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Headache Symptoms in Pediatric Sickle Cell Patients

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Summary

The purposes of this study were to determine the characteristics of headaches in children with sickle cell disease (SCD) and to assess the relationship between headache symptoms and children's physical and emotional status. A detailed headache questionnaire using International Classification of Headache Disorders (ICHD-2) criteria was mailed to a cohort (n = 50) of children with SCD, ages 9 to 17 years. Respondents also completed measures of functional disability and psychological distress. Headaches had occurred over the previous 3-month period in 76.2% of the patients. Frequent headaches were common, occurring greater than once a week in 31.2% of children. Average pain severity was reported as moderate on a 0-to-10 scale (mean = 5.8). Duration of headaches ranged from 30 minutes to several days, with a mean of 5 hours. Based on ICHD-2 criteria, 43.8% of children had headache symptoms consistent with migraines, 6.2% with migraine with aura, and 50.0% with tension-type headaches. Children with symptoms of migraine had significantly greater functional disability compared with children with symptoms of tension-type headaches ($P < 0.01$). Further studies to determine the characteristics and determinants of headaches experienced in SCD patients will help maximize treatment of headaches and enhance daily functioning in these patients.

Keywords

sickle cell disease; headache; migraine; children

Clinical manifestations of sickle cell disease (SCD) vary by frequency and severity and may include episodes of severe vaso-occlusive pain, serious infections, cerebrovascular accidents, and exacerbations of anemia, among others.1,2 Headache has been described as a frequent symptom in SCD that is often attributable to anemia or cerebrovascular disease. Sources of headaches in SCD patients may include acute painful episodes involving the head, headache secondary to central nervous system involvement, and comorbid migraine or tension headache. For example, in a small case series, headache was a presenting symptom in children later diagnosed with pseudotumor cerebri.3 Moreover, Salman4 has described

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the clinical coexistence of migraine and sickle cell disorders. However, to our knowledge, there have not yet been any published reports of the characteristics of headaches that occur in children with SCD. Identification of the type of headache symptoms experienced by children with SCD is important for optimizing their medical management. For example, there are no data yet available on the value of migraine prophylactics on managing migraine headaches in children with SCD and whether special considerations are needed in using vasoconstrictive agents with these children.

In addition, the occurrence of headache may represent an important consequence of SCD, which if left untreated has significant implications for children's daily functioning and quality of life. Frequent vaso-occlusive pain has been associated with decrements in the quality of life of youth with SCD.5 Otherwise healthy children and adolescents who suffer recurrent headaches also experience reductions in their daily functioning (eg, missed school, limitations in social and athletic activities), increased emotional distress, and poorer quality of life.6 Thus, the comorbid existence of SCD and recurrent headache has the potential to lead to further declines in children's daily functioning and health status.

Therefore, the goals of the present study were to provide preliminary data on the frequency, severity, and characteristics of headaches and to assess the relationship between headache symptoms and children's physical and emotional status in a cohort of children with SCD. These data could help lead to earlier diagnosis and treatment of headaches, maximize therapy, and enhance the quality of life in this patient population.

METHODS

Subject Enrollment

Eligible study participants included a convenience sample of 50 school-aged children at the Sickle Cell Anemia Center at Rainbow Babies and Children's Hospital who were participating in a larger study about pain and disability in children with chronic health conditions. Children were recruited into the study when they were well (eg, were not experiencing acute febrile illnesses or vaso-occlusive pain episodes). All families of these patients were contacted and asked to participate. Of the 50 families contacted for participation, 42 school-aged children (range 9–17 years, mean = 13.4) were enrolled, representing 84% of eligible patients. Fifty percent were female, and all study participants identified themselves as African-American. The majority of children (83.3%) were diagnosed with homozygous sickle hemoglobin (SS), whereas 9.5% had a diagnosis of double heterozygous sickle hemoglobin and hemoglobin C (SC) and 7.2% were diagnosed with sickle beta+ thalassemia (Table 1).

Procedures

After Institutional Review Board approval, a packet of questionnaires was mailed to participants. Parents and children completed these questionnaires either through telephone interview administration with return via post mailing or during a regularly scheduled sickle cell clinic visit. Consent was obtained from parents and assent was obtained from all child participants. The packet contained a headache questionnaire, a measure of functional disability, and a measure of psychological distress. The child's hematologist completed a provider form recording the patient's disease classification, severity, and complications.

