CLINICAL RESEARCH STUDY

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Venous Thromboembolism in Adults with Sickle Cell Disease: A Serious and Under-recognized Complication

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ABSTRACT

BACKGROUND: Sickle cell disease is recognized as a hypercoagulable state; however, the frequency and characteristics of venous thromboembolism in sickle cell patients have not been well defined. The purpose of this study was to establish the prevalence and risk factors for venous thromboembolism in a large cohort of patients with sickle cell disease and determine the relationship between venous thromboembolism and mortality.

METHODS: We performed a cross-sectional study of 404 sickle cell disease patients cared for at the Sickle Cell Center for Adults at Johns Hopkins. Demographic, sickle cell disease-specific comorbidity, and venous thromboembolism data were collected on all patients.

RESULTS: One hundred one patients (25%) had a history of venous thromboembolism with a median age at diagnosis of 29.9 years. A history of non-catheter-related venous thromboembolism was found in 18.8% of patients. Sickle variant genotypes conferred a higher risk of non-catheter-related venous thromboembolism compared with sickle cell anemia genotypes (SS/Sβ^0) (relative risk [RR] 1.77; 95% confidence interval [CI], 1.18-2.66). Tricuspid regurgitant jet velocity ≥2.5 m/s also was associated with non-catheter-related venous thromboembolism (RR 1.65; 95% CI, 1.12-2.45). Thirty patients (7.4%) died during the study period. Adjusting for all variables, non-catheter-related venous thromboembolism was independently correlated with death (RR 3.63; 95% CI, 1.66-7.92).

CONCLUSION: Venous thromboembolism is common in adults with sickle cell disease. Sickle variant genotypes and tricuspid regurgitant jet velocity ≥2.5 m/s are associated with non-catheter-related venous thromboembolism. In addition, non-catheter-related venous thromboembolism appears to be an independent risk factor for death in our cohort. These results suggest that disease-specific prophylaxis and treatment strategies for venous thromboembolism should be investigated in sickle cell disease patients.

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KEYWORDS: Deep venous thrombosis; Mortality; Pulmonary embolism; Sickle cell disease; Venous thromboembolism

Microvascular and small-vessel arterial thrombosis is common in sickle cell disease, contributing to severe complications such as pulmonary hypertension, osteonecrosis, and stroke.[1-3] Various mechanisms have been hypothesized to contribute to thrombogenesis in sickle cell disease patients, including erythrocyte adhesion,[4] endothelial dysfunction,[5] leukocyte activation in the setting of chronic inflammation,[6] platelet aggregation,[7-10] coagulation defects,[11] and free hemoglobin-induced oxidative damage.[10,12] Nitric oxide scavenging secondary to intravascular hemolysis also results in hypercoagulability in sickle cell disease and may be an important mediator of thrombotic complications.[10] While it is widely recognized that sickle cell disease is associated with a hypercoagulable state, most research has focused on in situ thrombosis as the primary clinical manifestation, and previous reports investigating the risk and characteristics of venous thromboembolism have yielded conflicting results.

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Prior studies using large databases with de-identified records found the prevalence of pulmonary embolism in hospitalized sickle cell patients younger than 40 years of age to be significantly higher than black controls[13] but did not find the overall prevalence of pulmonary embolism to be higher in sickle cell disease.[13,14] In addition, the risk of deep venous thrombosis was not found to be increased in patients with sickle cell disease.[13] In contrast, autopsy studies have demonstrated pulmonary emboli in 20%-50% of sickle cell patients,[15-18] and studies evaluating thrombotic complications in pregnancy have demonstrated an increased risk of deep venous thromboses in sickle cell disease patients compared with controls.[19,20] Furthermore, because sudden death accounts for a significant proportion of mortality in adult sickle cell disease patients,[21] venous thromboembolism may be an important and unrecognized cause of morbidity and mortality in the sickle cell population.

CLINICAL SIGNIFICANCE

- Twenty-five percent of adult patients with sickle cell disease have a history of venous thromboembolism, with a median age at diagnosis of 30 years.
- Sickle cell variant genotypes, such as SC or Sβ^+, are associated with non-catheter-related venous thromboembolism.
- A history of non-catheter-related venous thromboembolism appears to be an independent risk factor for death in adults with sickle cell disease.

We hypothesized that venous thromboembolism is more common in sickle cell disease than previously reported. We performed a retrospective analysis of a large cohort of adult sickle cell patients to assess the prevalence and mortality associated with venous thromboembolism in sickle cell disease. In addition, we sought to identify traditional and sickle cell disease-specific risk factors for venous thromboembolism in our cohort.

METHODS

We conducted a retrospective cross-sectional study of sickle cell patients cared for at the Sickle Cell Center for Adults at Johns Hopkins between August 2008 and January 2012. Inclusion criteria included an age ≥18 years and a known genotype. Patients who had undergone successful bone marrow transplant before the study period were not included. The study was approved by the Institutional Review Board and was determined to be exempt from informed consent.

Data were collected via review of electronic charts. Information on genotype, age, sex, relevant comorbidities, and date of death were recorded for all patients. We defined sickle cell anemia genotypes as SS or Sβ^0, and sickle cell variant genotypes as all other sickle compound heterozygous states, such as SC or Sβ^+. As part of routine health maintenance, we collect information on sickle cell disease-specific comorbidities including a history of venous thromboembolism, stroke, avascular necrosis, end-stage renal disease, and leg ulcer on all patients with sickle cell disease. In addition, we refer all patients for screening echocardiograms to determine baseline tricuspid regurgitant jet velocity values. Patients who did not have complete data for the health maintenance evaluation were excluded from the study. Death was verified by available chart records and the Social Security Death Index.

Venous thromboembolism events were defined as those that were symptomatic and were subsequently recommended to be treated with full-dose anticoagulation. A diagnosis of venous thromboembolism was defined by a history of a positive duplex ultrasound, ventilation-perfusion scan, or computed tomography angiography in most cases. When radiology reports were not available, only patients who had a documented history of anticoagulation treatment were included as venous thromboembolism cases. This criterion has previously been verified as having high specificity for a history of venous thromboembolism.[22] For thromboembolism cases, data were collected on the date of diagnosis, first recurrence, site of thrombosis, and central venous catheter-related status. Additional triggering factors, including oral contraceptive use, pregnancy, active cancer, hospitalization, and surgery, also were recorded. Hospitalization-associated clots were defined as any venous thromboembolism occurring >24 hours after admission or within 90 days after discharge.

T test and chi-squared statistics were used for bivariate analyses. Poisson regression with a robust estimate of variance was used to identify independent risk factors associated with venous thromboembolism and death, and results are presented as relative risk (RR) and 95% confidence interval (CI). Regression models were performed using genotype, age, sex, and relevant comorbidities. Due to the high rate of central-line use in the sickle cell population, the variability in indication for central-line use including chronic transfusions, recurrent vasoocclusive crisis, and poor venous access, and the high incidence of catheter-triggered thrombosis in sickle cell disease,[23] patients who had only experienced a catheter-related event were excluded from the regression analyses in order to identify factors associated with venous thromboembolism and death, rather than factors associated with catheter use. In addition, because age was not normally distributed, it was analyzed as a categorical variable. Tricuspid regurgitant jet velocity ≥2.5 m/s also was used as a categorical variable. Patients who had an unmeasurable tricuspid regurgitant jet velocity by echocardiogram were assumed to have values <2.5 m/s. All statistics were performed using STATA Data Analysis and Statistical Software (Version 10; College Station,