Headache and Migraine in Children with Sickle Cell Disease Are Associated with Lower Hemoglobin and Higher Pain Event Rates But Not Silent Cerebral Infarction

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Objective To identify risk factors for headache and migraine in children with sickle cell disease and test the hypothesis that either or both are independently associated with silent cerebral infarcts.

Study design In this cross-sectional study, we evaluated the health history, laboratory values, and brain magnetic resonance imaging findings of participants with sickle cell disease (hemoglobinSS or hemoglobinSβ°-thalassemia) with no history of overt stroke or seizures. Participants characterized headache severity and quality. Migraine was defined by International Headache Society criteria modified for increased sensitivity in children. Neuroradiology and neurology committees adjudicated the presence of silent cerebral infarction by review of magnetic resonance imaging and standardized examination by pediatric neurologists.

Results The cohort included 872 children (51.1% males), ranging in age from 5 to 15 years (mean age, 9.1 years). Of these children, 317 (36.4%) reported recurrent headaches, and 132 (15.1%) reported migraines. In multivariable logistic regression analyses, both were associated with lower steady-state hemoglobin ($P = .01$ for headaches; $P < .01$ for migraines) and higher pain rate ($P < .01$ for headaches; $P < .01$ for migraines), defined as the number of admissions requiring opioids in the previous 3 years. The presence of silent cerebral infarction was not associated with recurrent headaches or migraines. Only 1.9% (6 of 317) of children with recurrent headaches received medication for headache prophylaxis.

Conclusion Recurrent headaches and migraines are common and undertreated in children with sickle cell disease. Low hemoglobin levels and high pain rates are associated with recurrent headaches and migraines; whereas, silent cerebral infarction is not. *(J Pediatr 2014;164:1175-80)*.

Children with sickle cell disease (SCD) are at risk for neurologic complications, including overt stroke, silent cerebral infarction, cerebral vasculopathy, neurocognitive decline, and seizures. The most common neurologic complaint, headache, occurs in one-quarter to one-third of children with SCD, a higher prevalence than in the general pediatric population.[1-4] There are multiple potential causes of headache in SCD, including tension and migraine headache, as well as causes more specifically related to SCD, including infection, bony infarction,[5,6] idiopathic intracranial hypertension,[7,8] severe anemia,[9] and pain medication overuse or withdrawal.[10,11]

Headache can be a significant contributor to the pain and disability associated with SCD. Children with SCD and headaches have higher functional disability scores and depressive symptoms compared with those without SCD and headaches.[12] In children without SCD, migraines can impair school performance, family activities, and socialization.[4,13] The impact of headaches on quality of life is comparable to that of rheumatologic diseases or cancer.[14]

ACS	Acute chest syndrome
CBF	Cerebral blood flow
Hgb	Hemoglobin
MRI	Magnetic resonance imaging
SCD	Sickle cell disease
SIT	Silent Cerebral Infarct Transfusion
TCD	Transcranial Doppler ultrasound
VIF	Variance inflation factor

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An important clinical question in SCD is whether there is an association between headaches or migraines and cerebral infarcts.[15] In adults without SCD, neuroimaging studies[16-19] and a meta-analysis[20] have revealed an association between migraines and white matter ischemic lesions. Moreover, acute headaches at the time of stroke onset are more prevalent in children than in adults.[21] In contrast, no association between headaches and silent cerebral infarction was demonstrated in previous single-institution studies of children with SCD.[3,22,23]

Given the high prevalence of 2 common neurologic complications in SCD, headaches (25%) and silent cerebral infarction (27% by age 6 years[24] and 37% by age 14 years[25]), we sought to test the hypotheses that recurrent headaches, migraines, or both are independently associated with silent cerebral infarction in children with SCD screened for the Silent Cerebral Infarct Transfusion (SIT) Trial. We also sought to identify risk factors for headaches and migraines in this population.