Participants responded as to whether headaches were present or absent for the child in the preceding 3-month period. If headaches were present, participants then described specific headache characteristics based on the child's typical headaches. From these responses, headaches were classified via computer queries as migraine, migraine with aura, or tension headache using the second edition of the International Classification of Headache Disorders

(ICHD-2)7 criteria. For example, the criteria for migraine require that a throbbing or pulsatile headache of moderate to severe intensity be present with exacerbation with physical activity. Associated symptoms are required, including nausea or vomiting (or both), or light and sound sensitivity. The criteria allow for parental inference of these associated symptoms. In addition, there are several criteria modifications specific to children, including an expanded duration of headache attacks from between 1 and 72 hours, and localization of headache to bifrontal or bitemporal pain.

Measures

Demographic information was collected from the children's caregivers, including the child's age, race, gender, family income level, parental marital status, and parental work status. The child's hematologist completed a provider assessment form that included disease classification, history of complications, and treatment details, including medications and transfusions. The same provider rated his or her perception of the child's illness severity on a 10-cm visual analog scale with anchors of "not severe" to "extremely severe."

Parents completed a headache questionnaire that has been used in previous studies to characterize headaches in children.8 This detailed questionnaire consists of items regarding headache location, pain quality, severity, duration, associated symptoms, and frequency of the headaches. From the responses, ICHD-2 criteria for migraine, migraine with aura, and tension-type headache can be classified. Due to concerns about children's ability to read and understand the questionnaire, parents served as the primary respondent, completing the questionnaire together with their child present. This is similar to the administration described by Hershey et al,8 in which children and parents completed the headache questionnaire together.

The Revised Child Anxiety and Depression Scale9 was used to assess self-report of depressive symptoms in children. The measure consists of 47 items corresponding to several DSM-IV anxiety disorders along with major depression. Each item is rated on a 4-point scale from "never" to "always," and children respond how often each of the items happen. Items are then scored from 0 to 3; higher scores indicate greater frequency of the symptom. T-scores are calculated based on the child's gender and grade in school. For the purposes of the present study, the major depressive disorder (MDD) subscale was used to assess depressive symptoms. Good internal consistency has previously been reported for this subscale (alpha = 0.76). In receiver operator characteristic analyses, a cutoff score on the MDD subscale of 11 optimized sensitivity and specificity for the prediction of MDD in a clinical sample.10

The Functional Disability Inventory11 was used to examine the degree of limitation experienced by children in 15 daily activities occurring in school, home, recreation, and social interactions. Sample items include doing chores, being at school all day, and playing sports. Children rate their difficulty performing each activity over the past few days on a 5-point scale ranging from "0, no trouble" to "4, impossible." Total scores range from 0 to 60, with higher scores indicating greater functional disability.

Statistical Analyses

All data analyses were conducted using the SPSS Version 12.0.12 Headache frequency, duration, severity, pain quality, location, associated symptoms, and medications used were examined with descriptive statistics. The computer database was screened with queries designed to match the ICHD-2 criteria for migraine, migraine with aura, and tension-type headaches to classify children's headaches. Independent sample *t* tests and chi-square analyses were performed to compare children with headache to children without headache

on demographic and illness-related parameters (number and type of disease-related complications). One-way analyses of variance with Bonferroni post-hoc comparisons were conducted to examine mean differences in children's physical and emotional functioning by headache diagnosis. Specifically, three groups of children were compared (children with symptoms of migraine with or without aura, children with symptoms of tension-type headache, and children with no reported headache) on depressive symptoms and functional disability. An independent samples *t* test compared children with symptoms of migraine with or without aura to children with symptoms of tension-type headache on school absences due to headache.

RESULTS

Headache Incidence and Clinical Features

Of the 42 respondents, 76.2% (n = 32) had experienced at least one headache in the past 3 months. On average, children experienced their first headache approximately 3 years previously (mean = 2.77 years, SD = 1.85). Current headache frequency was less than once per month for 22% of children, one to three times per month for 47%, and once a week or greater for 31%. Average pain severity was reported in the moderate range (mean 5.8 on a 0-to-10 scale). Reported duration of headaches ranged from 30 minutes to several days (mean = 5 hours). Children reportedly missed an average of 2.0 school days per semester because of headaches. Children primarily experienced throbbing, bilateral headaches (Table 2). Many children experienced associated symptoms of photophobia, phonophobia, and lightheadedness.

