

Chronic kidney disease in an adolescent with hyperuricemia: familial juvenile hyperuricemic nephropathy

Demet Alaygut, Meral Torun-Bayram, Alper Soylu, Belde Kasap, Mehmet Türkmen, Salih Kavukçu

¹ Division of Pediatric Nephrology, Department of Pediatrics, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey.
E-mail: demetalaygut@yahoo.com

SUMMARY: Alaygut D, Torun-Bayram M, Soylu A, Kasap B, Türkmen M, Kavukçu S. Chronic kidney disease in an adolescent with hyperuricemia: familial juvenile hyperuricemic nephropathy. Turk J Pediatr 2013; 55: 637-640.

Chronic kidney disease (CKD) is a life-long condition associated with substantial morbidity and premature death due to complications from a progressive decrease in kidney function. Especially in children, early diagnosis and detection of the etiologic factors are important to improve their health outcomes. Familial juvenile hyperuricemic nephropathy (FJHN) is a rare autosomal-dominant disorder characterized by hyperuricemia with renal uric acid under-excretion and CKD. Genetic studies have revealed mutations in the uromodulin (UMOD) gene. Highlighting the importance of CKD in children, a 14-year-old girl with the rare diagnosis of FJHN is reported herein.

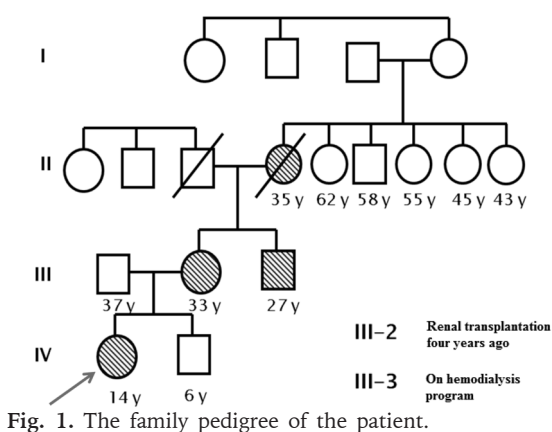
Key words: chronic kidney disease, children, familial juvenile hyperuricemic nephropathy, uromodulin gene mutation.

Familial juvenile hyperuricemic nephropathy (FJHN) is a rare primary tubulointerstitial disorder with autosomal-dominant inheritance. It is characterized clinically by chronic renal failure (CRF) progressing to end-stage renal disease (ESRD) and hypo-uricosuric hyperuricemia. The clinical appearance is characterized by renal insufficiency occurring in the late teenage years, with ESRD characteristically developing between 40 and 70 years of age¹. Histologically, interstitial fibrosis, tubular atrophy, and tubular basement membrane thickening and splitting are present in the renal biopsies². FJHN is caused by mutations in the uromodulin gene (UMOD) located at 16p11.2–12 that encodes for uromodulin, or Tamm–Horsfall glycoprotein, the most abundant protein in normal urine. Chronic kidney disease (CKD) is a significant and increasing global challenge for public health, and as such, it is important to estimate the cause of CKD. In this report, a girl with FJHN is presented, with emphasis on this rare cause of CKD in childhood.

Case Report

A 14-year-old girl was referred to our clinic with a probable diagnosis of hereditary nephropathy due to her family history. She had no complaint.

Her parents were nonconsanguineous, and the mother developed ESRD at the age of 29. Her grandmother was diagnosed with CKD and anemia at age 34 and died while in the hemodialysis program. Finally, her uncle on her mother's side was diagnosed with CKD at age 24 and is being followed in a nephrology clinic. Her family pedigree is shown in Figure 1. Her personal history was unremarkable; in particular, she had no history of urinary tract infection. On the physical examination, her weight and height were 59 kg and 161 cm, respectively, and both were at the 50th percentile. Her blood pressure was 110/70 mmHg, and the rest of the physical examination was unremarkable. Baseline laboratory test values were as follows: white blood cells 9000/mm³, hemoglobin 12.4 g/dl, hematocrit 39.5%, and platelets 252000/μL. Blood urea nitrogen, creatinine, and uric acid levels were found to be 44 mg/dl, 2.0 mg/dl, and 10.3 mg/dl, respectively, and creatinine clearance was measured as 30 ml/min per 1.73 m² (stage 3 CKD). The other electrolytes and liver function tests were normal. Urine analyses showed a normal density with unremarkable microscopic findings and no glycosuria or proteinuria. Urine culture showed no growth.



