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Improving the Recognition of Hereditary Interstitial Kidney Disease

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ABSTRACT

Autosomal dominant tubulointerstitial kidney disease is characterized by the poorly recognized inheritance of slowly progressive renal failure leading to ESRD in later life. Patients with this condition have bland urinary sediment, and renal ultrasound typically reveals normal to small kidneys, with occasional individuals having small medullary cysts. Diagnosis relies on the clinical acumen of the nephrologist. Obtaining a thorough family history and records of affected family members is especially helpful. Kidney biopsy is frequently unhelpful, whereas genetic linkage studies or mutations in the *UMOD* gene may identify the problem.

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Autosomal dominant tubulointerstitial kidney diseases are frequently misunderstood. Little is taught about these conditions during nephrology fellowship, and what is taught is often incorrect.[1] Characteristic findings of slowly progressive kidney failure, bland urinalyses, and unremarkable renal ultrasounds make the correct diagnosis elusive. As in polycystic kidney disease, there is a high frequency of ESRD, with morbidity and early mortality in affected parents, siblings, and children. Families are rarely given a specific diagnosis[2] and rather are told they have "some type of familial kidney disease"—information with which they are already too familiar. This commentary provides a clinical assessment for the proper diagnosis and evaluation of this condition.

A number of hereditary interstitial kidney diseases are included in the grouping of nephronophthisis or medullary cystic kidney disease (MCKD). Advances in molecular genetics have better delineated these syndromes, but many nephrologists are unaware of these recent developments. Nephronophthisis refers to a group of autosomal recessive disorders associated with renal failure, salt wasting, anemia, urinary concentrating defects, and occasional medullary cysts on ultrasound. These disorders have been extensively studied by Hildebrandt *et al.*,[3] and many result from mutations in genes encoding proteins that are components of the tubular cell cilia.

In contrast to these autosomal recessive diseases, there is another group of autosomal dominant interstitial kidney diseases. There are two well-recognized types that have been given a number of different names,[4] causing considerable confusion in the literature (see Table 1). The first type is called autosomal dominant interstitial nephropathy,[5] or MCKD 1,[2,6,7] with linkage to chromosome 1. The second type is due to mutations in the *UMOD* gene that encodes uromodulin (also known as Tamm-Horsfall protein)[8] and has been called uromodulin-associated kidney disease, MCKD 2, or familial juvenile hyperuricemic nephropathy in some families. There are other forms of autosomal dominant interstitial kidney disease with similar clinical manifestations that are either linked to another area of chromosome 1 or not linked to one of these areas.[9,10]

MCKD 1

MCKD 1 demonstrates linkage to chromosome 1q21 in a number of reports,[5–7,11] but only a few studies provide details of the clinical picture. The predominant and perhaps only clinical characteristic is insidious progression to kidney failure, with most other clinical manifestations being secondary to renal failure *per se*.[2,6] Age at onset of clinical renal failure is variable within and between families. Renal insufficiency may first be noted in the teenage years, although some affected individuals have relatively well-preserved renal function into the fourth decade of life. The rate of progression to renal failure is poorly documented, because many family members are initially identified late in the course of their disease. In the best characterized families, the average age of onset of ESRD is approximately 50 yr, ranging from 36 to 80 yr.[2,6] Hypertension occurs but is likely related to underlying renal failure. Hypertension was particularly severe in one family whose disease was linked to 1q21.[12] In a large cohort from Greece,[6] hypertension was found in approximately 50% of individuals linked to the affected genomic region but in only 12% of linked individuals who had nor-

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mal renal function. Polyuria and anemia, which may be present in autosomal recessive nephronophthisis, are usually not clinically evident in early MCKD 1. Gout also occurs but typically in the setting of advanced renal failure. Urinalyses are usually bland with urinary protein excretion <1 g/d in most patients. Renal cysts are observed in fewer than half of affected individuals, and medullary cysts are uncommon; in some families, they are not found. In this large Greek cohort,[6] renal cysts were present in 40% of patients, with unilateral solitary cysts in 12.3%, bilateral single cysts in 5.3%, and tiny bilateral medullary cysts in 5.3%. The presence of renal cysts is nonessential to the diagnosis. The findings on kidney biopsy are often unimpressive. Focal global sclerosis of glomeruli (likely secondary to the tubulointerstitial disease process) is often present, and tubular atrophy and interstitial fibrosis are most common.[2] Some investigators[6] noted tubular basement membrane thickening with "splitting and lamellation"; however, definitive and specific pathologic changes are not present in this disease, and the diagnosis is usually not made by a pathologist.[2]

The approach to diagnosis may be troublesome for the nephrologist. In many cases, a young to middle-aged patient presents with renal insufficiency and a strong family history of kidney disease. A normal urinalysis and unremarkable renal ultrasound exclude polycystic kidney disease, leaving the diagnosis uncertain. Renal biopsy, when performed, typically reveals only chronic interstitial kidney disease, and a specific diagnosis is not made. One is then inclined to search the medical literature—but for what? A Medline search for hereditary interstitial kidney disease reveals few relevant articles. Articles on MCKD 1 are incorrectly overlooked, because patients are unlikely to have medullary cysts detected on either their renal ultrasound or biopsy material; therefore, it is difficult to determine the correct diagnosis without some previous knowledge of the condition.

