High Prevalence of Sickle Cell Trait in African Americans with ESRD

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Sickle cell trait (HbAS) is present in 7 to 9% of African Americans1,2 and has typically been described as a benign carrier state with little effect on the health of affected individuals. Although uncommon, several adverse effects of HbAS have been reported in settings of low oxygen tension or high oxygen demand, including splenic infarction at high altitude, sudden death with extreme physical exertion, venous thrombembolism, and glaucoma from anterior chamber hemorrhage.1,3–7

Renal microvascular obstruction also occurs with HbAS, presenting most frequently as asymptomatic hematuria and most dramatically as renal papillary necrosis.3,6,7,10,11 The rare renal medullary carcinoma is seen almost exclusively among HbAS patients.6,11,12

In epidemiologic studies, the presence of HbAS has been associated with microalbuminuria and proteinuria, particularly among diabetic men.13,14 And African Americans with autosomal dominant polycystic kidney disease (ADPKD) and HbAS have been shown to progress to ESRD more rapidly than those without the trait.15 With its associated structural and physiologic changes, HbAS could adversely affect renal function, especially in the setting of comorbid disease, and may represent a potential risk factor for kidney disease.16,17

We postulated that HbAS may be more common among African Americans with ESRD and examined the prevalence of HbAS in a group of African Americans receiving renal replacement therapy.

Hemoglobin phenotyping was performed on 188 of the 206 African-American patients receiving treatment through four of our affiliated dialysis centers, 172 of whom were receiving hemodialysis and 21 receiving peritoneal dialysis. We obtained newborn hemoglobinopathy screening results in the corresponding three North Carolina counties from the inception of the newborn screening program to the planned date of the study. This included 6729 African-American individuals born be-
in over one third of patients with normal adult hemoglobin phenotype and HbAS and two thirds of patients with HbAC. More patients with HbAS had hypertension as their cause of ESRD. Only one (4%) patient with HbAS had GN, compared with 24 (16%) from the portion of patients with normal adult hemoglobin phenotype. Only three patients in the entire cohort were identified as having cystic kidney disease, all of whom had normal hemoglobin phenotypes. The one 32 year-old female patient with β-thalassemia minor and hypertensive ESRD at age 22 was not included in the above analyses.

In this study of 188 African-American patients receiving dialysis, we found that the prevalence of HbAS was more than twice that of the general population, present in one in seven ESRD patients. We also found that HbAC was more common in the dialysis patients.

To our knowledge, this study is the first to evaluate the prevalence of these hemoglobinopathies among African-American ESRD patients relative to an appropriate reference population. Our analysis, which was based on an *a priori* hypothesis, is exploratory in nature. HbAS, as examined in a group of prevalent ESRD patients, could be a risk factor or risk indicator for ESRD or merely associated at a statistical level. Acknowledging that we cannot exclude residual confounding, we propose potential mechanisms for our observation.

First, HbAS may directly lead to loss of renal function. Episodic sickling could lead to chronic parenchymal ischemia and eventually fibrotic changes as reported in autopsy and biopsy studies. Although not proven to be causative, the presence of HbAS has even been reported in the setting of GN. Second, HbAS could accelerate the effects of another process. Medullary structural and physiologic abnormalities provide a background pathology in which a primary disease would have an accelerated effect. Although HbAS may not be sufficient to cause ESRD by itself, it could contribute to progression of renal insufficiency to ESRD in the presence of additional factors, such as diabetes or hypertension. As noted previously, microalbuminuria and proteinuria have been reported in higher frequency among diabetic men with HbAS, further suggesting this possibility.

If HbAS is a cofactor for renal disease, identifying HbAS in patients otherwise at risk for chronic kidney disease could be important for preventive measures. Overt sickle cell disease (HbSS) is associated with lesions of glomerular hypertension, and angiotensin converting enzyme inhibitors improve proteinuria in these patients. Similar pathology may occur in the HbAS state and identifying these patients would allow aggressive monitoring for albuminuria and early intervention with antiproteinuric agents.

The presence of abnormal hemoglobin, particularly HbAS, may also affect the course and care of ESRD patients. HbAS may be an independent risk factor among African Americans for venous thromboembolism and could add to the already high risk for pulmonary embolism among ESRD patients. Additionally, this predisposition for thrombosis could affect arteriovenous fistula failure and access loss, already known to occur at higher rates among African Americans. African Americans with ESRD also appear to require larger doses...
of erythropoiesis stimulating agents (ESAs) to achieve their hemoglobin targets. Results of the Correction of Hemoglobin and Outcomes in Renal Insufficiency study suggested higher target hemoglobin may be associated with more cardiovascular outcomes, and adverse outcomes were seen primarily in those who failed to reach their target hemoglobin. The presence of HbAS and other hemoglobinopathies may play a role in this relative resistance, placing these patients at higher risk with increasing ESA exposure.

