pediatric stroke

# Headache in Sickle Cell Disease: A Scoping Review

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**Abstract**

Objectives: Headaches are thought to be common neurological manifestations of sickle cell disease (SCD). We reviewed headaches in SCD to determine their prevalence, characteristics, and knowledge gaps and to identify new directions in clinical research.

Methods: We carried out a scoping review and followed guidance from the Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for Scoping Reviews (PRISMA-ScR). Our team evaluated 1414 articles based on a formal search process conducted across the MEDLINE (PubMed), Cochrane Library (Wiley), Embase (Elsevier) and Scopus (Elsevier) databases. We selected information on the prevalence and associated features of headaches in SCD, excluding secondary causes of headaches and studies dealing with treatments for SCD. Abstract review was managed using the Rayyan system.

Results: 30 articles were included for final review. They generally employed small sample sizes, disparate methods, and retrospective analyses. The overall prevalence of headaches was 34% though a few larger studies showed prevalence of headaches in SCD ranging from 47% to 60%. Headache severity varied and could have features of migraine headaches, however, information on headache characteristics was limited.

Discussion: There are gaps in our knowledge about the prevalence, characteristics, and underlying mechanisms of headaches in SCD. Since headaches in SCD are common and sometimes severe in intensity, clinicians must distinguish between those that are primary, and those secondary to a serious underlying cause. Knowledge gaps in characterizing headaches in SCD need to be bridged. Clinical trials in SCD provide an opportunity to study pre- and post-intervention prevalence, characteristics, and mechanism(s) of the headache. Well-designed large observational studies provide similar opportunities to better define headaches in SCD.

## Introduction

Neurologic manifestations are common in patients with sickle cell disease (SCD) and may include ischemic or hemorrhagic stroke, cognitive impairment, and epilepsy. [1, 2] Pain, a common complaint associated with SCD [3] may present as headache. [4-7] Whereas headache in SCD is believed to be common, potentially debilitating, and life-altering [8], the prevalence and characteristic features of headache, such as the quality of pain, provoking factors, region of the head affected, timing, and severity are not well described. We have undertaken a scoping review of headaches in SCD to better understand the prevalence and clinical features and to identify knowledge gaps and new directions in clinical research. We have followed the research and reporting methods guidance for the Preferred Reporting Items for Systematic reviews and Meta-analyses Extension for Scoping Reviews (PRISMA-ScR). [9]

## Methods

Eligibility Criteria

The team developed and followed a protocol of pre-determined screening eligibility criteria. The protocol was uploaded prior to screening to Northwestern University's digital repository PRISM [available at: https://prism.northwestern.edu/records/epdhg-dd611]. This scoping review included studies of human participants found in case reports, case series, clinical trials, surveys, and observational studies. Study participants could be adults or children and must have a diagnosis of SCD. Subjects with a diagnosis of sickle cell trait, sickle C, or sickle thalassemia were excluded from the review unless the study had a majority of participants with a diagnosis of SCD. The search for articles was restricted to those published in English language journals or those translated into English, and there was no limitation on publication date.

Information Sources and Search Strategy

The following information sources were utilized: MEDLINE (PubMed), Cochrane Library (Wiley), Embase (Elsevier) and Scopus (Elsevier). A formal search strategy was developed by a Northwestern University Galter Health Sciences Library research librarian and study collaborator, AW, and the lead investigators, AJ and PBG. The search combined database-specific controlled vocabulary and title/abstract key terms to capture records that discussed SCD and headache. Databases were searched from inception to 14 July 2023. All results captured by the search were downloaded and deduplicated using citation management software (EndNote) and uploaded by AW to the online abstract software (Rayyan) for blind review.

The search terms used in this scoping review for all databases are included in a supplemental file.

Study Selection and Data Collection

The abstract review team included 2 senior neurologists of which one was a headache specialist, 2 senior neurology residents, 1 neurology fellow, and 1 research assistant. There were 3 teams of 2 reviewers each. Prior to the formal grading of abstracts for selection in the scoping review, all reviewers attended a study orientation led by investigators AJ and PBG, who introduced the aims of the study and reviewed the study methods. At this time abstract reviewers were introduced to the methods of a scoping review and instructed on how to use the Rayyan system for grading abstracts. After completion of the orientation, all reviewers graded 100 abstracts in a pilot round to test their collective understanding of the study inclusion criteria, methodology, and techniques. After the pilot round, each abstract

reviewer from a team of two independently scored approximately 1/3 of the total of 1,414 abstracts selected for review. Once each of the three groups of 2 reviewers completed their abstract reviews and scoring, a central adjudication panel consisting of investigators AJ, YC, and PBG served to reconcile discordance between team members in abstract scoring within each team of two to determine whether an abstract would or would not be included. All abstracts were reviewed and scored within the Rayyan system.

