Published in final edited form as:
J Pediatr. 2014 May ; 164(5): 1175–1180.e1. doi:10.1016/j.jpeds.2014.01.001.

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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Abstract

Objective—To identify risk factors for headache and migraine 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 history, laboratory values, and brain MRI of participants with SCD (HbSS or HbSβ°-thalassemia) without history of overt stroke, or seizures. Participants described headache severity and quality. Migraine was defined by

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The other authors declare no conflicts of interest.

International Headache Society criteria modified for increased sensitivity in children. Neuroradiology and neurology committees adjudicated the presence of silent cerebral infarction by review of MRI and standardized examination by pediatric neurologists.

Results—Of 872 children, 51.1% were male, ages 5-15 (mean 9.1) years, 317 (36.4%) reported recurrent headaches and 132 (15.1%) reported migraine. In multivariable logistic regression analyses, both were associated with lower steady state hemoglobin ($p=0.01$ for headache, $p<0.01$ for migraine) and higher pain rate ($p<0.01$, $p<0.01$), defined as the number of admissions requiring opioids in the past three years. The presence of silent cerebral infarction was not associated with recurrent headache or migraine. Only 1.9% (6 of 317) of children with recurrent headaches received medications for headache prophylaxis.

Conclusions—Recurrent headaches and migraine are common and undertreated in SCD. Low hemoglobin levels and high pain rates are associated with recurrent headaches and migraine, and silent cerebral infarction are not.

Keywords

Sickle cell disease; headache; silent infarction; stroke; children

Children with sickle cell disease (SCD) are at risk of neurological complications, including overt stroke, silent cerebral infarction, cerebral vasculopathy, neurocognitive decline, and seizures. The most common neurological complaint, headache, occurs in one-quarter to one-third of children with SCD, which is higher than in the general pediatric population.[1–4] There are multiple potential causes of headache in SCD, including tension and migraine headaches, as well as causes more specifically related to SCD: 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 of SCD. Children with SCD and headaches have higher functional disability scores and depressive symptoms than those without.[12] In children without SCD, migraine can impair school performance, family activities, and socialization.[4, 13] The impact of headache on quality of life is comparable with that of rheumatologic diseases or cancer.[14]

An important clinical question in SCD is whether there is an association between headache or migraine and cerebral infarcts.[15] In adults without SCD, neuroimaging studies[16–19] and a meta-analysis[20] reveal an association between migraine and white matter ischemic lesions and in addition, acute headaches are more prevalent at the time of stroke onset in children than in adults.[21] In contrast, no association between headache and silent cerebral infarction was demonstrated in prior single-institution studies of children with SCD.[3, 22, 23] Given the high prevalence of two common neurological complications in SCD, headaches (25%) and silent cerebral infarction (27% by 6 years of age[24] and 37% by 14 years of age[25]), we sought to test the hypotheses that either recurrent headache, migraine or both are independently associated with silent cerebral infarction in children with SCD screened for the Silent Infarct Transfusion (SIT) Trial. We also sought to identify risk factors for headache and migraine in this population.

Methods

The SIT Trial is a multi-center randomized controlled clinical trial to determine if 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 strokes.[26, 27] Institutional Review Board approval was obtained at all 26 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, ages 5–15 years with no prior history of overt stroke were screened by MRI. Those with 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 3 months were also excluded, as were children with other neurological problems, including epilepsy, lead poisoning, neurofibromatosis, or 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 two views (axial and coronal), measuring at least 3 mm in two planes, based on the consensus of two of three study neuroradiologists. These infarct-like lesions are adjudicated as silent or not by the Neurology Committee, based on histories and examinations performed by site pediatric neurologists. Silent cerebral infarction is defined as an infarct-like lesion in a patient with a normal neurological examination, or an abnormality on examination that cannot be explained by the location of the lesion.

Headache and migraine were defined by response 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 one 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 International Headache Society-II (2004) criteria for migraine,[28] modified for increased sensitivity for migraine in children.[29–31]

The primary, pre-specified covariate analyzed for association with headache or migraine was the presence or absence of silent cerebral infarction. Other pre-specified covariates included: age, sex, daytime hemoglobin oxygen saturation, and blood pressure (systolic and diastolic) recorded in the well state within the year prior to enrollment. Pre-specified laboratory covariates included baseline hemoglobin, white blood cell (WBC) count, and reticulocyte count in the well state within the year prior to registration and percent hemoglobin F levels measured after 3 years of age. Additional pre-specified 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 prior to 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 subjects were ineligible (Figure; available at www.jpeds.com). Of the remaining 872 eligible subjects, the logistic regression models included a slightly reduced subset of 809 subjects, as 63 (7.2%) had missing data for one or more variables among the pre-specified covariates in the full model (list-wise exclusion was used for all missing data).

