Venous Thromboembolism in Children with Sickle Cell Disease: A Retrospective Cohort Study

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Objectives To describe the cumulative incidence of venous thromboembolism (VTE) in children with sickle cell disease (SCD) followed at a single institution and report on the risk factors associated with VTE development.

Study design Charts for all patients with SCD, aged 0-21 years, followed at Nationwide Children's Hospital over a 6-year period (January 1, 2009, to January 31, 2015) were reviewed. Data on VTE diagnosis, sex, body mass index/weight-for-length, SCD genotype, SCD clinical complications, central venous catheter (CVC) placement, and thrombophilia testing were collected.

Results Cumulative incidence of VTE in children with SCD followed at a single tertiary care institution was found to be 2.9% (12/414). Nine of the 12 VTE were CVC-associated. On univariate analysis, hemoglobin SS genotype (OR 10.7, 95% CI 1.4-83.5), CVC presence (OR 34.4, 95% CI 8.9-134.6), central nervous system vasculopathy (OR 19.4, 95% CI 5.6-63.4), chronic transfusion therapy (OR 30.6, 95% CI 8.9-122.2), and older age ($P = .03$) were associated with VTE. However, presence of CVC was the only independent risk factor identified on multivariable logistic regression analysis (OR 33.8, 95% CI 8.7-130.9).

Conclusion In our institution, nearly 3% of children with SCD had a history of VTE. CVC is an independent predictor of VTE in children with SCD. *(J Pediatr 2018;■■:■■-■■).*

Epidemiologic studies conducted in Canada and the Netherlands nearly 2 decades ago estimated the incidence of venous thromboembolism (VTE) in children to be 0.07-0.14/10 000 children.[1,2] These studies also identified that >95% of pediatric VTE occurred in the setting of acquired risk factors such as a central venous catheter (CVC), cancer, congenital heart disease, nephrotic syndrome, or inflammatory bowel disease. The last decade, however, has seen a paradigm shift in our understanding of the epidemiology and pathophysiology of pediatric VTE. The incidence of VTE, particularly in hospitalized children, has increased dramatically.[3-5] This increase is most pronounced in tertiary care children's hospitals and may have resulted from improved survival of critically ill children, increased use of CVC, and increased awareness of VTE in children.[3,6] Given the changing landscape of pediatric VTE, it is incumbent on us to re-evaluate risk factors associated with VTE.

Sickle cell disease (SCD) is an autosomal-recessive condition that affects 80 000-100 000 individuals in the US, with an estimated incidence of 1 in 500 in the African American community.[7] SCD has long been recognized to be a hypercoagulable state, in that nearly every component of hemostasis, including platelet function, procoagulant and anticoagulant pathways, and fibrinolysis, are altered in patients with SCD.[8-14] Multiple studies in adults have documented a high prevalence of VTE in patients with SCD.[15-19] Evolving pediatric data, including case reports,[20,21] case series,[22-24] and 1 retrospective cohort study,[25] suggest an increased prevalence of VTE in children with SCD who undergo CVC placement.

Over the last few years, we noted an increase in VTE in children with SCD followed at our tertiary care children's hospital. This prompted us to perform a retrospective chart review, the principal objective of which was to describe the cumulative incidence of VTE in children with SCD and report on the risk factors associated with development of this complication.

BMI	Body mass index
CNS	Central nervous system
CVC	Central venous catheter
HEMORIO	State Institute of Hematology at Rio de Janeiro
NCH	Nationwide Children's Hospital
PAC	Port-a-catheter
PE	Pulmonary embolism
SCD	Sickle cell disease
VTE	Venous thromboembolism

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Methods

Nationwide Children's Hospital's (NCH) electronic enterprise data warehouse was used to identify patients with SCD who received care at NCH between January 1, 2009, and January 31, 2015. January 2009 was chosen as the start date because it coincided with the implementation of electronic medical records at our institution. Eligible patients were defined as patients with all SCD genotypes who were followed in the comprehensive sickle cell program at NCH during the allotted time frame. The patient list obtained through the data warehouse was compared manually with the institutional sickle cell registry to ensure complete enumeration of patients. Manual review of patient's electronic medical records was performed, and data were abstracted with a data collection instrument designed for the study. Information on SCD genotype, sex, body mass index (BMI) or weight-for-length (depending on subject age), history of CVC placement, VTE diagnosis, central nervous system (CNS) vasculopathy, chronic transfusion therapy, and pulmonary hypertension was obtained.