Ninety-seven percent of children used analgesics to manage their headaches (80% used acetaminophen or ibuprofen, 25% used acetaminophen with codeine). No patients were taking migraine prophylactics. None of the patients had their headache symptoms evaluated or treated by a neurologist.

Headache Classification

Headaches were classified using ICHD-2 criteria for migraine, migraine with aura, and tension-type headache. Of the children with reported headache, 43.8% (n = 14) had symptoms consistent with migraine headache, 6.2% (n = 2) had symptoms consistent with migraine with aura, and 50% (n = 16) had symptoms consistent with tension-type headache. In our total sample, the prevalence of migraine headache in children ages 9 to 14 years was 33% (25% migraine and 8% migraine with aura); in adolescents ages 15 to 17 years it was 47% (all migraine without aura). In our total sample, the prevalence of tension-type headache in children ages 9 to 14 years was 36%; in adolescents ages 15 to 17 years it was 42%.

Comparison of Children With and Without Headache on Demographics and Illness Variables

As shown in Table 1, there were no significant differences in age, gender, sickle cell diagnosis, or provider-reported disease severity in children with headache versus without headache. Furthermore, chi-square analyses did not reveal any significant differences in the number or type of disease-related complications, including acute chest syndrome, pneumonia, stroke, documented small vessel infarction, severe anemia, gallstones or extreme jaundice, priapism, sepsis, osteomyelitis, and pancreatitis, between children with or without headache.

Effect of Headache Symptoms on Physical and Emotional Functioning

Approximately 42% of children reported a functional disability score of 10 or above (mean = 10.34, range 0–35), which is considered the moderate to high range of disability.13 The majority of children reported depressive symptoms in the average range (T score mean = 49.33, range 30–75). However, approximately 26% of children reported a raw score equal to or above 11 on the MDD subscale, which is considered the cutoff score for prediction of MDD.10

A significant effect for headache diagnosis was found on children's functional disability, $F(2,37) = 5.05$, $P = 0.01$. Post-hoc comparisons showed that children with symptoms of migraine with or without aura had significantly greater functional disability compared with children with symptoms of tension-type headache or with no headache (Table 3). Similarly, there was a significant effect for headache diagnosis on children's depressive symptoms, $F(2,39) = 3.18$, $P = 0.05$. Post-hoc comparisons revealed a trend where children with symptoms of migraine with or without aura had more depressive symptoms compared with children without headaches ($P = 0.08$). There was also a trend for children with symptoms of migraine with or without aura to miss more school days due to headache than children with symptoms of tension-type headache, $t(30) = 1.93$, $P = 0.06$.

DISCUSSION

Our study showed that recurrent headaches are common in children with SCD: over 75% of children sampled had had at least one headache in the previous 3 months. Most of these children were experiencing frequent headaches: 47% at least once a month and 31% weekly. In epidemiologic studies of the general pediatric population, prevalence rates for recurrent headaches are estimated at 25.3 per 1,000.14 Migraine, the most common type of headache, is estimated to occur in 10.6% of children ages 5 to 15 years old15 and in 28% of adolescents between 15 and 19 years old.16 In an urban sample in the greater Cleveland area (the same location from which the sickle cell sample was recruited), 8.6% of children ages 5 to 13 years met IHS criteria for migraine.17 Episodic tension-type headache has been estimated at a prevalence rate of 12.2% in school-aged children, with 15.2% of these children having a history of weekly headache.18 In comparison, 33% of 9-to 14-year-olds and 47% of 15- to 17-year-olds in our sample reported symptoms consistent with migraine and 36% of 9-to 14-year-olds and 42% of 15- to 17-year-olds reported symptoms consistent with tension-type headache. Thus, the prevalence of recurrent headache appears to be similar to but higher in the SCD patient population, particularly for migraine, compared with children and adolescents in the general population.

We also found that, as expected, the occurrence of headache in children with SCD affected their physical and psychological functioning, particularly for children with symptoms consistent with migraine headaches. Children with migraine symptoms with or without aura had significantly greater functional disability than children with tension-type headaches or no headaches. There was a trend for children with migraine headaches with or without aura to have more depressive symptoms than children without headaches. Last, there was a trend for children with migraine headaches with or without aura to have missed more school days than children with tension-type headaches. A similar impact of migraine on children's physical and psychological functioning and school attendance has been described in otherwise healthy samples,19,20 highlighting the need to consider management strategies for the comorbidity of migraine and pediatric SCD.