Statistical analyses

We performed separate analyses for factors associated with recurrent headache and those associated with migraine (a subset of recurrent headache patients). First, logistic regression modeling with the dependent variable being the presence or absence of recurrent headaches (both migraine and non-migraine) was performed with the pre-specified covariates. The second model compared those with migraine headache with those without any recurrent headache. For these analyses, a full model was constructed with all covariates, then a reduced model entered covariates with $p<0.20$ from the full regression. We considered $p<0.05$ to be statistically significant. There was no study-wide correction for multiple comparisons. Data were analyzed with IBM SPSS Statistics 20.0 (SPSS Inc., 2011).

The presence of multi-colinearity among the covariates was assessed with two methods. First, bivariate correlations were examined between all covariate pairs. No correlation was above a cutoff of ±0.70. Second, the variance inflation factor (VIF) was calculated for each covariate. The VIF indicates to what extent the variance (standard error) of a covariate is inflated by its association with other covariates. A standard cutoff for VIF is 4, and no VIF values were above 1.5, indicating little, if any, multi-colinearity.

Two analyses were done to assess the effect of the eligibility criteria or of missing data using either a t-test or chi square test, as appropriate. First, the 872 subjects who met eligibility criteria were compared with the 304 who did not. Significant ($p < 0.05$) differences were found for age, percent hemoglobin F levels, and reticulocyte count. Subjects not included were younger (8.5 versus 9.1 years), had higher hemoglobin F (14.8% versus 12.1%) and higher reticulocyte count (13.1% versus 11.6%). Second, the 63 subjects who were eligible, but had missing covariates for logistic regression were compared with the 809 subjects included in the main analyses. Significant differences were found only for WBC count with subjects not included having higher values (14,206/mm^3 versus 12,409/mm^3).

Results

Of the initial 1176 children registered for the trial, this analysis includes 872. Mean age was 9.1 years (range 5-15 years), 51.1% were male, and 265 (30.4%) had silent cerebral infarction. Recurrent headaches were reported by 317 (36.4%; 95% CI 33.2 to 39.6%), with migraine in 132 (15.1%; 95% CI 13.0 to 18.0%). Table I presents potential laboratory and clinical risk factors among 872 children with SCD screened by MRI with and without recurrent headache.

Relative Anemia and Higher Pain Rate but not silent cerebral infarction are Associated with Recurrent Headaches and Migraine

For the first model, we compared the 317 children with recurrent headaches with the 555 without headaches, and 809 children had valid data on all variables. In a logistic regression model to predict the presence of recurrent headache, we identified four clinical factors associated with recurrent headache at the level of $p<0.20$: age, hemoglobin concentrations, pain and ACS event rates. Silent cerebral infarction was not associated with the presence of recurrent headaches ($p=0.374$). In the reduced model, which included only these four covariates, only two were significant at $p<0.05$: Lower hemoglobin concentration and higher pain event rate were associated with recurrent headache (Table II).

For the second model, we compared the 132 children with migraine with the 555 without headaches, and 639 children had valid data on all variables. Using logistic regression modeling to predict the presence of migraine, we identified four clinical factors associated with migraine at the level of $p<0.20$: age, hemoglobin concentration, pain event rate, and ACS event rate. Silent cerebral infarction was not associated with the presence of migraine ($p=0.595$). In the reduced model, which included only these four covariates, three were significant at $p<0.05$: Older age, lower hemoglobin concentration and higher pain event rate were associated with migraine (Table II).

Infrequent Pharmacologic Prophylaxis of Recurrent Headaches

Despite the high prevalence of headache and migraine in this group of children (36.4% and 15.1% respectively), fewer than 1% (7/872) were taking medications with the potential for headache prophylaxis. This included one child without headache who was on imipramine, and three with recurrent headaches and three with migraine who were on atenolol (1), cyproheptadine (1), fluoxetine (1), gabapentin (2), or topiramate (1). Only three reported they were taking the medications specifically for headache prophylaxis (cyproheptadine, gabapentin, and topiramate). The others may have been taking these medications for another clinical indication. Thus, fewer than 1.9% (6/317) of the children reporting recurrent headaches were taking headache prophylactic medications.