Supplementary data collected for patients with a history of CVC included date of first CVC placement, date/site/type of most recent CVC, and indication for most recent CVC. For patients with a VTE diagnosis, additional data collected included date of VTE diagnosis, thrombophilia testing, acute management, and duration of anticoagulation therapy. For this subcohort, data were also collected on documentation of recent hospitalization, surgery, trauma, and/or prolonged immobilization in the month before VTE diagnosis, and oral contraceptive use. Permission for this study was obtained from the institutional review board.

Study Definitions

Eligible subjects included patients with SCD of all genotypes except hemoglobin S with a hereditary persistence of fetal hemoglobin, aged 0-21 years, who were followed in the comprehensive sickle cell program at our institution between January 1, 2009, and January 31, 2015. Patients who were briefly admitted to NCH for management of acute sickle cell–related complications but were not followed in our comprehensive SCD program were excluded.

A VTE diagnosis was defined as a positive imaging study by ultrasound, computed tomography angiography, or magnetic resonance imaging in a patient with at least 1 documented VTE symptom, including limb pain, swelling, and erythema, chest pain, or dyspnea.[2] CVC included peripherally inserted central catheter, subcutaneous port-a-catheter (PAC), vortex PAC, tunneled central catheter (ie, Broviac), or apheresis catheter.

For children <2 years of age, weight-for-length was obtained, whereas BMI was calculated for children >2 years.[26] Patients were classified as overweight if their BMI percentile for age and sex was between the 85th and 95th percentiles (for patients between 2 and 20 years of age), or a weight-for-length percentile at or above the 95th percentile (for children <2 years of age); and as obese if the BMI percentiles for age and sex were greater than the 95th percentile (for patients between 2 and 20 years of age).[27]

Patients were considered to have CNS vasculopathy if they had a documented abnormal transcranial Doppler based on the Stroke Prevention Trial in Sickle Cell Anemia (STOP) criteria and/or abnormal brain magnetic resonance angiography.[28] A tricuspid regurgitation jet velocity on echocardiogram of >2.5 m/s was considered abnormal and concerning for pulmonary hypertension based on the American Thoracic Society clinical practice guideline for pulmonary hypertension assessment and management.[29] Transfusion therapy was considered chronic in patients receiving packed red blood cell transfusions for >6 continuous months.

Standard thrombophilia testing following a thromboembolic event at our institution includes antiphospholipid antibodies (ie, lupus anticoagulant, IgG and IgM isotype anticardiolipin antibodies, and IgG and IgM beta-2 glycoprotein 1 antibody), factor V Leiden *R506Q* mutation, prothrombin *G20210A* mutation, antithrombin activity, protein C activity, protein S activity, fibrinogen level, factor VIII activity, fasting lipoprotein (a), and homocysteine levels. Thrombophilia testing at our institution is typically performed immediately after VTE diagnosis. If an abnormality is detected, repeat testing is performed at follow-up appointments.

Statistical Analyses

The risk of VTE development was studied using univariate analysis. The first analysis evaluated patients with SCD who had a VTE diagnosis and those that did not. The second analysis compared patients with CVC and VTE and those with CVC but no VTE. Categorical variables were analyzed with χ^2 tests or Fisher exact test and continuous variables with Wilcoxon rank-sum tests. To investigate age as a risk factor for VTE, we compared age at VTE (for patients with a history of thrombosis) with age on January 31, 2015 (for those who did not develop a VTE). Since there is a fairly uniform distribution of age at our institution, using patient age on January 31, 2015 for those who did not develop a VTE should reflect the distribution of age in the general pediatric SCD population. Variables that were found to be significantly associated with VTE on univariate analysis were considered for a multivariable logistic regression model using a stepwise selection method. All calculated *P* values were 2-sided, and *P* values <.05 were considered statistically significant. All analyses were performed with SAS software, version 9.2 (SAS Institute, Cary, North Carolina).

Results

The study cohort included 414 patients (208 males; 206 females) (**Table I**). Mean age of the cohort on January 31, 2015 was 12 years. Study cohort included 215 HbSS, 135 HbSC, 35 HbSβ+, 15 HbSβ0, and 14 other sickle genotypes (7 hemoglobin FS pattern on neonatal screening where the genotype had not yet been confirmed, 3 SK Woolwich, 2 SHope, 1 SC Harlem, and 1 SE). Forty-one patients had a CVC in place during the study period. Twenty-one patients had only 1 CVC placed, and 20

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