Methods

The SIT Trial is a multicenter randomized controlled clinical trial examining whether prophylactic blood transfusion therapy in children with SCD and silent cerebral infarction will reduce the rate of subsequent new or progressive silent cerebral infarction or overt stroke.[26,27] Institutional Review Board approval was obtained at all 26 study sites, and informed consent and assent were obtained from guardians and participants. A total of 1176 children with SCD (either homozygous sickle cell anemia or sickle-β^0 thalassemia), aged 5-15 years, and with no previous history of overt stroke were screened by magnetic resonance imaging (MRI). Children with a history of overt stroke or known abnormal transcranial Doppler ultrasound (TCD) velocities indicative of an increased risk of overt stroke were excluded. Children treated with hydroxyurea within the previous 3 months also were excluded, as were children with other neurologic problems, including epilepsy, lead poisoning, neurofibromatosis, and tuberous sclerosis.[26,27] Children found to have silent cerebral infarction were eligible for randomization to receive blood transfusion therapy or observation for 36 months.

The SIT Trial defines a silent cerebral infarction-like lesion as a T2-weighted MRI signal abnormality visible on 2 views (axial and coronal), measuring at least 3 mm in 2 planes, based on the consensus of 2 of 3 study neuroradiologists. These infarct-like lesions are adjudicated as silent or not by the Neurology Committee, based on health history and examination performed by a pediatric neurologist. Silent cerebral infarction is defined as an infarct-like lesion in a child with a normal neurologic examination, or an abnormality on examination that cannot be explained by the location of the lesion.

Headaches and migraines were defined by responses to study questionnaires. Caregivers were asked "Does your child have recurring headaches?" Those responding "yes" were classified as having recurrent headaches, and data were obtained regarding their frequency, duration, location, severity, and other associated symptoms. Migraine was defined as recurrent headaches with a frequency >1 per month, duration >10 minutes, any time of day preference, severity rated as at least some disruption of normal life activities, any localization (including those reported as "nonlocalized, diffuse"), and associated with 1 or more of the following: nausea or vomiting, excessive sensitivity to light or sound, fatigue or malaise, or visual symptoms. These criteria were adapted from the 2004 International Headache Society II criteria for migraine,[28] modified for increased sensitivity for migraine in children.[29-31]

The primary, prespecified covariate analyzed for association with headaches or migraines was the presence or absence of silent cerebral infarction. Other prespecified covariates included age, sex, daytime hemoglobin (Hgb) oxygen saturation, and blood pressure (systolic and diastolic) recorded in the well state within the year before enrollment. Prespecified laboratory covariates included baseline Hgb, white blood cell count, and reticulocyte count in the well state within the year before registration and percent Hgb F levels measured after age 3 years. Additional prespecified covariates included the 3-year pain event rate (defined as the number of events requiring opiate treatment as an inpatient) and 3-year acute chest syndrome (ACS) rate. Both of these event rates were from the 3 years before enrollment. All study data were checked by screening for outliers and missing data. Data points below the 5th or above the 95th percentile were confirmed by the local site or corrected if a discrepancy was identified. Missing data were sought and added when available.

We did not adjust analyses for the use of prophylactic medications for headache, but reviewed the medication lists to identify children receiving medications with potential headache prophylactic activity, regardless of clinical indication for use, including amitriptyline, atenolol, cyproheptadine, divalproex sodium, fluoxetine, gabapentin, imipramine, levetiracetam, mirtazapine, memantine, naldolol, nortriptyline, propranolol, timolol, tizanidine, topiramate, verapamil, and zonisamide.[32,33]

A total of 304 participants were deemed ineligible (**Figure**; available at www.jpeds.com). Of the remaining 872 eligible participants the logistic regression models included a slightly reduced subset of 809 participants after eliminating 63 participants (7.2%) with missing data for 1 or more variables among the prespecified covariates in the full model; listwise exclusion was used for all missing data.

We conducted separate analyses for factors associated with recurrent headaches and those associated with migraines (a subset of the children with recurrent headaches). First, we performed logistic regression modeling with the presence or absence of recurrent headaches (both migraine and nonmigraine) as the dependent variable with the prespecified covariates. We then compared those with migraine headaches with those without recurrent headaches. For these analyses, we constructed a full model with all covariates, then in a reduced model entered covariates with $P < .20$ from the