Sickle Cell Disease Association with Premature Suture Fusion in Young Children

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Background: Sickle cell disease (SCD) leads to the formation of an atypical hemoglobin tetramer with reduced capacity to carry oxygen. Although correlation between SCD and craniosynostosis (CS) has been mentioned, these are mostly small series or case reports. This article aimed to study any correlation between these entities in a large pediatric population.

Methods: We retrospectively reviewed head CT scans of SCD patients from 0 to 8 years of age who required a CT for issues unrelated to their head shape between 2012 and 2020. We excluded patients with known history of CS or any CS-related syndrome, hydrocephalus, shunt placement, history of cranial surgery, or any reported cerebral or cranial shape abnormality.

Results: Ninety-four CT scans were analyzed. The mean age at imaging was 4.48 ± 2.30 years. CS prevalence in this cohort was 19.1%. Analysis between independent variables and patients with +CS showed that SCD-associated vasculopathy, first-degree relatives with SCD, and the use of folic acid had a statistically significant association with CS development.

Conclusions: Approximately 20% of pediatric patients with SCD developed CS. This association was higher in those patients who had a family history of SCD, used folic acid, and had SCD-associated vasculopathy. While the clinical impact of these findings needs more extensive study, centers that manage patients with SCD should be aware of the relatively high concordance of these diagnoses, vigilantly monitor head shape and growth parameters, and understand the potential risks associated with unidentified or untreated CS. (Plast Reconstr Surg Glob Open 2022;10:e4620; doi: 10.1097/GOX.0000000000004620; Published online 27 October 2022.)

INTRODUCTION

Craniosynostosis (CS) is defined as the partial or complete premature/nonphysiologic closure of one or more cranial sutures before full brain development.1 This condition is usually detected prenatally and results in a characteristic change in cranial shape that typically signals its presence in infancy.2 Early surgical intervention involves normalizing cranial shape and volume and is almost invariably recommended to limit possible adverse effects on brain growth, intracranial pressure (ICP), and neurodevelopment.1,5-7 Most studies support early identification and treatment to ensuring the best clinical outcomes,8 yet delayed diagnosis and treatment can occur in subtle forms of CS or those that occur in the late postnatal period and create minimal or no change in cranial form.9-11 Such fusions have been documented in progressive postnatal pansynostosis,12,13 normocephalic scaphocephaly,9,11,14 shunt-related CS,15 and rickets.1,16-18

Sickle cell disease (SCD) results from a point mutation in the beta-globin chain of hemoglobin. Hemoglobin A, the primary oxygen carrier in normal red blood cells (RBCs), is a tetramer comprising two alpha and two beta globin chains. Sickle cell mutation leads to the formation of an atypical hemoglobin tetramer that has an abnormal and reduced capacity to carry oxygen, giving RBCs an inflexible, sickle-like structure.19,20 The rigid RBCs can adhere to the endothelium of the vasculature, resulting in vaso-occlusive crises that may lead to ischemia and infarction.21 Although skeletal alterations such as bone infarction and marrow hyperplasia have been described in patients with SCD,19,22 CS secondary to SCD has only been briefly mentioned by some authors.23 The purpose of this investigation is to determine the prevalence of CS in a larger cohort of children with SCD and identify any potential variables correlated with the development of CS in this population.

Disclosure: The authors have no financial interest to declare in relation to the content of this article.
METHODS

Following institutional review board approval, we retrospectively reviewed head CT scans of patients from 0 to 8 years of age with a confirmed diagnosis of SCD and who were seen in our tertiary care institution between 2012 and 2020 for issues unrelated to their head shape. Patients with known history of CS or CS-related syndrome, hydrocephalus, shunt placement, cranial surgery, or a radiology report with cerebral and/or overt cranial abnormality were excluded. All scans were reviewed individually by two craniofacial surgeons to identify the presence and severity of premature-fused sutures. Patient demographics, family history of neurodevelopmental disease, CS, SCD or sickle cell trait, chronic use of hydroxyurea, penicillin, folic acid, past medical history of blood transfusions, age at the time of CT scan, and radiologist report were recorded as covariates. Among the patients with CS, percentage of patency was measured relative to the total length of the suture, and cranial index (CI) was calculated using the CT axial images.