The focus of our inclusion criteria was on prevalence of headache in SCD and headache characteristics. During the formal abstract review, studies were prioritized for selection in the final scoping review evidence database if they contained information relating to the "PQRST" of headache. The "PQRST" of pain characteristics for headache in SCD were operationally defined as follows:

P (provocation): aggravating and relieving factors.

Q (quality): dull, throbbing, achy, sharp, or other description.

R (region): descriptive location in the cranium where pain occurred such as a unilateral, bilateral, frontal, parietal, or other area of the cranium.

S (severity): ordinal pain scale of 1 to 10 (1= least pain, 10= most severe pain), or pain scored as being mild, moderate, or severe, or some other scoring system.

T (timing): headache pattern (e.g., number of headaches per week or per month), and other timing descriptors (e.g., constant, intermittent, or other description).

Our inclusion criteria *did not aim to identify literature on the incidence of headache in SCD*. Instead, we prioritized studies to be selected as those which included information on the *prevalence of headache in SCD*. Further, our aim was to characterize the headache prevalence and features in SCD when headache was thought to be primary in origin, but not those related to secondary causes of headache in SCD. Secondary headaches were defined as headaches with causes outside of SCD. For example, headaches relating to causes such as infection, neoplasm, and stroke or those relating to drug or other interventions (e.g., as an adverse event) were excluded from the review as secondary causes of headache.

Data Management and Analysis

Information about prevalence of headache in SCD and "PQRST" headache characteristics were abstracted from the eligible texts by using a pre-tested worksheet and were entered into a Microsoft Excel database for tracking. The scoping review was largely a descriptive study and as such categorical variables were displayed as percentages and continuous variables as means. Tables and figures were utilized when appropriate to compare results.

Statistical Analysis

The meta-analysis was performed with STATA.[10] The heterogeneity between studies was evaluated to highlight additional knowledge gaps resulting from low comparability between studies. The confidence interval for study-specific prevalence was computed using normal theory methods with $\alpha = 0.05$.

In relation to the accompanying forest plot (Figure 2), the pooled prevalence of headache was estimated by the random effects model using the Freeman-Tukey double arcsine transformations of proportions. For pooling, the transformed proportions and corresponding standard errors were used in the calculation of pooled variance for estimating weights. Point estimation of headache prevalence was included in the forest plot, in which square size shows that the weight of every study and lines on both sides indicate confidence intervals of 95%. The presence of heterogeneity between studies was evaluated using $I^2$ statistics. A random effects model was considered assuming that prevalence data vary between population characteristics. In random effects models we take into account two sources of error, within and between study error. Freeman-Tukey transformed proportions are preferred over logit transformed proportions in a meta-analysis of pooled proportion estimates. The width of the confidence intervals (CI) is observed as weight,[1] with wider CI having lower weights versus higher weights for narrower CI. Tests of heterogeneity, the $I^2$ statistic, should be cautiously inferred in prevalence data. This statistic describes the variability between proportions between each study expressed as a percentage. Heterogeneity is expected in prevalence estimates due to differences in time, place, and population characteristics. Therefore, high $I^2$ statistics in context of a proportional meta-analysis does not necessarily mean inconsistency in data.

**Results**

PRISMA Diagram for Identification of Studies via Databases and Registries

*Figure 1* includes information about the number of records identified for study and those screened, deemed eligible or excluded, and the final number of full texts included in the review. Overall, 1414 abstracts were identified by our search, and after review by our abstract grading teams, 84 were selected for final review. Of the 84 texts, 10 were excluded as duplicates, 23 for insufficient information, 20 as secondary causes of headache, and 1 as a non-English text. This left 30 final full texts for inclusion in the study.