Tubular resorption of phosphate was 84% (normal range: $\geq 85\%$), and fractional excretion of uric acid (FE_{Ua}) was 4.3% (normal range: $>14 \pm 5.3\%$). The remaining tubular tests - $FENa$ (0.2%) and calcium excretion (3 mg/kg/day) - were in normal limits. Renal ultrasound (USG) demonstrated normal kidneys bilaterally with normal dimensions and echogenicity, without renal cysts or ureteral dilatation. She was diagnosed as having a moderate CRF of unknown etiology. Due to this diagnosis and her family history, a renal biopsy was performed, and one globally sclerosed glomerulus and mild periglomerular fibrosis were found. The biopsy revealed chronic interstitial nephritis and moderate tubular atrophy and interstitial fibrosis (Figs. 2-4). Direct immunofluorescence studies showed no significant immunoglobulin or complement deposition. Her clinical picture was hereditary CRF with an autosomal-dominant inheritance, characterized by hyperuricemia, low

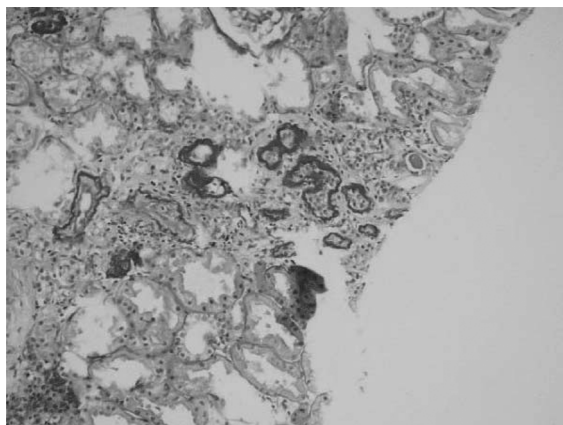


Fig. 2. Moderate tubular atrophy (hematoxylin and eosin, X40).

FE_{Ua} , and chronic interstitial nephritis. She was eventually diagnosed as FJHN. FJHN is caused by mutations in the uromodulin gene (*UMOD*) located at 16p11.2-12 that encodes for uromodulin, or Tamm-Horsfall glycoprotein, the most abundant protein in normal urine. Thus, to achieve an exact diagnosis, the patient was tested for *UMOD* mutations by polymerase chain reaction (PCR) amplification of genomic DNA, and a c.189 C>G mutation and C63W amino acid change were detected in exon 4. The patient was given allopurinol for treatment and followed in our clinic.

Discussion

The clinical differential diagnosis of renal failure in conjunction with hyperuricemia includes partial hypoxanthine-guanine

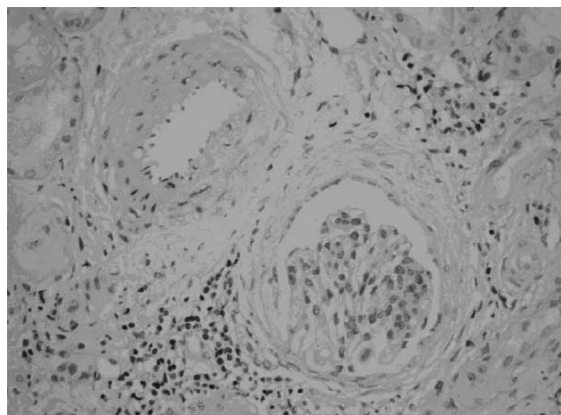


Fig. 3. Periglomerular fibrosis (hematoxylin and eosin, X40).