Statistical Analysis

Baseline patient characteristics were presented descriptively and summarized as mean with standard deviation for continuous data and frequencies with percentages for categorical data. The demographic and clinical variables were compared between patients with (+CS) and without (~CS) evidence of CS using unpaired t test for continuous data, and χ2 test and/or Fisher exact test (if any of the expected cell size <5) for binary and categorical data. To explore the possible association between these variables and the development of CS, we performed an adjusted analysis using a multivariable Firth logistic regression model. In the multivariable Firth logistic regression model, we only included the variables that were significant at the level 10% (P < 0.10) in the univariate analysis as well as the predefined demographic variables age and gender. All statistical tests were two-sided and performed at the 0.05 level of significance. Statistical analysis was performed using R statistical software, version 4.0.3. 24

RESULTS

A total of 94 patients met the inclusion criteria, and their respective head CT scans were analyzed. The mean age at imaging was 4.48±2.30 years. Nearly all patients were African American (96.8%), and the majority were male (54.3%); 9.6% of the patients (n = 9) were preterm. Of the total population, 76 (80.9%) patients had a diagnosis of homozygous disease (HbSS), while heterozygous HbS with another defective globin gene such as HbC (HbSC) or beta-thalassemia (HbSBThal) was seen in 11 (11.7%) and seven (7.4%) patients, respectively.

CS was observed in 18 patients, for a prevalence of 19.1% (95% CI, 11.8–28.6). All affected patients were African American, and the majority were female (55.6%). All the cases showed fusion of the sagittal suture, with a percentage of fusion ranging from 65% to 100%, and one patient had concomitant bilateral coronal suture closure.

Patients were grouped by age using 12-month interval ranges, and the prevalence of CS divided by age group is summarized in Table 1 and Figure 1. CS was documented by the radiologist in only one (5.6%) patient, and none of the patients had a CI value below 0.7 (mean 0.798±0.06). Figure 2A shows axial CT scan images of a patient with SCD showing patency of the sagittal suture at age 4 years with complete sagittal fusion 27 months later.

Comparing patients with and without CS, significantly more patients in the +CS group had a family history of the neurodevelopmental disease (44.4% versus 17.1%), at least one first-degree relative with SCD (44.4% versus 14.5%), and received folic acid (88.9% versus 53.9%) as part of their SCD chronic treatment. All other demographic and clinical variables were not statistically different between the two groups (Table 2).

Further adjusted analysis between independent variables and patients with +CS showed that sickle cell vasculopathy, first-degree relatives with SCD, and the use of folic acid had a statistically significant association with CS development. The odds of developing CS were eight times higher in patients with SCD-associated vasculopathy (odds ratio, 8.2; 95% CI, 1.4–51.8; P = 0.019) and almost 14 times higher in patients who had a first-degree relative with SCD (odds ratio, 13.6; 95% CI, 2.9–85.4; P = 0.002). Patients who received folic acid medication had seven times higher odds of developing CS (odds ratio, 7.1; 95% CI, 1.4–58.3; P = 0.002). Furthermore, a family history of neurodevelopmental disease (odds ratio, 2.5) was found to be associated with increased CS development, but this association did not reach statistical significance (Table 3).

| Age Category | No. CS | Prevalence (%) |
|--------------|--------|----------------|
| <1 y         | 0/9    | 0.0            |
| 1-2 y        | 1/8    | 12.5           |
| 2-3 y        | 2/12   | 16.7           |
| 3-4 y        | 3/8    | 37.5           |
| 4-5 y        | 0/12   | 0.0            |
| 5-6 y        | 3/13   | 23.1           |
| 6-7 y        | 5/17   | 29.4           |
| 7-8 y        | 4/15   | 26.7           |

Table 1. Prevalence of CS in Patients with SCD Divided by Age Group

Takeaways

Question: What is the prevalence of craniosynostosis (CS) in children with sickle cell disease (SCD)?

Findings: CS prevalence in the studied cohort was 19.1%. Multivariable Firth logistic regression showed that independent variables, such as SCD-associated vasculopathy, first-degree relatives with SCD, and the use of folic acid, had a statistically significant association with CS development in patients with CS.