Most of the children in our sample were self-medicating their headaches using nonprescription analgesics or acetaminophen with codeine. None of our patients were taking migraine prophylactics, nor had they been evaluated or treated by a neurologist. Future

research is clearly needed to evaluate the effectiveness of analgesics and migraine-specific medications for treatment of headache in children with SCD.

A few limitations of the study should be considered when interpreting our findings. One limitation is that our description of headache symptoms relied entirely on retrospective self-report and may have introduced recall bias. Prospective measurement of headache symptoms (eg, using electronic pain diaries) has been shown to be a reliable and valid measure of recurrent pain in children with other chronic health conditions.21 Moreover, the participants did not have a clinical diagnosis of headache established by a neurologist. Future studies are needed that incorporate clinical impressions from a neurologist in the diagnosis and workup of headache symptoms. Last, the study used a small sample of children at one sickle cell clinic and did not include a local comparison group of healthy children. Therefore, the generalizability of our findings to other SCD patients is unknown. We are also unable to directly compare the prevalence of headache symptoms in our sickle cell sample to healthy same-age children. Future comparison studies are needed to address the question of whether the prevalence of migraine headaches is greater in children with SCD compared with healthy children.

This is the first report, to our knowledge, that examines the characteristics of headaches in children with SCD and their impact on children's physical and psychological functioning. Our finding that comorbid headache is not only common but is also typically not evaluated or treated by a neurologist in children with SCD is important and highlights the need for further research on this topic. Clinicians may want to consider routine assessment of headache complaints in their pediatric patients with SCD to identify treatment needs and potentially develop management plans to improve the overall quality of life for children with SCD.

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TABLE 1

Demographics

Characteristics	Total Sample (n = 42)	Headache (n = 32)	No Headaches (n = 10)
Age (yrs), mean ± SD	13.36 ± 1.34	13.69 ± 1.32	12.30 ± 1.36
Gender			
Male	21 (50%)	15 (46.9%)	6 (60%)
Female	21 (50%)	17 (53.1%)	4 (40%)
Sickle hemoglobinopathy			
SS disease	35 (83.3%)	26 (81.3%)	9 (90%)
SC disease	4 (9.5%)	3 (9.4%)	1 (10%)
Sickle beta+ thalassemia	3 (7.1%)	3 (9.4%)	0 (0%)
Disease severity (0–10)			
Mean ± SD	3.92 ± 1.67	3.50 ± 1.59	5.27 ± 1.84

TABLE 2

Headache Characteristics

	Total (n = 32)
Frequency (days/mo), mean ± SD	5.14 ± 3.08
Duration (hr), mean ± SD	
Mean of shortest	2.88 ± 4.46
Mean of longest	15.08 ± 16.09
Mean of average	5.07 ± 5.01
Average severity (0–10), mean ± SD	5.77 ± 0.95
Pain quality	
Throbbing	14 (43.8%)
Pressure	5 (15.6%)
Constant	1 (3.1%)
Location	
Unilateral	7 (21.9%)
Bilateral	13 (40.6%)
Frontal	15 (46.9%)
Bitemporal	5 (15.6%)
Associated symptoms	
Nausea	9 (28.1%)
Vomiting	7 (21.9%)
Photophobia	13 (40.6%)
Phonophobia	14 (43.8%)
Lightheadedness	13 (40.6%)
Anorexia	4 (12.5%)
Fatigue	8 (25.0%)
Hard to think	6 (18.8%)
Medications	
Ibuprofen	15 (46.9%)
Acetaminophen	10 (31.2%)
Aspirin	3 (9.4%)
Acetaminophen with codeine	8 (25.0%)
Naproxen	8 (25.0%)

TABLE 3

Impact of Headaches on Physical and Emotional Functioning

	Migraine ± Aura (n = 16)	Tension (n = 16)	No Headache (n = 10)
Functional disability	15.81 ± 4.69[a]	7.12 ± 4.89[b]	4.71 ± 3.58[c]
Depressive symptoms	55.0 ± 4.78[a]	46.88 ± 6.34[a]	44.20 ± 6.62[c]
School absences due to headache*	2.88 ± 1.54	1.13 ± 0.96	NA

Data are given as mean ± SD. Means in the same row that do not share superscripts are significantly different at $P < 0.01$.

*$P = 0.06$.