Prevalence of Headache in Sickle Cell Disease

*Table 1* includes a summary of key background information from select studies listed in chronological order such as author and year of publication, country in which the study was carried out, study participant age, whether study participants were undergoing treatment for SCD, type of study design, and SCD genotype. In addition, *Table 1* includes information on the prevalence of headaches by the study to answer our first key study question about

the prevalence of headaches in SCD. Of the 30 studies that we identified, there were 28 such studies with information on headache prevalence. [1,4,7,8,11-34] Prevalence ranged from as low as 5% to as high as 77% (*Table 1*). The wide variation in the findings was not unexpected as there were disparate study designs (e.g., case series, case-control studies, population surveys), ascertainment methods, and participant ages, and variability in the total number of study participants in each study (e.g., as low as 20 [28] to as high as 2145 participants[8)]. If one considers only studies with over 1000 study participants, the prevalence of headaches ranged from 47% to 60%.[8, 31, 33] The overall prevalence of headache in SCD was 34% with the 95% confidence interval equal to 25 – 43% in a pooled sample from 28 studies. The heterogeneity among the 28 studies was 98.41% (*Figure 2*).

Characteristics of Headache in Sickle Cell Disease: Pattern, Severity, and Timing

*Table 2* includes information on the pattern, pain severity, and timing of headache episodes that occurred in patients with SCD. There were 13 such studies. [4,7,8,13,16,18,20,22,26,30,34-36] Headache pattern in SCD was described as frequent (>1 time/week or >1 time but <15 times/month), recurrent, or severe and frequent. Again, and as expected, there was a range of variation in the pattern of headache based on sample size, participant age, disparate study methods, and the primary purpose of the study. Overall, 7 of the studies had fewer than 100 study participants with as few as 42, and the prevalence in this group ranged from as low as 11.7% to as high as 76.2% (*Table 2*). When the information was available, the severity of headache ranged from mild to moderate in 1 study in 80.4% [36], was severe or the worst headache imaginable in 54% [8] in 1 study but included a wide range of severity in some of the other studies (*Table 2*). Only 1 study more precisely described the timing of the headache which lasted for as little as 30 minutes to up to several days, with a mean of 5 hours. [13]

Additional Characteristics of Headache in Sickle Cell Disease: Location (region), Associated Symptoms, Pain Quality, and Provoking Factors

The accompanying *histograms* include information on the location (region of the cranium), associated symptoms (e.g., nausea, vomiting, photophobia), quality (e.g., throbbing, pressure-like), and provoking factors (e.g., dehydration, physical activity, menstruation-related) for headache in SCD. [7,11,13,18,20,26,36] Concerning the headache location (Figure 3a), the headache was more commonly bilateral and located in the frontal regions than unilateral or bitemporal. In relation to associated symptoms (*Figure 3b*), photo- and phonophobia were common, though other symptoms might be present (e.g., nausea, vomiting, lightheadedness, difficulty thinking). For the quality of pain (*Figure 4a*), it was commonly described as throbbing or non-throbbing but could also be pressure-like or "constant" in character. Finally, factors that provoked pain (*Figure 4b*) were variable and included physical activity or exercise, or other factors.

**Discussion**

Our scoping review suggests that many of the studies on the prevalence of headaches in SCD are case series or other types of retrospective study designs that feature relatively small sample sizes, non-uniform data collection, and disparate study methods. This is exemplified by *Figure 2*, where the forest plot shows that the heterogeneity amongst studies was high, at $I^2$ = 98.41%. The overall prevalence statistic, calculated with smaller and larger sample sizes (the latter being given more weight in the calculation), was 34%. The studies with larger sample sizes and prospective data collection indicate that headache prevalence in SCD may be as high as about 47%-60%.[8,31,33] In general the more abundant, smaller sample size studies had a dilutional effect on the overall estimate of the prevalence of headache. In addition, there was limited information in relation to the following associated headache characteristics: 1. Pattern of headache (e.g., described as "frequent" or "recurrent") or number of headache occurrences (e.g., "</=1 time/month to up to <15/month"); 2. Severity which was described as being mild to severe; and 3. Duration which varied from 30 minutes to several days based on only 1 relatively small study.[13] Furthermore, there was somewhat limited information on headache quality which was described as throbbing (or non-throbbing) and bilateral with predisposition for the frontal lobes, and the number of provoking factors such as physical activity, or other factors. Based on the available but limited descriptive characteristics of the headaches in SCD (e.g., throbbing nature) and provoking or associated factors (e.g., physical activity, nausea, and vomiting), headaches in SCD may share characteristics of migraine headaches.[37]

A major aim of a scoping review is to identify gaps in the field and provide a direction forward for potential new research initiatives.[9] Overall, our scoping review findings suggest that the prevalence of headaches in SCD has been based largely on smaller-scale studies of a retrospective nature consisting of disparate methods and in need of a more robust methodology to characterize the prevalence of headaches with some exceptions.[8,33]