Meaning: The high prevalence of CS in children with SCD requires clinicians who manage these patients to remain vigilant, monitor head shape and growth parameters, and understand the potential risks associated with unidentified or untreated CS.
This is the first study to document and characterize the prevalence of CS in a large population of patients with SCD. We found that nearly 20% of children under 8 years of age with SCD have fusion of the sagittal suture, a prevalence that is markedly higher than reported in the general population; and that all patients had a normal CI. The timing of normal sagittal suture closure was previously thought to occur well after skeletal maturity, but more recent studies show that a small but not insignificant percentage of normal children develop asymptomatic fusion at a much younger age. We retrospectively evaluated 331 head CT scans of healthy patients under 5 years of age who visited the emergency department for concerns unrelated to their head shape. A total of 3.3% were found to have sagittal synostosis, although less than 20% were reported in the formal radiographic report. We further validated these results using the CT scans of a larger cohort of 870 normal children aged 0–71 months and found an even higher prevalence of sagittal suture fusion, 4.71% of the subjects. As in our previous report, the prevalence of fusion rose during the first 2 years and remained stable at over 7% for the remaining age ranges. In addition, a statistically significant association between family history of neurodevelopmental disease and premature fusion of the sagittal suture was encountered.
groups have reported similar results. A recent study by Corbett-Wilkinson et al examining the timing of normal suture fusion in subjects aged 0–21 found that 6% had partial or complete fusion of the sagittal suture with most patients having a normal head shape. Using these prevalence studies as a baseline, the 19.1% prevalence of CS in young children with SCD reported in the present study is three to five times what would be expected in the normal population. Against this statistical backdrop, it is unclear why 0% of children between 4 and 5 years of age had sagittal fusion, but given the higher than expected prevalence of 37.5% in the preceding 3–4-year age group and the consistency in prevalence in all subsequent age groups, we suspect this reflects mere sampling variability.

The reasons why these patients are at such a high risk of developing CS, and the implications of these findings are unclear. The etiology of CS is complex and heterogeneous, and a variety of causes have been reported in the literature. These include failure of mechanisms to maintain suture patency, a wide variety of genetic mutations, alterations in growth factor molecular signaling pathways, and even intrauterine environmental changes. Secondary CS due to preexisting mechanical forces, metabolic conditions, or medication exposure has also been described. For instance, an association between ventriculoperitoneal shunt placement and premature suture fusion was reported by our research group in 2019. In this study, nearly half of the subjects (48.8%) were found to develop CS after shunt placement. Medication exposure has also been correlated to the development of postnatal CS. Bérard et al extensively studied the association between maternal exposure to antidepressants during the first trimester of pregnancy and craniofacial malformations. This group showed that the use of sertraline and citalopram was associated with an increased risk of CS in the fetus. Zarella et al also reported a series of cases showing premature fusion of the cranial sutures after fetal methotrexate exposure. Furthermore, this study reports

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### Table 2. Demographic and Baseline Patient Characteristics by CS Status

