Published in final edited form as:

Semin Nephrol. 2010 July ; 30(4): 366–373. doi:10.1016/j.semnephrol.2010.06.003.

Hereditary Interstitial Kidney Disease

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Summary

Autosomal-dominant interstitial kidney disease is characterized by slow progression of chronic kidney disease in patients with bland urinary sediment and no or low-grade proteinuria. There are at least three subtypes. Patients with mutations in the *UMOD* gene encoding uromodulin suffer from precocious gout in addition to chronic kidney failure. Diagnosis can be achieved through genetic analysis of the *UMOD* gene. Patients with mutations in the *REN* gene encoding renin suffer from anemia in childhood, hyperuricemia, mild hyperkalemia, and progressive kidney disease. Genetic analysis of the *REN* gene can be performed to diagnose affected individuals. There is a third form of inherited interstitial kidney disease for which the cause has not been found. These individuals suffer from chronic kidney disease with no other identified clinical signs. Linkage to chromosome 1 has been identified in a number of these families. Proper diagnosis is valuable not only to the affected individual but also to the entire family and can facilitate treatment, transplantation, and research efforts.

Keywords

Hereditary interstitial kidney disease; medullary cystic kidney disease; uromodulin; renin; review

Hereditary interstitial kidney disease is a poorly understood and identified condition. The purpose of this review is to help physicians recognize and classify this condition.

Why is it important to identify the cause of inherited interstitial kidney disease? Some physicians believe that there are few treatments for inherited disease, and there is therefore little reason to aggressively pursue the cause of kidney disease. However, there are a number of reasons to properly identify potential causes. First, if the cause of inherited kidney disease is uncertain, it will not be possible to identify potential kidney donors among family members. Second, proper identification of the cause of disease will prevent the need for

kidney biopsy in family members. Third, disease identification provides information about prognosis for affected individuals and helps them to better cope with their illness and plan for their future. Fourth, some of these conditions have unique treatments, such as treatments for individuals with mutations in the *REN* gene encoding renin. Fifth, disease diagnosis gives family members information about how the disease potentially could affect their children. Sixth, although the diagnosis may not be helpful in one particular family member (eg, a dialysis or transplant patient), it may be very helpful in other affected family members (eg, a young patient newly diagnosed with renal insufficiency). Seventh, even without any potential treatments, patients receive solace in simply knowing the origin and name of the disease that is present in their family. Finally, correct diagnosis may encourage affected individuals to participate in or support research in their condition.

Even if physicians are slow to identify the cause of kidney disease, their patients frequently will not be. In our studies of inherited interstitial kidney disease, approximately half of the inquiries regarding a potential diagnosis for inherited kidney disease come directly from patients. The internet markedly has facilitated communication between the patient and interested specialists and researchers.

CLINICAL APPROACH TO DIAGNOSIS

The ability of the clinician to diagnose inherited kidney disease has changed markedly in the past decade owing to genetic identification of new disorders and the internet. Physicians now have access to many computer applications that allow for much easier identification of diseases. UpToDate®, PubMed®, and Google® allow searches with keywords and facilitate searching for disease characteristics. Further questions can be answered by contacting specialists anywhere in the world on the internet. The internet allows the patient with a rare disease to find the rare doctor interested in his/her condition.

The clinical approach to the diagnosis of inherited kidney disease begins first with the determination of the inheritance pattern of the disease (Fig. 1). In autosomal-dominant conditions, the inheritance of one mutated gene from an affected parent results in disease. Therefore, 50% of the children of an affected parent will have the disease. Many family members typically suffer from the disease. In contrast, in autosomal-recessive diseases, patients inherit a mutated gene from each parent. In these families, approximately one quarter of siblings will suffer from disease, but their parents will not. There usually will be no other family members with disease unless there has been familial intermarriage. In X-linked recessive diseases, the disease usually is present predominantly in men, and there is no male-to-male transmission of disease. It is therefore important to take a complete family history to help identify the inheritance pattern of the disease. This will be most helpful in elucidating the final diagnosis.

