Central Nervous System Events in Children with Sickle Cell Disease Presenting Acutely with Headache

Patrick C. Hines, MD, PhD, Therese P. McKnight, CRNP, Wendy Seto, CRNP, and Janet L. Kwiatkowski, MD, MSCE

Objective To determine the frequency of acute care visits and risk factors for central nervous system (CNS) events in children with homozygous sickle cell disease (SCD-SS) with an acute headache.

Study design This is a retrospective cohort study of acute care visits for headache in children with SCD-SS. The prevalence of headache visits, neuroimaging evaluation, and acute CNS events were calculated and clinical and laboratory variables assessed.

Results Headache was the chief complaint in 102 of 2685 acute care visits (3.8%) by children with SCD-SS. Acute CNS events were detected in 6.9% of these visits. Neuroimaging was performed in 42.2% of visits, and acute CNS events were identified in 16.3% of studies. Factors associated with acute CNS events included older age, history of stroke, transient ischemic attack, or seizure, neurologic symptoms, focal neurologic exam findings, and elevated platelets.

Conclusions Acute headache is common in pediatric SCD-SS and more frequently associated with acute CNS events than in the general pediatric population. A history of stroke, transient ischemic attack, seizures, neurologic symptoms, focal neurologic exam, or elevated platelet counts at presentation warrant confirmatory imaging studies. Whether a more limited workup is adequate for other children should be confirmed in a larger, prospective study. *(J Pediatr 2011;159:472-8)*.

Headache is a common complaint among children, especially those with sickle cell disease (SCD). A study by Niebanck et al[1] demonstrated an overall prevalence of frequent headache in children with SCD at a major US medical center of 32.4%, similar to that of all ethnically matched control subjects, but significantly higher in children younger than 13 years. A similar study demonstrated that 24.5% of Nigerian children and adolescents with SCD reported frequent headaches, significantly higher than healthy control subjects in that population.[2] Additionally, acute headache represents 0.5% to 1.2% of total Emergency Department (ED) visits in the general pediatric population.[3-5] Unlike the general pediatric population, children with SCD have a higher baseline risk of central nervous system (CNS) events, such as infarctive stroke, intracranial hemorrhage, or sinovenous thrombosis.[6-8] As a result, clinicians worry that an acute headache in a child with SCD presenting to the ED may foreshadow an acute CNS event. Head computerized tomography (CT) scans and/or a brain magnetic resonance imaging/angiography (MRI/A) are often undertaken to assess the etiology of the headache in this setting. These tests are time-consuming and expensive, and CT scans expose the patient to radiation that will contribute to the patient's cumulative lifetime exposure.[9,10] Outcomes data from headaches presenting to the acute care setting could help guide when a more extensive workup is warranted.

The objectives of this study were to determine the frequency of acute headache visits in children with homozygous sickle cell disease (SCD-SS) compared with previously reported data in the general pediatric population, to determine the rate of neuroimaging in the evaluation of acute headache in SCD-SS, and to determine the prevalence of acute CNS events among children with SCD-SS in an acute care setting with a chief complaint of headache. We also identified historical, clinical, and laboratory factors associated with acute CNS events in this context. We hypothesized that children with a history of stroke or high risk of stroke and those with neurologic symptoms or new neurologic exam finding at presentation would have a greater risk of an acute neurologic event. Clarifying which children with SCD-SS presenting with acute headache are at greatest risk for acute neurologic events could help practitioners utilize appropriate medical resources in the acute care setting more quickly and efficiently.

CNS	Central nervous system
CT	Computed tomography
ED	Emergency Department
HACU	Hematology Acute Care Unit
MRI/A	Magnetic resonance imaging/angiography
SCD	Sickle cell disease
SCD-SS	Homozygous sickle cell disease
TCD	Transcranial Doppler
TIA	Transient ischemic attack

From the Division of Hematology Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia, PA (P.H., T.M., W.S., J.K.); and Division of Pediatric Critical Care Medicine, Children's Hospital of Michigan, Wayne State University School of Medicine, Detroit, MI (P.H.)

Supported in part by the Center of Excellence for Diversity in Health Education and Research at the University of Pennsylvania School of Medicine, Health Resources and Services Administration (grant D34HP04035-13-00). The authors declare no conflicts of interest.

