJHN is mostly caused by mutations in the uromodulin gene located at 16p12. The course of FJHN is highly variable. Treatment includes management for hyperuricemia, gout and progressive kidney disease. Individuals with gout have been usually treated with allopurinol. But controversy exists as to whether uric acid lowering therapy prevents the progression of chronic kidney disease.

Key words: Hyperuricemia, Uromodulin, Tamm-Horsfall protein, Mutation

Introduction

Familial juvenile hyperuricemic nephropathy (FJHN) is a rare genetic disease transmitted as autosomal dominant trait. It is characterized by under-excretion type hyperuricemia, gout and the development of chronic kidney disease. Renal impairment typically appears as early as the teenagers, leading to end-stage renal disease (ESRD) between the ages of 20 and 70 years. Duncan and Dixon first described FJHN in 1960 and Hart et al. reported that mutation in the uromodulin (UMOD) gene is responsible for FJHN.

The UMOD gene is located on chromosome at 16p12 and in close proximity to the gene for medullary cystic kidney disease type 2 (MCKD2, OMIM 603860). FJHN and MCKD2 are two facets of the same disorder secondary to mutations in the UMOD gene, encoding UMOD protein. Clinical findings show striking similarities between FJHN and MCKD2, which are characterized by hyperuricemia and slowly progressive chronic kidney disease. Therefore, the conditions caused by mutations in the gene encoding UMOD are preferentially called as uromodulin-associated kidney disease.

Although FJHN is mostly caused by mutations of UMOD gene (FJHN1, OMIM 162000), it is genetically heterogeneous. Mutations in UMOD gene occur in only 40% of probands. Recently, mutations of different genes have been reported in a few families with FJHN: renin (REN) and hepatocyte nuclear factor-1 beta (HNFIB) on chromosomes 1q32.1 and 17q12, respectively. Mutations in REN gene were found to be responsible for a similar presentation; family history of gout and childhood anemia (FJHN2, OMIM 613092). Mutations in HNFIB genes together account for 2.5% of FJHN. Mutations in other, as yet unidentified genes, may also account for some cases.

Recent discovery of UMOD genetic variants as a cause of FJHN led a new concept. We previously reported a Korean family with...
FJHN and five male members of them had gout and chronic kidney disease, which were diagnosed at teenage. In this review, we aimed to report our experience in diagnosis and treatment of FJHN.

**Genetics**

Mutations of *UMOD* gene have been known as the main causes of FJHN. Until now, more than 50 mutations in *UMOD* have been identified on chromosome 16p12 (Fig. 1). Many of these mutations are identified in exon 4 or 5 and rare families have mutations in exon 6 or 8. Over half of the defects identified in *UMOD* gene are missense mutations resulting in the deletion or addition of a cysteine residue. The abnormal UMOD proteins cannot assemble properly and are unable to exit the endoplasmic reticulum. The UMOD accumulation within the tubular cells of the thick ascending limb in the kidney can lead to tubular atrophy and death.

**Pathophysiology**

The UMOD protein, also known Tamm-Horsfall protein, is an 80-90 kDa glycoprotein and the most abundant urinary protein. It consists of 640 amino acids, exclusively produced by tubular cells of the thick ascending limb and early distal convoluted tubule in the kidney. UMOD is expressed on their apical membrane of cells and shed into the urine. Healthy adults typically excrete 20-70 mg/day of Tamm-Horsfall protein.

Mutations of the *UMOD* gene cause FJHN, characterized by hyperuricemia of underexcretion type, suggest a candidate regulator of plasma uric acid. The mechanisms by which *UMOD* mutation reduced uric acid excretion are not understood. One hypothesis is that uromodulin may contribute to regulation of renal reabsorption of uric acid and sodium. *UMOD* has a permissive role in the modulation of Na-K-2Cl cotransporter and renal outer medullary potassium channel (ROMK) function on the apical surface of the thick ascending limb. Urinary UMOD excretion is low in individuals with FJHN. Reduced UMOD might lead to a decrease of sodium reabsorption through the thick ascending limb, perhaps compensated through increased reabsorption of sodium by the proximal tubule. As sodium reabsorption joins together increased reabsorption of uric acid in the proximal tubule, plausible mechanisms of uromodulin on plasma uric acid are apparent. Recently, a genome-wide association study demonstrated the common genetic variants rs4293393 in the *UMOD* gene promoter was associated with serum uric acid.

Progressive tubulointerstitial nephritis may be associated with cell death in the thick ascending limb caused by accumulation of abnormal uromodulin. However, there is no proven role of uric acid accumulation and uric acid crystals have not been identified in renal biopsy.

![Fig. 1. Mutations in UMOD genes reported in the literature.](11, 17, 27)
Clinical manifestations

Hyperuricemia prior to renal impairment and decreased fractional excretion of urinary uric acid are hallmarks of FJHN. Hyperuricemia typically begins early in life and frequently leads to gout during the teenage years. In the review of 205 patients with UMOD mutations,7 hyperuricemia and gout prevalence was 75% and 65%, respectively. 70% had chronic kidney disease. Renal disease progressed in 80% of these subjects and results in ESRD usually between the ages of 20 and 70 years.

Hematuria usually is not present and proteinuria is less than 1 g/day at most. In the early course of the disease, hypertension does not appear to be prominent.39 Decreased ability to maximally concentrate urine may cause enuresis or polyuria.7

Diagnosis

The clinical diagnosis of FJHN is suspected based upon family history and clinical manifestations. Molecular genetic test is the gold standard for diagnosis and a definitive diagnosis can be made in patients with genetic mutation. If there are family history of kidney disease in a pattern of autosomal dominant inheritance and development of hyperuricemia or gout prior to onset of renal dysfunction in a number of family members, this condition should be considered.

