Variable Presentations of Rare Genetic Renal Interstitial Diseases

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In his book entitled *How Doctors Think*, Jerome Groopman uses case studies to shed light on the thought processes that physicians use when they encounter a patient and attempt to make a diagnosis and formulate a treatment plan (1). One of the points that he emphasizes is how much doctors rely on a variety of cognitive heuristics, or shortcuts, in order to expedite the decision making process. When cognitive heuristics are based on solid reasoning and applied thoughtfully, they can be life saving. However, if they are flawed, the outcomes for patients can be disastrous. One such potential heuristic, or the tendency to judge the likelihood of an event based on the ease with which relevant examples come to mind (1). If this psychologic insight is correct, then it would suggest that if doctors cannot easily think of a clinical category that is germane to a case, they will not consider the diagnosis. One might call this the “inaccessible” heuristic.

The report by Anthony Bleyer and his colleagues in this issue of *CJASN* vividly illustrates the problem encountered by nephrologists who must make the diagnosis of supposedly rare conditions (2). Over a 14-year period, this international team has assembled a sample of approximately 400 families with hereditary interstitial kidney disease. In 24 families (8 with prior evidence of linkage to chromosome-1) who had evidence of an autosomal dominant pattern of inheritance for renal disease and negative testing for the uromodulin (UMOD) and renin (REN) genes that cause medullary cystic kidney disease type-1 (MCKD1) (3), there was an identifiable disease-causing mutation in the gene encoding mucoprotein-1 (MUC1). MUC1 was recently linked to the development of MCKD1 (4). There were 186 individuals from these 24 families who underwent MUC1 genetic testing, and 95 were found to have a cytosine insertion after a string of seven cytosines in the variable number of tandem repeat-coding sections of MUC1. These patients with genetically confirmed MCKD1 were combined with 111 historically affected patients (i.e., they were related to a genetically affected person in a way that ensured that they were genetically affected and they had CKD stage 4 or worse). Practicing nephrologists will be interested in the fact that clinical findings and routine laboratory testing results from the total sample of 206 patients were unremarkable except for the abnormal serum creatinine level in patients with CKD. There was no hypertension or peripheral edema and there were no striking abnormalities in the urinalysis. The mean BP was 126/76 mmHg and only 21% of patients had any proteinuria. The age at onset of ESRD in the 147 patients who reached this outcome was widely variable within and between pedigrees, ranging from 16 to >80 years. Finally, there were no prominent extrarenal findings.

How does one go about assessing the possibility of this new genetic cause of MCKD1 in particular and interstitial disease in general? One could assert that it should be considered in any family in which there are people in successive generations with evidence of impaired kidney function without signs of glomerular involvement. However, in the initial stages of the disease when early detection may be most valuable, the inaccessible heuristic rears its head. If the patients have no obvious clinical clues pointing to the kidney, it is unlikely that the diagnosis of chronic interstitial disease will be entertained and genetic testing will not be pursued.

Is there any way to change the dynamic and make MCKD1 an “available” disease that easily comes to mind when evaluating patients with interstitial kidney disease? A first step might be to consider a name change. MCKD is a misnomer because the anatomic distinction between the renal cortex and medulla has no clinical traction and medullary cysts are often not present at the time of diagnosis. The term medullary cystic kidney disease evokes images of abnormal cilia and enlarged kidneys, neither of which is involved in the diseases that fall under the type 1 rubric. In the report by Bleyer et al., although nearly half of the 27 patients who had renal imaging done had renal cysts, none of them had characteristic medullary cysts. The adoption of a term like renal interstitial disease might broaden nephrologists’ field of vision and spur identification of new cases and more intensive investigation of genetic causes.