Table 1. Terminology

Autosomal dominant tubulointerstitial kidney disease linked to chromosome 1
MCKD 1
autosomal dominant interstitial nephropathy
Autosomal dominant tubulointerstitial kidney disease caused my mutations in the *UMOD* gene encoding uromodulin (Tamm-Horsfall protein)
MCKD 2
uromodulin storage disease
uromodulin associated kidney disease
familial juvenile hyperuricemic nephropathy

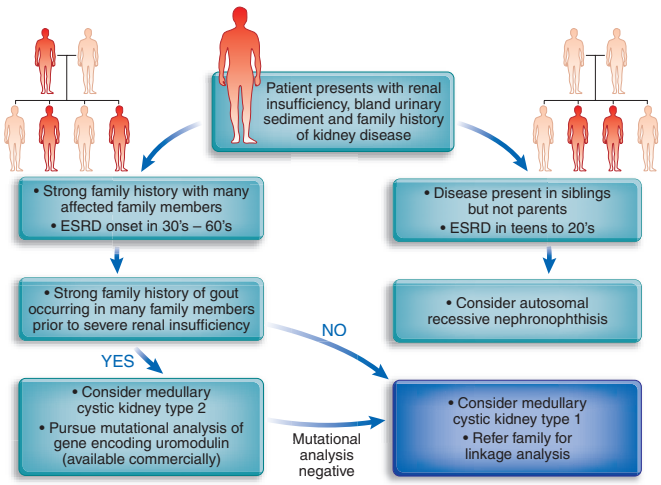

Figure 1. Schema for evaluation of families with hereditary renal tubulointerstitial disease.

Appropriate diagnosis of MCKD 1 relies primarily on clinical acumen (see Figure 1). The key to diagnosis is obtaining a proper, extended family history. When this is performed, it will become clear that a large number of family members have had this condition. The clinical history and biopsy reports of other family members should be obtained, because these will reveal similar features as that of the presenting patient. Screening to rule out mutations in the *UMOD* gene should be performed (see MCKD 2). If mutational analysis is negative, then one should consider referring the family to an interested research group for genetic linkage studies.

The nonspecific features of the disease and the inability to find the causative gene have hampered research into the cause of MCKD 1. Wolf *et al.*[7] reported linkage of MCKD 1 to a 1.19-Mb region on chromosome 1q21; however, mutational analysis of 37 genes under the linkage peak did not reveal any causative mutations. The inability to identify the genetic cause of this disease is attributable, in part, to the lack of coexisting systemic features and late age at onset of symptomatic illness. It may be difficult to identify clearly the affection in the young members of multiplex families. The rarity of the disease and difficulty in diagnosis have led to relatively few families being referred for genetic linkage analysis. Despite these difficulties, linkage has been detected, and it is hoped that identification of additional families will help to identify the causative gene(s). Clinical characterization will remain difficult until the genetic causes are identified. Genetic diagnosis will then allow us to study the disease at earlier stages.

MCKD 2

MCKD 2 is similar to MCKD 1, with the exception that family members often experience repeated attacks of gout. The associated precocious gout makes for an easier diagnosis, because it occurs in ap-

proximately 50% of affected family members, often beginning in the teenage years. Patients frequently present after their first gouty attack, because the family realizes gout is a harbinger of progressive renal failure. Individuals who do not have gout may be evaluated for this disease because of their family history or as part of routine evaluations. Kidney failure is slowly progressive, usually beginning in the teenage years and leading to ESRD in the fourth through sixth decades. As in MCKD 1, the urinalysis is bland, renal ultrasound may reveal small kidneys, and medullary cysts occur infrequently. The cause of MCKD 2 is a mutation in the *UMOD* gene, encoding uromodulin or Tamm-Horsfall protein. Commercial testing is available to make the diagnosis,[13] and is preferable to a kidney biopsy. Several recent reviews have detailed the characteristics of this condition.[14]

CONCLUSIONS

At present, no specific treatments are available for MCKD 1 given that it is often diagnosed late. Potential therapies for MCKD 2 include allopurinol or angiotensin-converting enzyme inhibition, although the effectiveness of these treatments is unclear.

The epidemiology and clinical characteristics of MCKD 1 and MCKD 2 will be better understood with better genetic testing. Their true prevalence is difficult to determine because these conditions are infrequently recognized by clinicians. We have formed a registry for affected individuals and families (ableyer@wfubmc.edu), in an attempt to better understand the factors associated with disease progression and to test novel therapies.

When faced with a family who has an extensive history of chronic kidney disease with inactive urinary sediment and unremarkable renal ultrasounds, one should consider the causes of hereditary tubulointerstitial nephritis in the differential diagnosis and aggressively pursue the correct diagnosis. These endeavors may ultimately help the many families whose conditions have long been overlooked or ignored.

DISCLOSURES

Wake Forest School of Medicine and Dr. Bleyer have a licensing agreement with Athena Diagnostics (Worcester, MA) for MCKD 2 genetic testing.

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