High Prevalence of Sickle Cell Trait in African Americans with ESRD

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ABSTRACT

Sickle cell trait (HbAS) associates with impaired urinary concentration, hematuria, and renal papillary necrosis, but its prevalence among African Americans with ESRD is unknown. We performed a cross-sectional study reviewing available hemoglobin phenotypes for 188 of 206 adult African-American patients receiving renal replacement therapy in four dialysis units. Results from the state newborn screening program in corresponding counties provided the local population prevalence of sickle trait among African Americans. Compared with the general African-American population, HbAS was twice as common among African Americans with ESRD (15% versus 7%, P < 0.001). Prevalence of hemoglobin C trait (HbAC) was similarly more common (5% versus 2%, P < 0.01). The higher prevalence of HbAS and HbAC in the ESRD population raises the possibility that these hemoglobinopathies contribute to a decline in kidney function, either alone or in conjunction with other known risk factors for renal disease. The potential effect of HbAS on the development and progression of CKD and its effect on the course and management of patients with ESRD deserve further study.


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 thromboembolism, and glaucoma from anterior chamber hemorrhage.1,3–7 The low oxygen content of the renal medulla provides a propitious setting for intravascular sickling. HbAS has been associated with fewer and disrupted vessels of the vasa recta,8,9 which likely translates clinically to the highly prevalent impaired urinary concentration.3,6,7,10,11 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 prevalence of HbAS has been associated with microalbuminuria and proteinuria, particularly among diabetic men.13,14 And African Americans with autosomal dominant polycystic kidney disease (AD-PKD) 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-
between January 1, 1994 and November 30, 2008 who were used to determine the local population prevalence.

Among the tested African-American ESRD patients, 28 (14.9%) patients had HbAS, 9 (4.8%) were heterozygous for hemoglobin C [hemoglobin C trait (HbAC)], and 1 (0.5%) was heterozygous for β-thalassemia (β-thalassemia minor). In comparison, the local population prevalence among screened newborns was 7.1% (P < 0.001) for HbAS and 1.9% for HbAC (P < 0.01) (Figure 1).

We also sought to determine if there were any major differences among the ESRD patients when separated by hemoglobin phenotype (Table 1). Mean age for the entire group was 58.5 (SD 14.6) years, with similar values obtained among all groups. Gender distribution and age of ESRD onset did not differ among the variants of hemoglobin. Median dialysis vintage was greater in both groups with variant hemoglobin by approximately 2.5 years (P = 0.05). Most patients were using in-center hemodialysis as their chosen modality for renal replacement therapy.

Differences were noted in ascribed cause of ESRD, although these did not reach statistical significance (P = 0.1). Diabetes mellitus was the cause of ESRD 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 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 thromboembolism1,2 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...
Table 1. Characteristics of patients receiving renal replacement therapy by hemoglobin phenotype

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HbAA (%) (n = 150)</th>
<th>HbAS (%) (n = 28)</th>
<th>HbAC (%) (n = 9)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (SD)</td>
<td>58.4 (14.8)</td>
<td>59.8 (12.5)</td>
<td>59.7 (16.8)</td>
<td>0.9</td>
</tr>
<tr>
<td>Gender, n (SD)</td>
<td></td>
<td></td>
<td></td>
<td>0.9</td>
</tr>
<tr>
<td>female</td>
<td>71 (47.3)</td>
<td>13 (46.4)</td>
<td>5 (55.6)</td>
<td>0.9</td>
</tr>
<tr>
<td>male</td>
<td>79 (52.7)</td>
<td>15 (53.6)</td>
<td>4 (44.4)</td>
<td>0.9</td>
</tr>
<tr>
<td>Age of ESRD onset, years (SD)</td>
<td>54.1 (15.5)</td>
<td>54.0 (13.8)</td>
<td>54.5 (18.6)</td>
<td>1.0</td>
</tr>
<tr>
<td>Dialysis vintage, median years (interquartile range)</td>
<td>3.0 (1.2 to 5.8)</td>
<td>5.5 (2.2 to 8.5)</td>
<td>5.5 (1.8 to 6.5)</td>
<td>0.05</td>
</tr>
<tr>
<td>Modality</td>
<td></td>
<td></td>
<td></td>
<td>0.8</td>
</tr>
<tr>
<td>in-center hemodialysis</td>
<td>137 (91.3)</td>
<td>25 (89.3)</td>
<td>9 (100)</td>
<td>0.1</td>
</tr>
<tr>
<td>peritoneal dialysis</td>
<td>13 (8.7)</td>
<td>3 (10.7)</td>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>Cause of ESRDb</td>
<td></td>
<td></td>
<td></td>
<td>0.1</td>
</tr>
<tr>
<td>diabetes mellitus</td>
<td>59 (39.3)</td>
<td>10 (35.7)</td>
<td>6 (66.7)</td>
<td>0.1</td>
</tr>
<tr>
<td>hypertension</td>
<td>52 (34.7)</td>
<td>15 (53.6)</td>
<td>1 (11.1)</td>
<td>0.1</td>
</tr>
<tr>
<td>GN</td>
<td>24 (16.0)</td>
<td>1 (3.6)</td>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>cystic disease</td>
<td>3 (2.0)</td>
<td>0</td>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>other</td>
<td>12 (8.0)</td>
<td>2 (7.1)</td>
<td>2 (22.2)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

*aOne patient heterozygous for β-thalassemia (β-thalassemia minor, β-thalassemia trait) is not included here. This patient was a 32 year-old female on hemodialysis with hypertension as cause of ESRD and onset of ESRD at age 22.

*bHbAA, normal adult hemoglobin phenotype.

As reported in Medicare CMS-2728 form.

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 to July 1, 2008, the first day of the month after hemoglobin electrophoreses were collected. Cause of ESRD was obtained in a similar review and reflected the etiology provided in the Medicare CMS-2728 form. We categorized these causes into a schema similar to that used in the U.S. Renal Data System reporting.28 The University of North Carolina Institutional Review Board approved the extraction of all administrative data and laboratory study results.

The population prevalence of HbAS was determined from hemoglobinopathy screening results of the newborn screening program conducted by the North Carolina State Laboratory of Public Health. Screening for hemoglobinopathies was extended to all newborns in North Carolina in 1994. Specimens are typically collected via heel stick to filter paper and are performed within 2 to 3 days of birth. Data for the three counties in which the four dialysis units are based were used to estimate the population prevalence. All available data for live African-American births from the initiation of the screening program to the time of this study were included (January 1, 1994 to November 30, 2008).

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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