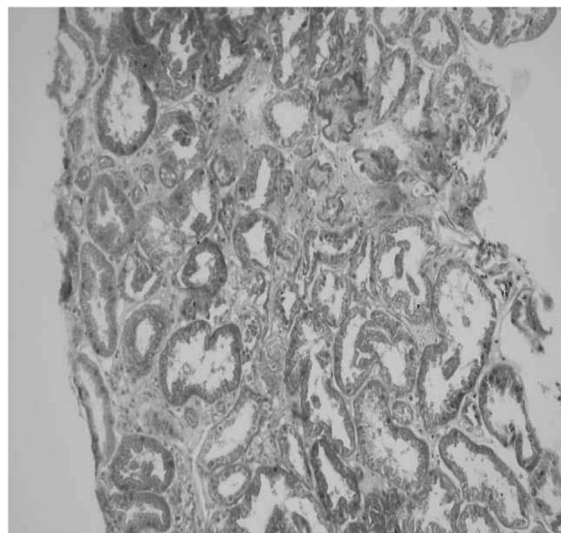


Fig. 4. Interstitial fibrosis (Masson's trichrome, X40).

phosphoribosyltransferase deficiency, medullary cystic kidney disease type 2 (MCKD2), and FJHN [3,4]. Hypoxanthine–guanine phosphoribosyltransferase deficiency is an X-linked disorder that results in the overproduction of uric acid. The patient's female gender and the absence of neurological symptoms, history of nephrolithiasis, or urate granulomas on renal biopsy argued against partial hypoxanthine–guanine phosphoribosyltransferase deficiency in our patient. On the other hand, renal ultrasound did not demonstrate renal cysts; therefore, the diagnosis of MCKD2 was ruled out. The most likely etiology of the hyperuricemic CKD in our patient could be FJHN. This clinical picture is an autosomal-dominant disorder characterized by hyperuricemia, low FE_{Ua} , progressive chronic interstitial nephritis, and CRF.

Familial juvenile hyperuricemic nephropathy (FJHN) is a rare autosomal-dominant disease caused by mutations in the *UMOD* gene located at 16p11.2–12 that encodes for uromodulin, or Tamm–Horsfall glycoprotein. Affected family members show impairment of urate excretion before puberty and usually develop hyperuricemia and gout after adolescence⁵. Renal function gradually deteriorates and results in ESRD within 10 to 20 years. Diagnosis is suggested by a FE_{Ua} of <5% (normal: 10–15%) with the symptoms and signs of FJHN^{2,6}. Our patient's age, clinic, and laboratory findings were compatible with FJHN. Allopurinol treatment was given for the high uric acid levels. Uric acid levels are also associated with other risk factors for kidney disease, including hypertension, metabolic syndrome and obesity. However, it is not clear whether these are mediators or confounders of a relationship⁷. Our patient was followed for these risk factors. She had no obesity or insulin resistance, and we did not observe hypertension or metabolic syndrome.

The majority of reported mutations involve an exchange resulting in the deletion or addition of a cysteine residue. The majority of *UMOD* mutations that have been identified are missense mutations in exon 4, as in our patient, which encodes for calcium-binding epidermal growth factor-like domains of *UMOD*⁸. Uromodulin, which is also called Tamm–Horsfall protein, is the most abundant

protein in normal urine and a major component of urinary casts; it has a pro-inflammatory potential such as activation of neutrophils and stimulation of monocytes to proliferate and release cytokines and gelatinases. *UMOD* gene knockout mice showed difficulty in clearing bacteria from the urinary bladder⁹. Several studies have demonstrated reduced levels of uromodulin in the urine of patients with FJHN, and other studies have reported tubulointerstitial immune complex nephritis in rats immunized with uromodulin protein¹⁰.