Discussion

Recurrent headache and migraine are common in children with SCD, and their management is often challenging. In this large, cross-sectional study of children with SCD, more than one-third reported recurrent headache and 15% had migraine. Prior investigations reported a 24% to 76% prevalence of headache in children with SCD, but addressed different

populations with different age ranges and included children who were excluded from SITT: specifically those with overt stroke, seizures, previously known abnormal TCD studies, and those treated with chronic transfusions or hydroxyurea.[2, 3, 12, 34] Risk factors may differ in these more severely affected children.

We did not find evidence to support our hypothesis that headache and migraine were associated with an increased prevalence of silent cerebral infarction. Our strict entry criteria may have biased our study against finding associations with silent cerebral infarction; however, prior studies that did not exclude severely affected SCD patients also failed to identify a relationship between recurrent headaches and silent cerebral infarction or overt stroke.[3, 22] A retrospective study of children with SCD presenting acutely with headache found that a history of stroke, TIA, seizures, neurological symptoms, or focal neurologic findings as well as increased platelet count were associated with central nervous system events detected by neuroimaging.[35] This observation and our findings suggest that the standard recommendations for the evaluation of children with recurrent headaches[36] may also apply to children with SCD. This would mean that imaging of the brain may not be needed for children with recurrent headache without additional risk factors, but imaging should be considered for those with new onset or change in headache pattern, absence of a family history of migraine, abnormal neurologic examination, or seizures.

In this selected population of children with SCD, we found that recurrent headaches and migraine were associated with lower steady state hemoglobin and a higher rate of hospitalization for pain events that required treatment with opioids in the previous three years. The observation that both factors were significantly associated with increased odds of headache and migraine models reinforces their importance. High pain event rate and low hemoglobin are both markers of disease severity in SCD.[37] Therefore, their association could be indirect; headaches could be triggered by pain and stress, worsened in more severe disease. Headaches and migraine are reported to be co-morbidities associated with other chronic pain conditions in children and young adults without SCD.[38] The association of high pain event rate and low hemoglobin with headaches also could be a consequence of withdrawal from or overuse of analgesics or opiates in children with more severe disease.[10, 11, 39] Alternatively, as headache and painful vaso-occlusive events are both common in SCD, they could share a common mechanism directly related to abnormal erythrocytes, vaso-occlusion, tissue ischemia, altered blood flow, or increased blood viscosity. Some headaches could be due to vaso-occlusive events involving the skull bones,[5, 6] which was not assessed in our study. Anemia itself, both acute and chronic, is associated with headache,[9] perhaps related to compensatory changes in cerebral blood flow (CBF). Supporting this possibility are observations that lower hemoglobin levels lead to increased CBF velocities by TCD.[40] Children with SCD and normal neurological evaluation and “vascular headaches” had increased cerebral blood flow compared with those without[34] and TCD velocities were significantly increased in young adults with SCD reporting severe and frequent headaches compared with those with mild or no headaches.[22] A prior analysis of factors associated with frequent headache in SCD[3] found significant associations with vaso-occlusive events (similar to our pain event rate), obstructive sleep apnea symptoms (data we did not collect), as well as with age, which we also found to be associated in the

model investigating migraine. Migraine prevalence increases with age in the general population.[36]

Treatment with prophylactic medications could have biased against finding associations between headaches and other factors; however, few children in this study (< 1.9% of those with headache or migraine) received medications for headache prophylaxis or took medications for another purpose that have been reported to decrease headache or migraine frequency. Thus, use of these medications is unlikely to alter the results of this analysis. We did not inquire about any other prophylactic strategies, such as an exclusion diet. As recurrent headache and migraine are amenable to treatment, it may be possible to decrease some of the overall pain burden on these children by treating their headaches with prophylactic medication or exclusion diet.

Our study is limited by the careful pre-screening of patients and the exclusion of those with prior overt stroke, seizures, or treatment for severe disease with chronic transfusions or hydroxyurea. Thus, we may have excluded many of the most severely affected, in whom other significant associations might be observed. In addition, magnetic resonance angiography was only done electively, so we could not address the contribution of vasculopathy to headache or migraine. Further, our pain definition includes any inpatient hospitalization with administration of opioids over the three years prior to enrollment in the study. Thus, this pain event rate could also include severe headaches, thereby increasing the observed degree of association between the frequency of painful events and headache in our study.