After inheritance has been determined, the nephrologist needs to turn his attention to the characteristics of the disease. Important factors include the following: First, results of renal ultrasound and other imaging should be done to rule out polycystic kidney disease. Second, one should determine whether the condition is glomerular or tubulointerstitial. In inherited diseases, it is important not only to consider the patient but also the disease in all family

members. For example, in inherited tubulointerstitial disease, most individuals, especially younger ones, will have limited proteinuria. However, as renal disease progresses, secondary focal sclerosis may occur, and individuals may develop some proteinuria. In addition, on occasion a patient with advanced disease and some cystic degeneration may have mild hematuria. For this reason, it is important to characterize as many family members as possible. Third, in most cases of inherited kidney disease, diagnosis can be made without biopsy. Often, a biopsy has been performed on another family member, and the results can be obtained. Unfortunately, biopsy results in autosomal-dominant interstitial kidney disease can be misleading. Patients frequently have secondary focal sclerosis on biopsy, and are diagnosed incorrectly as having hereditary focal and segmental glomerulosclerosis. Fourth, associated signs and symptoms, such as the presence of precocious gout, hyperuricemia, hyperkalemia, and anemia may point to a particular diagnosis.

From this approach, one should be able to classify the condition by its genetics and its location of origin within the nephron (see Fig 1).

Inherited tubulointerstitial kidney diseases characteristically are divided into autosomal-recessive and autosomal-dominant conditions. Autosomal-recessive conditions are termed *nephronophthisis* and are usually the result of mutations in various proteins found in the renal tubular cilia.¹ A number of forms of nephronophthisis have been described. Affected individuals usually suffer from anemia, salt wasting, and progressive kidney disease in childhood, culminating in dialysis in the teenage years. The characteristic patient with this disorder presents in childhood and may have siblings with the disease, but parents are unaffected. This is usually easy to distinguish from the autosomal dominant interstitial kidney diseases, in which many family members usually are affected, and one of the parents almost always is affected.

There are at least three forms of autosomal dominant interstitial kidney disease that have been identified: (1) mutations in the *UMOD* gene encoding uromodulin, also referred to as *medullary cystic kidney disease type 2*; (2) mutations in the *REN* gene encoding renin; and (3) medullary cystic kidney disease type 1, a condition in which the genetic cause has not been identified but has been linked to chromosome 1. All three forms of disease are characterized by slowly progressive chronic kidney disease, with end-stage kidney disease usually occurring between the ages of 30 and 70 years. There likely are other causes of autosomal-dominant interstitial kidney disease that will be identified as genetic identification of kidney disease progresses.

UROMODULIN-ASSOCIATED KIDNEY DISEASE

Pathophysiology

Uromodulin (also known as *Tamm Horsfall glycoprotein*) is the most common protein excreted in normal human urine.² Uromodulin is a polymeric protein produced exclusively in the thick ascending limb of Henle, where it adheres to the luminal surface of tubular cells.³ The protein contains many cysteine residues that are important in cross-linking uromodulin, and this cross-linking is likely an important feature in providing a water-tight boundary.⁴ The role of uromodulin remains unclear at this time. Animal models have shown

that absence of uromodulin results in an increased predisposition to urinary tract infection,⁵ although an increased incidence of urinary tract infections has not been noted in individuals with low uromodulin production.⁶ Uromodulin may also be helpful in providing maximum urinary concentration.⁶

In more than half of the mutations causing disease, there is a mutation that causes an amino acid substitution that results in the addition of a new cysteine or the deletion of a cysteine that is normally present. These mutations result in an inability for uromodulin to fold properly, and the molecule cannot be exported out of the endoplasmic reticulum.⁷⁻⁹ The abnormal uromodulin then precipitates in the endoplasmic reticulum, resulting in two separate effects: (1) it prevents the synthesis of the normal uromodulin in the endoplasmic reticulum, resulting in loss of function of normal uromodulin;¹⁰ and (2) the abnormal uromodulin that is deposited leads to accelerated apoptosis of tubular cells with subsequent nephron drop-out and progressive kidney failure.