In FJHN, it has been suggested that the intracellular uromodulin overload impairs sodium reabsorption by the thick ascending limb of Henle (TALH), leading to defective urine concentrating capacity. The resultant volume depletion may be compensated for by increased proximal tubular reabsorption of sodium, which in turn may promote heightened proximal tubular urate resorption and reduced secretion, similar to the mechanism responsible for hyperuricemia in patients receiving loop diuretics^{2,11}. *UMOD* mutations potentially cause disruption of the molecule's stable tertiary structure, resulting in altered protein folding, accumulation within the endoplasmic reticulum, and impaired trafficking¹¹. Immunohistochemical staining for uromodulin can be performed, and intracellular *UMOD* inclusions can be detected by light and electron microscopy. Furthermore, on electron microscopy, the inclusions may appear as abundant fibrillar or granular storage material within bundles of endoplasmic reticulum. It is important to note that not all families with *UMOD* mutation have *UMOD* inclusions, and genetic testing remains the definitive diagnostic tool¹¹. The gene causing FJHN has been mapped to chromosome 16p11–p13 and is in close proximity to the gene for MCKD2. Mutations in the *UMOD* gene as a cause of FJHN and MCKD were first described in 2001, and the *UMOD* gene mutations were termed uromodulin storage disease, which includes FJHN, MCKD2 and glomerulocystic kidney disease².

On the basis of the overlapping clinical and pathologic features of FJHN and MCKD2 and the recent discovery that both entities exhibit mutations in the *UMOD* gene on chromosome 16p12, they can be considered different phenotypes of the same disease. Some

patients with *UMOD* mutations have medullary cysts; these are most frequently seen at autopsy and are inconsistent findings in individuals and families with the disease. Glomerulocystic kidney disease is a rare histopathologic entity characterized by prominent cystic dilatation of Bowman's space with primitive glomerular tufts².

In conclusion, it is important to diagnose FJHN as a cause of CKD. The presence of asymptomatic renal insufficiency, normal urine sediment, evidence of tubulointerstitial nephropathy, and a positive family history in a patient should prompt testing for hyperuricemia, and FE_{Ua} should be assessed.

REFERENCES

1. Schäffer P, Gombos É, Meichelbeck K, et al. Childhood course of renal insufficiency in a family with a uromodulin gene mutation. *Pediatr Nephrol* 2010; 25: 1355–1360.
2. Nasr SH, Lucia JP, Galgano SJ, et al. Uromodulin storage disease. *Kidney Int* 2008; 73: 971–976.
3. Puig JG, Miranda ME, Mateos FA, et al. Hereditary nephropathy associated with hyperuricemia and gout. *Arch Intern Med* 1993; 153: 357–365.
4. Tinschert S, Ruf N, Bernascone I, et al. Functional consequences of a novel uromodulin mutation in a family with familial juvenile hyperuricaemic nephropathy. *Nephrol Dial Transplant* 2004; 19: 3150–3154.
5. McBride MB, Rigden S, Haycock GB. Presymptomatic detection of familial juvenile hyperuricemic nephropathy in children. *Pediatr Nephrol* 1998; 12: 357–364.
6. Lhotta K, Gehringer A, Jennings P, et al. Familial juvenile hyperuricemic nephropathy: report on a new mutation and a pregnancy. *Clin Nephrol* 2009; 71: 80–83.
7. Nashar K, Fried LF. Hyperuricemia and the progression of chronic kidney disease: is uric acid a marker or an independent risk factor? *Adv Chronic Kidney Dis* 2012; 19: 386–391.
8. Nakayama M, Mori Y, Ota N, et al. A Japanese family suffering from familial juvenile hyperuricemic nephropathy due to a rare mutation of the uromodulin gene. *Case Rep Nephrol Urol* 2012; 2: 15–19.
9. Bates JM, Raffi HM, Prasad K, et al. Tamm-Horsfall protein knockout mice are more prone to urinary tract infection: rapid communication. *Kidney Int* 2004; 65: 791–797.
10. Hoyer JR. Tubulointerstitial immune complex nephritis in rats immunized with Tamm-Horsfall protein. *Kidney Int* 1980; 17: 284–292.
11. Scolari F, Caridi G, Rampoldi L, et al. Uromodulin storage diseases: clinical aspects and mechanisms. *Am J Kidney Dis* 2004; 44: 987–999.