This study addressed the relationship, epidemiology, treatment and risk factors for headaches and migraines in children with SCA. We demonstrated a high prevalence of recurrent headache (36%) and migraine (15%), but found no association of recurrent headache or migraine with silent cerebral infarction. Thus, the presence of isolated recurrent headache or migraine in neurologically normal children with SCD may not require additional evaluation with imaging studies. The occurrence of new severe headaches or headaches associated with neurologic signs or symptoms warrants further investigation.[35] Both recurrent headache and migraine were associated with a lower hemoglobin concentration and a higher pain event rate. Recurrent headaches are disabling and impair quality of life, but very few children in this study received any prophylactic therapy for recurrent headaches. Optimal strategies need to be determined for this common complication in children with SCA, as currently none exist.

Acknowledgments

The authors wish to thank Linda Hynan, PhD (University of Texas Southwestern Medical Center), and Cindy Terrill, CCRP, CCRM (Washington University School of Medicine; supported by the SIT Trial),for their assistance with this project.

Supported by the National Institutes of Health (<<>>). M.D. and C.Q. were supported by the North and Central Texas Clinical and Translational Science Initiative from the NIH (KL2 RR024983), and M.D. is supported by the Doris Duke Charitable Foundation and First American Real Estate Information Services, Inc. J.C. has received an honorarium and travel expenses in the past and presently receives salary support through Johns Hopkins for providing consultative advice to Adventrx Pharmaceuticals regarding a proposed clinical trial of an agent for treating vaso-occlusive crisis in sickle cell disease. That company had no input into the design, analysis, interpretation, or content of this study and did not influence the decision to submit this manuscript. J.C. is an

inventor and a named party on a patent and licensing agreement to ImmunArray for a panel of brain biomarkers for the detection of brain injury. The contents of this article represent the personal opinion of the authors and should not be construed as the opinion or position of the National Institutes of Health or its affiliates.

Abbreviations

ACS	acute chest syndrome
BP	blood pressure
Hgb	hemoglobin
MRI	magnetic resonance imaging
SCD	sickle cell disease
SIT	Silent Infarct Transfusion Trial
TCD	transcranial Doppler ultrasound
VIF	variance inflation factor
WBC	white blood cell

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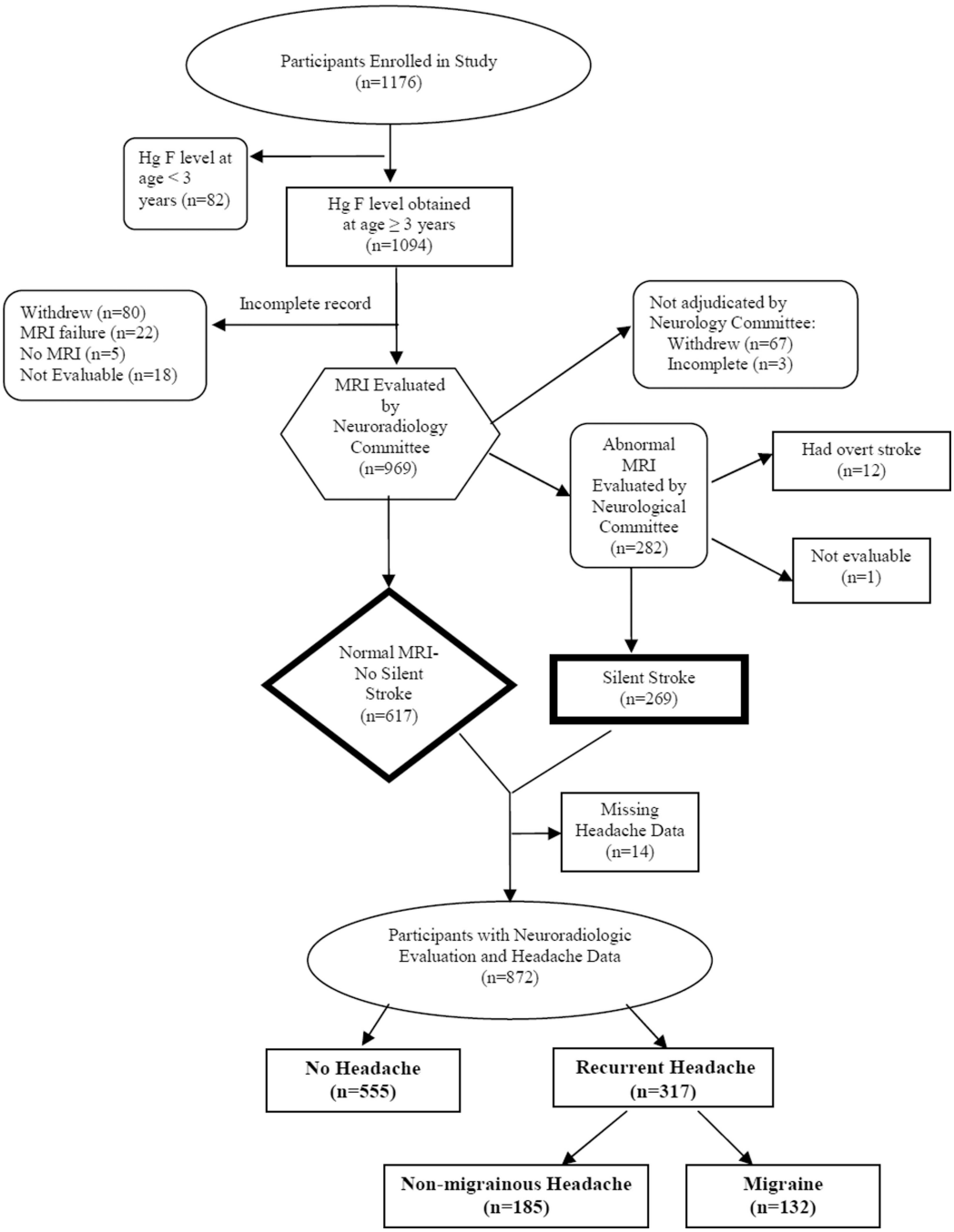