If MCKD is considered a rare cause of chronic tubulointerstitial disease (TID), because of the inaccessible heuristic, nephrologists may be less likely to consider it as a possibility when encountering a patient with a reduced GFR. The disparity between the supposedly low incidence of UMOD, REN, and MUC1 mutations and the epidemic nature of CKD stages 3–5 (5) suggest a mismatch between the two entities. It fosters the view that the genetic entities are clinically
irrelevant. Making a diagnosis of MCKD1 is like searching for the proverbial kidney needle in the haystack of routine practice. Yet what if interstitial disease in general and MCKD1 are more prevalent than people think? There are no population-based studies that have evaluated the frequency of UMOD, REN, or MUC1 disease-causing mutations that would prompt a reassessment of the frequency of MCKD1. However, there are suggestive data that genetic variations in these proteins may be more common than previously thought. Single nucleotide polymorphisms in the UMOD gene are associated with an increased risk of CKD (6–8). Genetic variations in the noncoding promoter region may contribute to kidney injury and interstitial disease in animals by enhancing sodium reabsorption and promoting salt-dependent increases in BP (9). If these findings are confirmed in patients, they could transform MCKD1 into a representative of an expanded group of renal interstitial diseases that trigger kidney injury and CKD. It does not make the presentation more exciting but it makes it more available for consideration and comprehensive testing. The burden will still fall on the nephrologist to make the diagnosis; however, the weight of numbers, evidenced by the rising incidence of CKD in adults over the last 2 decades (10), should foster consideration of genetic causes in a larger cohort of patients.

MUC1-related interstitial disease still requires recognition of a clinical problem. Unfortunately, the face of the disease is quite bland. It is not a high-profile disease with unusual features that calls attention to itself. Renal interstitial disease blends into the normal population and easily eludes detection. This is consistent with the longstanding view of TID as the poor cousin to its more glamorous relative, GN. Although TID has been catching up over the last 2 decades with growing recognition that it correlates better than glomerulonephritis with the rate of progression of CKD, most of the diagnostic workup and therapeutic interventions focus on the glomerulus. Bleyer et al. (2) focus on the diagnosis of gout because of the association of renal interstitial disease, hyperuricemia, and gout in patients with UMOD and REN mutations (3). It would be of interest to have more data about evidence of tubular dysfunction such as nocturia, urinary concentrating defect, glycosuria, phosphaturia, and aminoaciduria in patients with MUC1 genetic abnormalities. Nonetheless, the article by Bleyer et al. (2) underscores the need for nephrologists to be more aware of the contribution of the renal interstitium to CKD and be attuned to subtle signs of tubular dysfunction.

The next question is which patients should be tested for MUC1 mutations? The authors are to be commended for placing their findings into the full perspective of known causes of MCKD1 and have presented a thoughtful scheme to guide genetic testing that takes into account the technical difficulties involved in detecting MUC1 mutations. However, this should be considered provisional and open to change as new mutations are identified and more information is gathered about the prevalence of specific mutations. The availability of a targeted therapy will increase the pressure to perform genetic testing to identify patients who are most likely to benefit from the intervention. The experience with atypical hemolytic uremic syndrome is a good example of how advances in basic science and clinical therapeutics affect protocols for genetic testing in rare diseases (11).

Finally, the following question needs to be asked: does this new genetic finding make MCKD1 a ‘druggable’ problem? The hope when identifying a genetic basis for a clinical disorder is that it will shed light on the mechanism of disease and spur development of a novel agent that can improve outcomes (12). This is not always a straightforward exercise, as the experience with polycystic kidney disease demonstrates (13). The authors of this report are unable to link MUC1 to the pathogenesis of MCKD1 or renal interstitial disease and this only reflects the need for basic scientists to catch up. One encouraging point is the absence of evident disease in other MUC1-expressing tissues, such as the lung, breast, and stomach. This suggests that therapeutic interventions that target MUC1 may be able to selectively reduce tubulointerstitial damage and progression to CKD.

In conclusion, Bleyer and colleagues are to be applauded for highlighting the clinical profile of a newly identified genetic basis for MCKD1, namely mutations in the MUC1 gene. Changing the MCKD1 moniker, placing it in the larger context of renal interstitial disorders, and reassessing the true prevalence of these disorders may enhance the clinical applicability of the new findings. Nephrologists will still be faced with the challenge of timely recognition of interstitial diseases because of the unobtrusive presentation of these disorders compared with glomerulopathies. It is hoped that the genetic findings will spur discovery into the mechanism of disease and stimulate the design of new effective treatments that target the primary abnormality.

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Disclosures

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See related article, “Variable Clinical Presentation of an MUC1 Mutation Causing Medullary Cystic Kidney Disease Type 1,” on pages 527–535.