Heterozygosity for HbAC was also twice as common in this cohort compared with the geographically matched African-American population and to the reported national prevalence. Hemoglobin C is more likely to precipitate, and when present with hemoglobin S it leads to a syndrome similar to but less severe than HbSS disease. Heterozygosity is thought to be clinically silent. The elevated prevalence of HbAC in our cohort is of unclear significance but may have similar consequences as those of HbAS.

Of note, mean age of onset of ESRD in our study population was similar among all groups, whereas dialysis vintage was higher in the groups with either hemoglobinopathy by a median of 2.5 years. The small sample size and borderline statistical significance limit our ability to conjecture a potential explanation or draw meaningful conclusions from this difference. However, the greater length of vintage, in part, could influence our assessment of prevalence. The extended presence of those with hemoglobinopathies in this ESRD population could increase the prevalence of HbAS when surveyed in a cross-sectional manner.

The findings of this study must be interpreted in the context of several limitations. Primarily, the assessment of population prevalence of hemoglobinopathies via newborn screening results may not be accurately reflective of the population from which our ESRD cohort is derived. North Carolina newborn screening results include births occurring after 1994, and our cohort is of a different era. Any large migration into or out of these regions would lead to prevalence discrepancies between the time of our cohort and the advent of newborn screening. However, because our measured prevalence is similar to that found in the general African-American population nationally, we do feel confident in our assessment of the baseline population prevalence.

Our findings may not translate to all African-American ESRD populations. The aforementioned study of African-American ADPKD patients did include an assessment of HbAS in ESRD patients without ADPKD, finding it in only 6 of their 80 patients (7.5%). Although the local prevalence of HbAS was not evaluated, this discrepancy from our study does implicate that our findings should be confirmed in another cohort, perhaps larger and more geographically diverse.

Lastly, the cross-sectional design prevents the determination of the exact nature of the observed associations. Initial cross-sectional findings are primarily useful for informing subsequent prospective studies. The size of the cohort is also relatively small and geographically compact, such that any familial clustering might provide an exaggeration of the prevalence.

The prevalence of abnormal hemoglobin, HbAS and HbAC in this African-American ESRD cohort, was found to be over twice that of the baseline African-American population in the same geographic region. The high prevalence of these hemoglobinopathies suggests that they may contribute to progression to ESRD by providing a background of renal injury. Our findings also raise ques-
tions as to how the presence of HbAS or HbAC may affect management of ESRD patients. Longevity of hemodialysis access and response to ESAs may be altered. Although these results require confirmation, knowledge of a patient’s hemoglobin status may be important to the management of ESRD patients and before ESRD may even identify individuals who would benefit from aggressive interventions to attenuate progression of renal disease.

CONCISE METHODS

Study Design
We used a cross-sectional design to determine the prevalence of HbAS and other hemoglobin variants among African-American patients with ESRD. Hemoglobin status was determined in June 2008 for the patients attending four University of North Carolina-affiliated dialysis centers as part of their clinical anemia evaluation. All patients receiving hemodialysis in three of the units and all patients receiving hemodialysis or peritoneal dialysis at the fourth unit were included in this evaluation. Blood samples were obtained with the routine monthly laboratory studies. We determined patient-specific characteristics including race, age, gender, modality of dialysis, and date of initial dialysis from review of administrative data from each dialysis center. All African-American patients with available hemoglobin phenotype results were included in our study of prevalence. Age of onset of ESRD was calculated by subtracting the patient’s date of birth from the date of first-ever dialysis. Vintage was calculated from the time of first-ever dialysis. Age of onset of ESRD was calculated by subtracting the patient’s date of birth from the date of first-ever dialysis. Vintage was calculated from the time of first-ever dialysis. All African-American patients with available hemoglobin phenotype results were included in our study of prevalence.

Laboratory Studies
All studies for the ESRD patients were performed at the same laboratory site (Laboratory Corporation of America [LabCorp], Raritan, NJ). Hemoglobin variants were identified using HPLC. The North Carolina State Laboratory of Public Health ascertained hemoglobin status for newborn screening in its own laboratory first by isoelectric focusing; all abnormal variants were then confirmed by HPLC.

Statistical Analysis
In evaluating the prevalence of hemoglobin variants, proportions of variants in the ESRD cohort were compared with those proportions from the newborn screening population data using Fisher’s exact test. We evaluated characteristics of ESRD patients using ANOVA for continuous measures and Fisher’s exact test for categorical measures. Kruskal-Wallis testing was used for nonparametric variables. A sole patient with β-thalassemia minor in the ESRD group was not included in these comparisons because a single observation would be inappropriate to include in these analyses. Two-sided hypothesis testing with α = 0.05 was used for these statistical inferences. For those categorical variables with multiple groups that were found to have statistically significant differences, Fisher’s exact test was repeated to compare specific group pairs. We adjusted the level of significance for these repeated measures using Bonferroni correction (<0.025 for a second level of testing). All statistical analyses were performed using Stata 10.1 (StataCorp, College Station, TX).

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DISCLOSURES
None.

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