Hyperuricemia usually result in gout after adolescence.10 Not all affected individuals have gout, and individuals had a history of gout with onset between 8 and 38 years.8,40 Fractional excretion of uric acid is typically decreased in FJHN.43 This can be calculated as follows: (urinary uric acid concentration x serum creatinine concentration)/(urinary creatinine concentration x serum uric acid concentration). Underexcretion is defined as fractional excretion of uric acid usually less than 6% in adult (normal: 10-15%).44 Uric acid underexcretion is an early event even prior to the development of renal failure.41,42 But this test is insensitive in individuals who have an estimated glomerular filtration rate less than 70 mL/min.45

Patients usually develop azotemia between the ages of 10 and 70 years, but most do not enter stage 3 chronic kidney disease until fourth decade.45 Progression to advanced kidney disease is highly variable.18 Some require dialysis early in life, whereas other patients do not receive dialysis until sixty decade. In our study, there was an extensive family history of hyperuricemia and gout and adolescent onset azotemia, none of five family members had progressed to ESRD.46

Renal ultrasound examination may reveal normal kidneys or small kidneys depending on renal function.46 Medullary cysts may be seen in advanced disease, and are too nonspecific to reliably identify the causative disorder.46 Renal biopsy shows chronic tubulointerstitial kidney disease. The main pathologic findings include tubular basement membrane thickening and attenuation in distal tubules and collecting ducts.39,47 Histological examination is generally not performed to establish a diagnosis because pathologic findings are not sensitive for diagnosis.

In an individual with clinical manifestations consistent with FJHN, a definitive diagnosis can be made by genetic molecular test. UMOD molecular genetic test is commercially available. We previously performed DNA sequence analysis of the 10 exons of the UMOD genes to diagnosis genetically.45 In Korea, molecular genetic test of UMOD gene is available at Asan Medical Center (http://amcmg.amc.seoul.kr).

Urinary excretion of uromodulin consistently is decreased in FJHN individuals with normal renal function.73 On the other hand, urinary UMOD is lower in proportion to kidney function in patients with other renal diseases.74 Urinary UMOD measurement is not reliable for diagnosis of FJHN, and this test is available on a research basis only.

Differential diagnosis

Problems to be considered in the differential diagnosis of FJHN include early onset gout, autosomal dominant polycystic kidney disease (ADPKD) and genetic glomerular diseases. If young patients presents with gout, other potential conditions promoting hyperuricemia, such as renal insufficiency, hematologic disease, psoriasis, thyroid disorder, parathyroid disease, obesity or diuretics, should be also considered.

If an individual presents multiple renal cysts by an imaging study, inherited cystic diseases such as ADPKD excluded. In ADPKD, a large number of renal cysts are seen on ultrasound in affected individuals older than age 30 years.

If a young patient presents family history of unexplained kidney disease, the urinalysis may be a useful test. Bland urinary sediment may exclude other genetic glomerular disorders such as Fabry disease, Alport syndrome and familial focal segmental glomerulosclerosis which show abnormalities in urinalysis.

Management

A specific therapy for FJHN has not been established yet. In patients diagnosed with FJHN, periodic measurement of serum
creatinine and uric acid concentration are recommended.

Allopurinol should be strongly considered in individuals with gout.\textsuperscript{101} As stated above, the hyperuricemia in FJHN is resulted from underexcretion of uric acid, not from overproduction as in acute urate nephropathy. Also, uric acid crystals have not been identified in renal pathology.\textsuperscript{401} It is unclear whether allopurinol prevent disease progression. There have been several observational studies that examined the association between early allopurinol treatment and the prevention of progression of CKD in patients with FJHN.\textsuperscript{10, 48, 491} In a study of 27 individuals with FJHN,\textsuperscript{481} the importance of early treatment of allopurinol appeared. Five of six patients in whom allopurinol treatment was started when the serum creatinine level was higher than 2.3 mg/dL progressed to ESRD. But, progression to ESRD occurred in none whom received allopurinol treatment when the serum creatinine level was lower than 2.3 mg/dL. To determine whether uric acid lowering therapy slow progression of renal disease, prospective controlled study will be needed.

Febuxostat may be considered in patients who do not tolerate allopurinol. However, no data on the use of febuxostat in FJHN has reported yet. There was also no evidence that benzbramorane, a uricosuric agent, prevent renal disease progression.\textsuperscript{501}

Most patients with FJHN are normotensive and have little proteinuria. Therefore, it is less likely that FJHN responds to renin-angiotensin system blockers. There has been no evidence that angiotensin-converting enzyme inhibitors or angiotensin receptor blockers prevent renal disease progression in patients with FJHN.

Individuals with FJHN are good candidates for renal transplantation because the transplanted kidney does not develop the disease. Disappearance of tophi in FJHN after kidney transplantation has been reported. It was probably due to the absence of the mutated UMOD gene in the transplanted kidney.\textsuperscript{511} Family members of patients with FJHN should perform molecular genetic test before kidney donation.

**Conclusion**

FJHN is a rare autosomal dominant disorder, mostly caused by UMOD gene mutation. Patients develop early onset hyperuricemia, gout and progressive kidney disease. A definitive diagnosis of FJHN can be made by genetic testing in many cases. Mutational analysis of the UMOD gene is available commercially. FJHN patients who have gout are usually treated with allopurinol. It is not clear yet if lowering uric acid levels or initiating therapy with angiotensin inhibitors slows the progression of renal disease.

**References**


