


Time to Recognize an Overlooked Trait

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In this era of identifying genetic risk factors for kidney disease, it may be appropriate to revisit one of the most common genetic disorders: Sickle cell hemoglobinopathies. Although sickle cell disease is a rare cause of ESRD, there is only a limited literature examining sickle cell trait (HbAS) in advanced kidney disease. In fact, in the most recent US Renal Data System report describing the primary cause of incident ESRD from 2003 through 2007, sickle cell trait accounted only for 29 of 536,877 cases.1 Progressive chronic kidney disease (CKD) leading to ESRD is often not included in the description of kidney injury resulting from sickle cell trait.2 Considering that the reasons behind the racial disparity of progression of kidney disease and ESRD remain unknown, it seems an obvious hypothesis to consider a widely known genetic disorder such as sickle cell trait.

In this issue of JASN, Derebail et al.3 describe the prevalence of HbAS in a sample of black patients who had ESRD and were receiving either hemodialysis or peritoneal dialysis. They then compare this observed prevalence with that of newborn screening programs in local counties and report the prevalence of HbAS in maintenance dialysis patients to be twice that of the newborn screening programs. The authors also characterize the prevalence of heterozygous hemoglobin C trait (HbAC) in this population by the same method and find a significantly higher prevalence. The authors speculate the increased prevalence of HbAS in this sample may indeed be due to accelerated progression of kidney disease as either a direct consequence of HbAS or by HbAS's enhancing the deleterious effects of another comorbid condition such as diabetes or hypertension. Given the limited literature about sickle cell trait in ESRD, this is a very worthy question to address. This is the first reporting of a systematic characterization and examination of sickle cell hemoglobinopathies in a relatively large sample of dialysis patients. The authors also capitalize on a valuable resource—the detailed and comprehensive population-based sickle cell evaluation of newborns—to serve as their control.

Importantly, as with most observational cohorts, the authors note several limitations to their study. One additional consideration may be that the four dialysis units that compose this sample population all are affiliated with an academic medical center that specializes in sickle cell disease. This feature may disproportionately direct patients who either are identified with HbAS or have family members cared for within this system to these specific dialysis units. In addition, the prevalence of HbAS worldwide can vary by region as much as 10 to 40%.2 Although the authors present arguments that migratory patterns have not changed in the locale of this study, without more specific information about pedigree, it remains possible that 60 years ago, when these patients were born, there was a different ethnic composition in this area compared with that of the past 15 years. The observation of the higher prevalence of HbAC, which has yet to be described to have any significant association with kidney disease, creates an additional reason to consider the unique aspects of this sample of patients with ESRD.

The authors recognize in this cross-sectional study that causation cannot be inferred and assert only hypotheses suggesting that HbAS is detrimental to progressive kidney disease. What if, like the observation with falciparum malaria, the presence of HbAS is actually protective from death in ESRD? In this study of prevalent dialysis patients, those with HbAS had a dialysis history on average 2 years more than those with normal hemoglobin genes—despite no significant difference in age. Recognizing that the risk for death once dialysis is initiated is eight times that of the general population,3 it is interesting that patients, despite having HbAS, seem to survive. If it is true that...
HbAS provides some protection from mortality, then that also would elevate the observed prevalence of HbAS in this sample.

Implications for care are also raised by the authors’ suggesting a possible need for additional monitoring of dialysis access and possible modifications for anemia management. This assertion is likely a bit premature, because we do not have any evidence that practices specific to patients with HbAS alter outcomes related to either of these key components of dialysis care; no data regarding erythropoietin-stimulating agents or hemoglobin levels are presented in this study. Additional research is needed before calling for modification of clinical practice. There also is not enough convincing evidence for universal screening for sickle cell hemoglobinopathies in patients with kidney disease. Overall, the therapeutic approach is the same whether it is for CKD or dialysis therapy. Again, until additional research provides evidence for efficacy of a unique approach for patients with HbAS and CKD, screening has little utility.

One other important point made by the authors addresses the issue of prevention. If the presence of HbAS affects the outcome of renal function in patients who are at risk for the development of ESRD from all causes, then the question becomes whether screening all black individuals, so that they are aware of their genotype, might change outcomes. The data presented by Derebail et al. are too preliminary to suggest that kind of screening effort to prevent renal disease, but it suggests that further study is required for full understanding of the risk to this population.

Finally, if we agree with assumptions presented in this study—that HbAS actually contributes significantly to development of ESRD—then we may need to reevaluate what this means for live-donor kidney transplants. A recent survey of transplant centers in the United States found that 83% have no policy for screening for HbAS, and 63% exclude such a donor rarely or never.4 The justification for this indifference is the lack of studies examining this important question—calling for more work in this area.

This study is an important contribution to break the ice, but additional examination of HbAS is needed in larger, well-characterized, and geographically diverse populations with advanced kidney disease. It may also be interesting to examine the interaction of HbAS with other, recently identified genetic risks for ESRD in black individuals, such as the MHY9 gene.5 We look forward to better understanding of the role of sickle cell gene abnormalities in renal disease and translating this to improved care for our patients.

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DISCLOSURES

None.

REFERENCES


Dependence of Renal Microvessel Density on Angiotensin II: Only in the Fetus?

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During renal development, coordinate positioning and lengthening of the postglomerular microvasculature takes place as the tubular compartment expands and lengthens to form the renal papilla.1 The three-dimensional relationship of peritubular capillaries and vasa recta to their specific nephron segments1,2 is essential for effective water and solute reabsorption in balance with glomerular filtration,3 for regulated salt excretion through the pressure natriuresis mechanism,4,5 and for formation of hypertonic urine.6,7 Conversely, rarefaction of the peritubular vasculature associated with tubulointerstitial fibrosis is a hallmark of chronic allograft nephropathy8 and probably most other progressive renal diseases.9,10 Hence, there is an obvious need to understand mechanisms that control the formation and maintenance of the peritubular vasculature.

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