Autosomal Dominant Tubulointerstitial Kidney Disease

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There are 3 major forms of autosomal dominant tubulointerstitial kidney disease (ADTKD): ADTKD due to *UMOD* mutations, *MUC1* mutations, and mutations in the *REN* gene encoding renin. Lack of knowledge about these conditions contributes to frequent nondiagnosis, but with even limited knowledge, nephrologists can easily obtain a diagnosis and improve patient care. There are 3 cardinal features of these disorders: (1) the conditions are inherited in an autosomal dominant manner and should be considered whenever both a parent and child suffer from kidney disease; the presence of even more affected family members provides further support. (2) These conditions are associated with a bland urinary sediment, ruling out glomerular disorders. (3) There is a variable rate of decline in kidney function. The mean age of ESRD is approximately 45, but the range is from 17 to >75. ADTKD-*UMOD* is often but not always associated with gout in the teenage years. ADKTKD-*REN* is associated with signs of hyporeninemia: mild hypotension, mild hyperkalemia, anemia in childhood, and hyperuricemia and gout in the teenage years. The only clinical manifestation of ADTKD-*MUC1* is slowly progressive CKD. Diagnosis should be made by genetic testing, and kidney biopsy should be avoided.

Key Words: Autosomal dominant, Tubulointerstitial, Renin, Uromodulin, Mucin-1

Autosomal dominant tubulointerstitial kidney disease (ADTKD) refers to disorders with the following characteristics: (1) autosomal dominant inheritance, (2) bland urinary sediment with no or trace proteinuria, and (3) slowly progressive CKD with a variable age of onset of ESRD, ranging from ages 17 to >75 (see Table 1). There are 3 major subgroups of ADTKD. ADTKD-*UMOD* is caused by mutations in the *UMOD* gene encoding uromodulin (Tamm-Horsfall glycoprotein) and associated with a high prevalence of adolescent gout; ADTKD-*MUC1* is caused by mutations in the *MUC1* gene encoding mucin-1. ADTKD-*REN* is caused by mutations in the *REN* gene that encodes renin and is associated with signs of relative hyporeninemia.

CASE EXAMPLE

A 21-year-old white man is referred for evaluation of an elevated serum creatinine level of 1.4 mg/dL (124 mmol/L), which was found as part of routine laboratory studies for a life insurance physical. The patient is otherwise healthy, on no medications, and has no known risk factors for kidney disease. The patient's father required kidney transplantation at age 45, and the patient's paternal uncle has CKD at the age of 55. The paternal grandfather died at 70 of kidney failure before the advent of dialysis. Physical examination is unremarkable, and the patient's urinalysis surprisingly reveals no protein or blood. A kidney ultrasound is normal. A kidney biopsy is performed and is nondiagnostic, revealing tubulointerstitial scarring without an inflammatory infiltrate. A diagnosis of hereditary nephrosclerosis is made. Several months later, the patient attends a family reunion and finds out that several of his family members have been diagnosed with ADTKD-*MUC1*. He undergoes *MUC1* genetic testing and is found to have a mutation in the *MUC1* gene.

GENERAL PRINCIPLES IN DIAGNOSIS

The key diagnostic feature of ADTKD is the presence of at least an affected parent and child with CKD. From a clinical standpoint, the lifetime chance for a white individual of developing ESRD is about 3.6%.[1] The chance that 2 individuals from the same family will have different kidney diseases and develop ESRD is about 1 in 1000, whereas the chance that the child of an affected individual will have kidney disease due to an autosomal dominant inherited disorder is 1 in 2. Thus, when a parent and child have kidney disease, autosomal dominant disorders should be strongly considered. Once the inheritance pattern has been identified, it is important to evaluate the urine. The presence of blood or protein in the urine suggests a hereditary glomerular disorder, such as Alport syndrome. The presence of a bland urinary sediment suggests ADTKD. In the vast majority of patients with ADTKD, there is no proteinuria or trace proteinuria. Occasional individuals may have proteinuria up to 500 mg/d. A kidney biopsy is usually nonspecific in ADTKD, showing interstitial scarring with the absence of glomerular disease or an inflammatory infiltrate. These findings are not pathognomonic for ADTKD, and thus, a definitive diagnosis cannot be made. For this reason, genetic analysis is the preferred diagnostic approach.

Why is it important to pursue a genetic diagnosis? (1) Once a genetic diagnosis is established, family members who wish to donate a kidney can be tested for the genetic mutation to see if they qualify as donors. In both ADTKD-*MUC1* and ADTKD-*UMOD*, affected individuals may have normal serum creatinine values past age 20, and there

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are at least 3 cases known to the authors of affected individuals being kidney donors to family members. (2) Identifying a genetic diagnosis is helpful in establishing follow-up and preventing kidney biopsies for diagnosis in other family members. (3) For ADTKD-*REN*, specific therapies are available, and for ADTKD-*UMOD*, family members may wish to consider taking allopurinol (see "ADTKD-UMOD: Treatment"). (4) Once a disease is diagnosed, family members may wish to work with groups that are trying to identify treatments for these disorders. (5) ADTKD has affected many families for generations. Often, affected individuals simply want to know the specific cause of their disorder.