The clinical details of headache characterization (i.e., "PQRST" of head pain) were often missing. Thus, there is room for additional studies whereby headache prevalence and character in SCD is more comprehensively and carefully studied. This might be accomplished in clinical trials conducted in children and adults with SCD as such studies may have a reasonable sample size and can capture the pattern and other characteristics of headaches before and after an SCD treatment intervention. In addition, such a study may provide an opportunity to understand better the mechanism(s) of headaches in SCD and potential treatments based on the treatment being assessed in a clinical trial of SCD. Furthermore, and according to a subgroup analysis of other concomitant treatments that might be administered in SCD participants (e.g., antidepressants), additional data on preventing or treating headaches in SCD might be garnered. Alternatively, additional well-designed large scale observational studies could be useful in defining the prevalence and characteristics of headache in SCD.

Headaches in SCD may represent a manifestation of underlying SCD pathophysiology or could be associated with a serious secondary cause of headache such as stroke, central nervous system infection, or another malady associated with SCD.[38,39] Headaches in SCD could present like migraine or tension headaches, and recurrence of headaches in children or adolescents with SCD may be common (estimated range: 24.0-43.9%). Clinicians may not be able to distinguish between a primary headache, such as migraine or tension headache, in an SCD patient, and a headache from a serious underlying secondary cause. Thus, it may be helpful for clinicians to be familiar with 'red flags' for headaches due to secondary causes.[40] 'Red flags' suggestive of underlying secondary causes of headache include features such as but not limited to systemic symptoms (e.g., fever or night sweats especially in an immunocompromised person), accompanying neurological symptoms or focal signs, sudden and severe headache onset (e.g., thunderclap headache), occurrence of headache in a person who generally does not experience headache, progressive worsening of headache (i.e., headache is not episodic), presence of papilledema, and change in headache severity with change in position (e.g., when coughing, straining, or with a Valsalva maneuver). Based on screening examination for 'red flag' clinical manifestations, such features should trigger the clinician to consider appropriate laboratory testing, neuroimaging (e.g., MRI head), and neurological consultation. As stroke is common in SCD, a sudden severe headache, especially one with focal neurological symptoms and/or signs, for example, should lead to an appropriate diagnostic workup to rule out stroke.

Of interest, in 1 study lower hemoglobin and higher headache intensity were associated with recurrent headache and migraine in SCD but not with silent cerebral infarction.[4] Whereas relatively higher transcranial doppler (TCD) velocities have been associated with migraine-like frequent and severe headaches in SCD when compared to milder headaches [7], high TCD velocities are also a well-known marker of risk for stroke in SCD. Of interest, the rate of use of prophylactic medication for recurrent headaches in children with SCD may be woefully low (1.9%) despite its common occurrence.[4]

Our study has several limitations. As anticipated with a scoping review, we dealt with many studies of small sample sizes, disparate study methodologies, and needing more information on headache characteristics, making it difficult to compare results between studies. In addition, based on the previously mentioned gaps, there were limitations about generalizability of our findings as additional rigorous studies are needed to accurately characterize prevalence and headache features in SCD. Furthermore, although a large proportion of the study participants in the studies we chose to include in this scoping review were homozygous for SCD, there were some cases included in the studies with variants such as sickle C. Also, migraine is a common headache type in the population, but based on the available information in our scoping review we were not able to determine if the mechanism of the underlying headaches in our study was secondary to SCD, some other factor such as migraine, or a combination of factors. For example, CT and MRI brain imaging were not available in larger studies, likely due to cost considerations and participant willingness to

enroll in such a study. Finally, we did not aim to characterize headache prevalence and associated features with commonly used SCD treatments or experimental interventions, or general treatments for headaches. These latter topics may be studied in the context of future clinical trials or other large-scale studies.

**Conclusions**

We have identified gaps in knowledge regarding the prevalence and clinical features of headaches in SCD. Additional rigorous study of headache prevalence and clinical characteristics in general SCD clinical trials may provide a useful setting and efficient mechanism to collect such information and advance our knowledge about the mechanism(s) and treatment of headaches in SCD. Well-designed large scale observational studies may provide similar opportunities.

**Study Funding:** None.

**Disclosures:** Dr. Gorelick serves on a data safety and monitoring board for a trial of a monoclonal antibody in the prevention of migraine headache.

**Tables:** attached as separate files

**Figures**: attached as separate files

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