Figure 1.

Flow diagram for participants in SIT Trial with data analyzed for assessment of risk factors for headache

Table 1

Potential laboratory and clinical risk factors among 872 children with SCD screened by MRI with and without recurrent headache

	Recurrent Headache				
	No (n= 555)		Yes (n= 317)*		Sig. (2-tailed)
Measures	**N**	**Mean**	**N**	**Mean**	
Age at Registration (y)	555	8.97	317	9.39	.014
Sex (% male)	555	50.6%	317	52.1%	.687
Steady state hgb (g/dl)	554	8.22	317	8.05	.029
Hemoglobin type F (%)	555	12.54	313	11.34	.086
Systolic BP (mmHg)	550	107.54	316	108.86	.103
Diastolic BP (mmHg)	550	60.45	315	60.43	.982
Steady state WBC (count/μL)	548	12644.1	315	12307.1	.399
Baseline O2 saturation (%)	534	96.56	305	96.14	.048
3-year ACS rate (events/y)	553	0.12	313	0.18	.007
3-year pain rate (events/y)	553	0.56	311	0.74	.004
Silent Cerebral Infarct (%)	555	29.0%	317	32.8%	.241

BP=Blood Pressure WBC= White Blood Cell Hgb= hemoglobin ACS=Acute Chest Syndrome

*Among those with migraine (n=132), a subset of those with recurring headaches, differences from those with no recurrent headache are consistent with those in the larger group of all those with recurrent headache.

Table 2

Final logistic regression models predicting recurrent and migraine headache, using only four biologically plausible covariates from screening models with $p<0.2$.

Model predicting recurrent headaches compared with those with no headache (n=809)					
Measure	B	Std. Error	P Value	Odds Ratio	95% C.I.
Age	0.06	0.03	0.06	1.06	(1.00 – 1.12)
Hemoglobin	−0.18	0.07	0.01	0.84	(0.73 – 0.96)
Pain event rate	0.25	0.09	<0.01	1.28	(1.08 – 1.52)
ACS event rate	0.48	0.26	0.06	1.62	(0.98 – 2.68)
Model predicting migraine headaches compared with those with no headache (n=639)					
Age	0.09	0.04	0.04	1.09	(1.00 – 1.19)
Hemoglobin	−0.38	0.10	<0.01	0.69	(0.56 – 0.84)
Pain event rate	0.40	0.11	<0.01	1.49	(1.20 – 1.85)
ACS event rate	0.51	0.32	0.11	1.67	(0.90 – 3.10)

ACS= Acute chest syndrome

Hemoglobin level and pain event rate were associated with recurrent headaches and migraines.