Rare inherited disorders may be difficult for the nephrologist to diagnose as there are a large number of these conditions, and new ones continue to be identified. Both patients and nephrologists may initiate data searches on the Internet to identify the causes of such conditions. For some rare disorders, patient-led foundations or clinical centers may have a specific interest and may have developed excellent, informative Web sites. Unfortunately, many Web sites regarding these conditions may be outdated or inaccurate. Web sites from many medical centers often provide limited, generic text that serves as a form of advertisement and are unhelpful. It is, therefore, important that patients and physicians have access to current information about these disorders. Resources that are highly reliable and provide pertinent accurate information when performing such a search include UpToDate, GeneReviews, and PubMed. Searching these sites will usually provide a clue to the diagnosis. If these sites are unhelpful, a search of the Internet may still be used. For ADTKD, we recommend the following Web sites: http://www.uptodate.com/contents/autosomal-dominant-tubulointerstitial-kidney-disease-medullary-cystic-kidney-disease, http://kdigo.org/home/conferences/adtkd/, http://rarediseases.org/rare-diseases/autosomal-dominant-interstitial-kidney-disease/, http://www.ukdcure.org/learn_more. https://ghr.nlm.nih.gov/condition/uromodulin-associated-kidney-disease, and http://www.wakehealth.edu/Nephrology/Medullary-Kidney-Disease/Research-Team-Mucin-1-Kidney-Disease.htm.

CLINICAL SUMMARY

- There are 3 primary causes of autosomal dominant tubulointerstitial kidney disease (ADTKD): mutations in the UMOD gene encoding uromodulin (Tamm-Horsfall glycoprotein), mutations in the REN gene encoding renin, and mutations in the MUC1 gene encoding mucin-1.
- These conditions should be suspected if both a parent and child have kidney disease and if the urinalysis reveals a bland sediment.
- In all 3 conditions, there is a variable rate of progression of CKD, with the age of onset of end-stage kidney disease ranging from 17 to ≥75 years.

The conditions causing ADTKD are rare, but because of the autosomal dominant inheritance, a significant number of family members may be affected. Thus, obtaining a diagnosis in 1 family member will be beneficial to many other family members who may be affected. Once a diagnosis is made, it is important to contact other potentially affected family members and provide information regarding the specific familial condition. Often, unaffected family members believe the condition can "skip a generation" and live under a persistent fear that their children will develop kidney failure. Thus, providing information to all family members, including unaffected individuals, is important. Although it is important to inform other family members of the possibility they may have the condition, the decision for genetic testing is personal. At present, there are no specific treatments for ADTKD other than ADTKD-*REN*. Testing of children for genetic conditions in which a specific therapy is unavailable is discouraged.[2]

ADTKD-*UMOD*

ADTKD-*UMOD* is considered a rare disease, with less than 2000 families identified worldwide with this disorder.

Clinical Manifestations

The most common manifestations of ADTKD-*UMOD* include hypouricosuric hyperuricemia and CKD. It is important to note that hyperuricemia is present in most but not all individuals and families with this condition.[3] Affected individuals frequently have an elevated serum urate level early in life, resulting from decreased urinary uric acid excretion.[4] In the early-to-late teen years, patients may develop gout. The symptoms are typical of those found in older individuals, with the big toe or ankle often being affected. Gout is often misdiagnosed by clinicians as overexertion or a sports injury. As there is frequently a strong family history of gout, family members often make the diagnosis. As patients grow older, glomerular filtration rate declines. There is a large variation in the rate of progression of kidney disease that remains unexplained. The mean age for starting dialysis in our cohort is 47 years, with a range of 19 to >75.

Genetics and Pathophysiology

Mutations in the *UMOD* gene encoding uromodulin (also known as Tamm-Horsfall glycoprotein) have been identified as the cause of ADTKD-*UMOD*.[5] Uromodulin is a membrane-anchored protein that is expressed only in tubular cells in the thick ascending limb of Henle.[6] The uromodulin protein has a very high cysteine content. As it traverses the endoplasmic reticulum, the cysteine residues form disulfide bonds that allow the protein to achieve its final conformation.[7] The protein is then transported to the apical surface of the tubular cell where it is anchored to the membrane initially. Uromodulin then undergoes extracellular enzymatic cleavage and is excreted in the urine.[8]

Although uromodulin has been studied for over 5 decades,[9] its function remains unclear. A genome-wide association study suggested that uromodulin may have a very mild effect on the risk of kidney stone development.[10]