| Demographic and Baseline Characteristics | Overall (N = 94) | No CS (~CS) (N = 76) | CS (~CS) (N = 18) | P  |
|-----------------------------------------|-----------------|---------------------|-----------------|----|
| Age at CT scan (mo), mean (SD)          | 4.5 (2.3)       | 4.3 (2.3)           | 5.4 (2.0)       | 0.064 |
| Age category, n (%)                     |                 |                     |                 |    |
| <1 y                                    | 9 (9.6)         | 9 (11.8)            | 0 (0.0)         |    |
| 1–2 y                                   | 8 (8.5)         | 7 (9.2)             | 1 (5.6)         |    |
| 3–4 y                                   | 12 (12.8)       | 10 (13.2)           | 2 (11.1)        |    |
| 5–6 y                                   | 8 (8.5)         | 5 (6.6)             | 3 (16.7)        |    |
| 6–7 y                                   | 12 (12.8)       | 12 (15.8)           | 0 (0.0)         | 0.266 |
| 7–9 y                                   | 15 (16.0)       | 15 (14.5)           | 4 (22.2)        |    |
| Men, n (%)                              | 51 (54.3)       | 43 (56.6)           | 8 (44.4)        | 0.353 |
| Race, n (%)                             |                 |                     |                 |    |
| African American                        | 91 (96.8)       | 73 (96.1)           | 15 (100)        | 0.392 |
| Hispanic/Latino                         | 3 (3.2)         | 3 (3.9)             | 0 (0.0)         |    |
| Preterm, n (%)                          | 9 (9.6)         | 8 (10.5)            | 1 (5.6)         | 0.519 |
| Hemoglobin type, n (%)                  |                 |                     |                 |    |
| HbSS                                    | 76 (80.9)       | 59 (77.6)           | 17 (94.4)       |    |
| HbSc                                    | 11 (11.7)       | 10 (13.2)           | 1 (5.6)         | 0.236 |
| HbS/βthal                               | 7 (7.4)         | 7 (9.2)             | 0 (0.0)         |    |
| Developmental delay, n (%)              | 3 (3.2)         | 3 (3.9)             | 0 (0.0)         | 0.392 |
| Seizures, n (%)                         | 17 (18.1)       | 13 (17.1)           | 4 (22.2)        | 0.612 |
| Autism, n (%)                           | 2 (2.1)         | 2 (2.6)             | 0 (0.0)         | 0.487 |
| Headaches/migraine, n (%)               | 31 (33.0)       | 24 (31.6)           | 7 (38.9)        | 0.553 |
| G6PDH deficiency, n (%)                 | 4 (4.3)         | 4 (5.3)             | 0 (0.0)         | 0.320 |
| Sickle cell vasculopathy, n (%)         | 10 (10.6)       | 6 (7.9)             | 4 (22.2)        | 0.076 |
| Spleen sequestration, n (%)             | 17 (18.1)       | 14 (18.4)           | 3 (16.7)        | 0.862 |
| Penicillin prophylaxis, n (%)           | 89 (94.7)       | 71 (93.4)           | 18 (100.0)      | 0.263 |
| Folic acid, n (%)                       | 57 (60.6)       | 41 (53.9)           | 16 (88.9)       | 0.006 |
| Blood transfusions, n (%)               | 35 (37.2)       | 26 (34.2)           | 9 (50.0)        | 0.213 |
| Hydroxyurea, n (%)                      | 17 (18.1)       | 12 (15.8)           | 5 (27.8)        | 0.235 |
| Iron chelating agent, n (%)             | 3 (3.2)         | 2 (2.6)             | 1 (5.6)         | 0.526 |
| Bone marrow transplant, n (%)           | 8 (8.5)         | 7 (9.2)             | 1 (5.6)         | 0.617 |
| First degree relative with sickle cell trait, n (%) | 79 (84.0)       | 66 (86.8)           | 13 (72.2)       | 0.128 |
| First degree relative with SCD, n (%)   | 19 (20.2)       | 11 (14.5)           | 8 (44.4)        | 0.004 |
| Family history of neurodevelopmental disease, n (%) | 21 (22.3)       | 13 (17.1)           | 8 (44.4)        | 0.012 |
| Any stroke/ACV before CT scans, n (%)   | 22 (23.4)       | 16 (21.1)           | 6 (33.3)        | 0.269 |

*P* values were obtained from unpaired *t* test for continuous data and chi-square/Fisher exact test for categorical data.

### Table 3. Adjusted Analysis to Explore the Association between the Variables and CS

| Variables                                      | Adjusted Odds Ratio (95% CI) | P   |
|------------------------------------------------|-----------------------------|-----|
| Age at CT scan (mo)                            | 1.4 (0.9–2.1)               | 0.118 |
| Female gender                                  | 0.5 (0.1–1.9)               | 0.301 |
| Sickle cell vasculopathy                       | 8.2 (1.4–51.8)              | 0.019 |
| Folic acid                                     | 7.1 (1.4–58.3)              | 0.033 |
| First-degree relative with SCD                 | 13.6 (2.9–85.4)             | 0.002 |
| Family history of neurodevelopmental disease   | 2.5 (0.6–10.1)              | 0.290 |
that children who received folic acid as part of their chronic treatment had seven times higher odds of developing CS, which contrasts to what has been reported in the literature throughout the years, in which folic acid has not been significantly associated with CS development.\textsuperscript{5,13} Metabolic conditions have been studied as well. Oussoren et al\textsuperscript{17} studied the correlation between mucopolysaccharidosis and CS development in a pediatric cohort of 47 patients. Premature fusion was observed in almost 80% of their cohort, some of which showed symptomatic elevated ICP. Hypophosphatemic rickets have also been reported to cause secondary CS.\textsuperscript{1,16–18} Vega et al\textsuperscript{17} studied the clinical course of patients with CS secondary to hypophosphatemic rickets and their work showed a 60% prevalence of sagittal synostosis. Furthermore, of the patients who required formal ICP monitoring, 75% showed elevated ICP levels. Even though hematologic conditions, such as sickle cell anemia, thalassemia, polycythemia vera, or congenital hemolytic icterus, have been mentioned as possible etiologies of secondary CS,\textsuperscript{21} to our knowledge, no study has confirmed a statistically significant association between these entities. This is the first study to report and analyze the correlation between SCD and CS, showing higher prevalence of premature suture fusion in young children with sickle cell anemia.