 10.1016/j.jpeds.2011.02.009

Methods

This study was approved by the Institutional Review Board at the Children's Hospital of Philadelphia. Requirement for informed consent was waived. Patients, 5 to 21 years of age, with SCD-SS who presented to the Children's Hospital of Philadelphia (460-bed teaching hospital) between June 1, 2001, and October 31, 2005, with a chief complaint of headache were included. These patients came through either the ED or to the Hematology Acute Care Unit (HACU), an inpatient service designed to facilitate efficient admission and discharge of hematology patients. Children younger than 5 years of age were excluded from this study because young children are less likely to report headache accurately.

The electronic medical record database was queried for visits of all patients with SCD-SS ages 5 to 21 years coming to the ED between June 1, 2001, and October 31, 2005 (1788 visits). The database was queried for "headache" or commonly used variations such as "HA" and "head pain" in the following search fields: "chief complaint," "current impression," from the nurse triage form, and the "discharge diagnosis" documented by the primary ED physician.

A total of 897 visits were also identified by searching the HACU database of SCD-SS patient admissions, ages 5 to 21 years, between June 1, 2001, and October 31, 2005. From this subset, all visits with headache listed in the chief complaint or final diagnosis were identified.

Data were obtained from the ED, HACU, hospital admission, and outpatient clinic charts. Clinical information regarding the acute headache presentation, including location, quality, intensity, and associated symptoms was collected.

The initial vital signs and neurologic exam findings for each visit were obtained from the physician ED note, admission history and physical exam, and the neurology consult note when present.

Information on the patient's history of headaches and family history of headache was obtained from both the outpatient clinic chart and from the acute visit record. All documented admissions from the previous 5 years for each patient were queried for history of headache.

Information on regular transfusion therapy, recent episodic transfusions, and hydroxyurea use as well as indications for these treatments was collected. Information was collected on other medications, particularly opiate and nonopiate pain medications and medications used to treat or prevent headaches.

Complete blood count and reticulocyte count were obtained from the initial laboratory studies for the acute visit. In addition, the complete blood count (and fetal hemoglobin level when available) was obtained from the most recent routine outpatient visit.

All official reports of brain MRI/A and CT scanning were reviewed from the current admission. CT scans obtained within 3 days after presentation and MRI scans obtained within 7 days after presentation were considered to be related to the acute headache event. Transcranial Doppler (TCD) results for both the most recent study and the highest historic time-averaged mean of the maximum velocity were obtained. Studies were analyzed using the highest time-averaged mean of the maximum velocity in the middle cerebral artery, distal internal carotid artery, and bifurcation, bilaterally, according to the Stroke Prevention trial in Sickle Cell Anemia (STOP) criteria.[11]

A history of overt stroke, silent stroke, transient ischemic attack (TIA), or seizures was obtained from the outpatient hematology chart. Prior head CT and MRI/A reports also were reviewed for evidence of past acute CNS events. Documentation of acute intracranial events, such as infarctive stroke, intracranial hemorrhage, or sinovenous thrombosis, for patients presenting with acute headache was obtained from the official interpretation of the CT or MRI/A scan by an attending neuroradiologist. Additionally, a database of all acute neurologic events/strokes in children with SCD was reviewed to ensure that all acute events presenting with headache were captured in our electronic medical record database query. No additional acute headache presentations were identified.

Data Analysis

Descriptive analyses including mean and standard deviation and proportions were used to describe patient characteristics. In exploratory analyses, continuous variables were compared between groups (CNS event and no CNS event) using *t* tests. The independence of categorical variables was assessed using Fisher exact tests. All statistical analyses were performed with Stata 9.0 software (StataCorp, College Station, Texas) and a P value of $< .05$ was considered statistically significant for all analyses.

Results

A total of 102 headache visits were identified in 73 patients with homozygous sickle cell (SCD-SS) disease (1 visit: 54 patients, 2 visits: 13 patients, 3 visits: 2 patients, 4 visits: 4 patients). Patient characteristics are shown in **Table I**. Of the total 102 acute headache visits, 85 acute headache presentations were evaluated initially in the ED, whereas 17 were evaluated initially in our HACU. The 85 ED visits for acute headache represented 4.8% of the total 1788 ED visits by children with SCD-SS during the study period, whereas the 102 total acute care visits represent 3.8% of the total 2685 acute SCD visits (includes ED and HACU visits). Of the 102 visits for acute headache, 60 (58.8%) were exclusively for headache, whereas 42 (41.2%) visits had an accompanying medical complaint of fever or vaso-occlusive pain episode.

Seven of the 102 (6.9%) headache visits were associated with acute intracranial pathology (**Table II**). One child (Patient 4) had two separate acute headache visits associated with CNS events. A brain CT and/or an MRI/A study were performed acutely in 42.2% of the 102 headache