Clinical Manifestations

Families with uromodulin mutations have several characteristic findings.

First, hyperuricemia occurs in many, but not all, individuals.¹¹ Hyperuricemia occurs early in life and is associated with a reduced fractional excretion of uric acid to less than 5%. Patients likely have relative volume depletion owing to the loss of uromodulin in the thick ascending limb with secondary increased proximal tubular urate reabsorption. Thus, there is not an increase in uric acid synthesis, but rather increased reabsorption results in higher serum urate levels. Gout frequently occurs in adolescence, especially in males in the family. In these families, the concerned parent is ever vigilant for the development of gout in their children because this is a known harbinger of the disease to physician and patient alike. Second, the patients have been found to have mild concentrating defects that usually are not clinically apparent. There is an increased prevalence of enuresis in childhood.¹¹ Third, the renal ultrasound usually is normal or may reveal small, contracted kidneys later in the disease. Although the condition is referred to as *medullary cystic kidney disease type 2*, this is actually a misnomer because medullary cysts are not diagnostic of this disease and frequently are absent.¹² Finally, chronic progressive kidney failure occurs, although there is variation within families and between families. Although some family members may not go on to dialysis until their 60s, other individuals may start dialysis in their 30s. The disease appears to result in more rapid progression in men than in women.

Diagnosis

The first step in the diagnosis is to obtain a proper family history with special reference as to family history of gout and kidney failure. It is very helpful to find out if other family members have ever been tested for mutations in the *UMOD* gene and to obtain the results. A urinalysis then should be obtained, which usually reveals a bland urinary sediment and less than 1 gram of urinary protein. Renal ultrasound is not particularly helpful, but can rule out polycystic kidney disease. A 24-hour urine collection should be obtained for uric acid and creatinine together with a serum uric acid and serum creatinine. It is helpful for the patients to be off of diuretics, aspirin, nonsteroidal agents, and angiotensin converting enzyme

(ACE) inhibitors/ angiotensin receptor blockers when this is performed. Typically, the 24-hour urinary uric acid is in the low normal or normal range, but the key to the diagnosis is the fractional excretion of uric acid. The fractional excretion of urate is, in general, less than 5% in this disorder. In any form of kidney disease, when the glomerular filtration rate decreases, the fractional excretion of urate increases.¹³ Therefore, the fractional excretion of urate may be greater than 5% in individuals whose glomerular filtration rate has decreased to less than 80 mL/min.

The definitive test for diagnosis is mutational analysis of the *UMOD* gene. This can be performed at one of several sites (www.genetests.org/servlet/access?prg=j&db=genestar&id=8888891&fcn=c&res=9999D&qry=224298). The test typically costs about \$900 to perform. Athena Diagnostics is a frequent provider of testing in the United States. Currently, only two of the exons of the uromodulin gene are sequenced by Athena, although this is likely to change in the near future. Rarely, mutations have been identified in the exons not sequenced by this laboratory.¹⁴ Insurance coverage for this test varies, and can be quite problematic in the pursuit of a diagnosis. If no family member has been tested, it is best to first test a person with definitive kidney failure (such as on dialysis or posttransplant) and/or a patient who has insurance to cover the cost of the test. Results from mutational analysis will document where the mutation is and the likelihood that the mutation is predictive of disease. In our experience, almost all mutations resulting in an amino acid substitution result in clinical manifestations of disease.

If mutational analysis is negative, one should consider referral of the family to investigators specifically interested in this condition for genetic linkage studies.