Asymptomatic sickle cell trait results from inheriting both a faulty and a normal beta-globin gene (Hb\textsubscript{SA}). In these cases, no clinical symptoms are observed. Symptomatic SCD arises when both inherited beta globin genes are mutated. SCD can be either homozygous Hb\textsubscript{S} (HbSS) or heterozygous HbS with another defective globin gene, such as HbC (HbSC) or beta-thalassemia (HbSBThal).\textsuperscript{19,20} Anemia is a chief clinical manifestation of SCD, as sickled RBCs have a significantly higher turnover than their disc-shaped counterparts. The deformed RBCs can adhere to the endothelium of the vasculature, causing vaso-occlusive crises that may lead to ischemia and subsequent infarction.\textsuperscript{21} Moreover, SCD pathophysiology leads to vasculopathic dysfunction, which increases the risk of stroke, priapism, and pulmonary hypertension in these patients.\textsuperscript{22} Skeletal complications of SCD are common sequelae of vaso-obclusion and anemia. Infants with SCD have an increased RBC production causing bone marrow hyperplasia, which leads to expansion of medullary spaces triggering cortical bone thinning, bone infarction, and altered skeletal growth.\textsuperscript{19,22,23,25,26} This pathophysiology may account for an important contributing factor, which may cause SCD patients to be more susceptible to developing CS and is bolstered by our finding that patients with SCD-associated vasculopathy were eight times more likely to develop CS. Further studies that include a bigger cohort of patients are needed to validate this theory.

Adverse sequelae of a delayed CS diagnosis and management may include brain growth restriction, elevated ICP, and negative neurodevelopmental outcomes.\textsuperscript{1,5,13} Hayenga et al\textsuperscript{1} suggested that children with unrepaired CS had high rates of developmental delay and headaches, the latter subjectively improving after surgical management. Mild developmental delays not attributable to any other sociodemographic factor were discovered by Speltz et al\textsuperscript{6} in children younger than 2 years of age with single-suture CS. This author also encountered that children with single-suture CS had lower average scores in IQ and math than their healthy controls.\textsuperscript{41} Moreover, Tandon et al\textsuperscript{42} recently reported a 32% prevalence of speech-language concerns in children with single-suture CS, which was not associated with morphologic severity of sagittal or metopic fusion. These adverse sequelae were described in children with more conventional forms of CS that are present at birth and manifest with characteristic changes in cranial shape. It is still unclear whether these concerns hold true for children like those in our SCD +CS cohort who developed temporally abnormal fusions later in infancy or childhood and, consequently, did not incur significant changes in cranial shape or volume. While we offer no guidance on this question now, it is important to identify, evaluate, and follow these patients to ensure that any adverse effects are addressed. Unfortunately, the lack of cranial shape changes in this population makes phenotypic diagnosis nearly impossible. Head CT imaging in patients with SCD may be performed for concerns related to stroke, mental status changes, and recurrent headache. When CT is ordered, neuroradiologists should actively look for CS in these patients, even if the reason for their head CT scan is completely unrelated to their head shape. It is impractical and perhaps detrimental to perform routine screening CT imaging on every child with SCD, but there are certain risk factors for developing CS that may allow clinicians to identify higher risk patients. For example, our results showed that patients with a first-degree relative with SCD (OR, 13.6), with SCD-associated vasculopathy (OR, 8.2), and who received folic acid medication (OR, 7) were at a notable increased risk of developing CS. Screening CT in patients with one or more of these risk factors may be reasonable.

Limitations of this article include its retrospective and cross-sectional nature, leading to an impossibility to predict the exact age at which the premature fusions occurred. Furthermore, the retrospective nature of this study limits the clinical follow-up and evaluation to what was documented in the medical record of affected patients. Because almost none of the patients were identified as having CS on their radiology reports, it is unclear whether the clinical teams who manage these patients would ever consider CS as a cause for symptoms that could easily be attributed to the SCD, such as headache or neurodevelopmental problems. We did not identify any patients in the +CS cohort in our chart review who had a diagnosis of elevated ICP, but in an older child, this can be asymptomatic and could easily go undetected.

**CONCLUSIONS**

The high prevalence of CS in children with SCD (19.1%) requires clinicians who manage these patients to remain vigilant and to consider this in the differential diagnosis for certain neurological symptoms. Those patients with a family history of SCD, who used folic acid as part of their chronic treatment, and with SCD-associated vasculopathy are at much higher risk of developing CS, and screening CT may be indicated. The
clinical relevance and impact of these findings is unclear and requires more study; however, centers that manage children with SCD should establish protocols for identification, evaluation, and follow-up of those who develop CS early in life.

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