Once the diagnosis has been established within a family, one must consider whether other family members should undergo genetic testing to definitely diagnose the condition, or if the diagnosis can be made on clinical grounds. Although each case is unique, the following general statements may be made.

- If a family member has some degree of chronic kidney disease and hyperuricemia, and there are no indicators of other kidney disease present, it may not be necessary to perform genetic testing.
- In individuals younger than 20 years of age, a diagnosis frequently is requested. This diagnosis likely will have long-term ramifications. Significant hyperuricemia, gout, and renal insufficiency in this age group almost certainly would suggest inheritance of a *UMOD* mutation. However, the absence of these findings, although suggestive that the patient does not have the disease, is not unequivocal. These patients can be counseled that there is no evidence of disease, but laboratory studies should be followed. Alternatively, they can undergo mutational analysis for definitive diagnosis.
- Individuals who are interested in donating a kidney for transplantation should undergo mutational analysis.

- Once a diagnosis is made, the family can be tested for the specific mutation, and such information can be forwarded to the genetics laboratory performing the test. This may result in a decreased cost of the test.

Treatment

At present, there is no specific treatment for this condition. The slow progression of disease leads to difficulties in testing new therapies and understandable reluctance to participate in trials.

Current potential treatments include the following.

Allopurinol—Some groups believe that allopurinol may slow progression of kidney disease, although this remains unclear at present.¹⁵ Even though there is progression in some individuals on allopurinol,¹⁶ it still is possible that allopurinol slows the progression. Allopurinol is especially indicated in young men or others who develop gout because the uric acid burden will increase over time, and allopurinol will prevent the development of tophi and crippling gout.

ACE Inhibitors—ACE inhibitors may decrease production of uromodulin, and, hence, abnormal uromodulin may lead to accelerated apoptosis. Given their general benefit in kidney disease, it is reasonable to consider these agents. Losartan may be preferable because it has a hypouricemic effect.¹⁷

Transplantation—Transplantation results in a cure of the disease because the mutated gene occurs exclusively in the native kidney and produces a protein that remains within the native kidneys.

MUTATIONS IN THE RENIN GENE

Pathophysiology

Recently, mutations were identified in the gene encoding renin in families with inherited interstitial kidney disease.¹⁸ In endothelial cells in the juxtaglomerular apparatus, renin is first produced as the pre-protein preprorenin. This molecule has a signal peptide that directs the preprorenin molecule into the endoplasmic reticulum. Families have been identified that have mutations resulting in substitutions in the amino acids in the signal peptide. These mutations affect the ability of renin to enter the endoplasmic reticulum. The altered preprorenin then precipitates in the cell cytoplasm and leads to accelerated apoptosis.

Patients with this condition have two distinct abnormalities: first, abnormal preprorenin is formed, leading to accelerated apoptosis. In addition, low renin levels *in utero* may lead to abnormalities in kidney development. It is likely that one or two of these factors lead to the chronic kidney disease found in this condition. Second, the abnormal preprorenin interferes with production of normal renin, leading to low, but not absent, renin and aldosterone levels.

Clinical Manifestations

Patients suffer from findings related to both low renin and chronic kidney disease.

Anemia associated with low erythropoietin levels begins in infancy and is out of proportion to the level of renal insufficiency. Hemoglobin levels are typically in the range of 9 to 11 g/dL. Anemia resolves in adolescence, when hemoglobin levels return to the normal range. They subsequently decline again with more advanced renal failure.¹⁸

Patients have a tendency to hyperkalemia and low normal blood pressures, although these are usually asymptomatic and mild.

Patients may be more prone to the development of acute kidney failure, especially in the setting of volume depletion and nonsteroidal agents.

Patients develop slowly progressive chronic kidney disease, with end-stage kidney disease developing in the age range of 40 to 60 years. Patients have a bland urinary sediment with minimal proteinuria. Renal ultrasounds are unremarkable early in the course of the disease. A decrease in renal size is seen as kidney disease progresses.

Hyperuricemia with a reduced fractional excretion of uric acid is common in these patients. The mechanism for this remains unclear.

Diagnosis

Physicians should consider this condition in individuals with autosomal-dominant inheritance of interstitial kidney disease. Particularly helpful diagnostic clues include the presence of anemia during childhood, hyperuricemia, and low normal blood pressure.

Random plasma renin and aldosterone levels should be obtained, as well as a 24-hour urine collection. Low levels of renin and aldosterone are suggestive, but not diagnostic of this condition. A reduced fractional excretion of uric acid and a low serum erythropoietin level in the setting of anemia are signs of this disorder.

These families can be diagnosed by mutational analysis of the renin gene. For information on laboratories providing testing for this condition, see GeneReviews (http://www.ncbi.nlm.nih.gov/sites/GeneTests?Db=genetests&Cmd=ShowDetailView&TermToSearch=54417&ordinalpos=1&itool=EntrezSystem2.PEntrez.GeneTests.GeneTests_ResultsPanel.GeneTests_RVDocSum&disease_id=319226&test_type=clinical).

Treatment

Specific treatment is directed at consequences of hyporeninemic hypoaldosteronism. Increased sodium intake or the use of fludrocortisone can compensate for decreased aldosterone. Improvements in blood pressure and hyperkalemia will occur. These treatments also may have the benefit of decreasing production of renin, and, hence, the abnormal renin that is being produced.

Anemia responds well to treatment with erythropoietin. However, anemia may be mild and well tolerated, such that erythropoietin may not be required.

Because production of renin and aldosterone is low, the patients have similar clinical findings to patients on ACE inhibitors. Therefore, volume depletion should be avoided, and nonsteroidal agents should be used cautiously.

MEDULLARY CYSTIC KIDNEY DISEASE TYPE 1

Pathophysiology

Because the genetic cause of this condition is unknown, the pathophysiology also is uncertain. Patients suffer from chronic progressive tubulointerstitial kidney disease of unknown cause.¹⁹ There is little clinical indication as to the underlying cause.¹⁹ The lack of specific findings makes it difficult to diagnose younger individuals correctly as affected or unaffected. This results in difficulties in genetic studies. The disease has been localized to a large area on chromosome 1.²⁰ Attempts to identify the gene to date have been unsuccessful.

Clinical Manifestations

Patients slowly develop progressive renal failure, usually first manifesting itself in the teenage years. Besides the chronic kidney failure and manifestations secondary to this, there are really no other clinical signs or symptoms that have been identified. There is not a preponderance of gout, anemia, or other conditions that are helpful in making the diagnosis.¹⁹

Diagnosis

The condition should be suspected in families with chronic progressive interstitial kidney disease of unknown cause. These families should be referred to academic centers interested in this condition. Linkage of these families then can be performed to determine if they indeed are linked to chromosome 1 and suffer from this condition. Frequently, in the evaluation of these families, linkage to other areas is identified, pointing to other clinical diagnoses.

TREATMENT

There is no specific treatment at this time.

Other Forms of Inherited Interstitial Kidney Disease

As genetic methods improve, it is extremely likely that other genetic causes of hereditary interstitial kidney disease will be identified.

SUMMARY

There are three known types of autosomal-dominant interstitial kidney disease. Patients with mutations in the uromodulin gene suffer from early onset gout and progressive kidney failure. Diagnosis can be pursued through several commercial laboratories. Allopurinol may help slow progression of disease. Patients with renin gene mutations suffer from anemia in childhood, hyperuricemia, mild hyperkalemia, and slowly progressive kidney disease. Genetic testing can be performed in research laboratories. Families with MCKD 1 have slowly progressive chronic kidney disease with no other evident clinical manifestations.

These families should be referred to an academic center for linkage studies to confirm diagnosis and aid in finding the causative gene.

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Figure 1.
Approach to the diagnosis of inherited interstitial kidney disease.