

# Cranial epidural hematomas: A case series and literature review of this rare complication associated with sickle cell disease

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## Abstract

**Background:** Patients with sickle cell disease (SCD) may experience many complications of the central nervous system (CNS) including stroke, silent cerebral infarcts, and neuropsychological deficits. Cranial epidural hematoma is a rare but potentially serious complication.

**Procedure:** Case series of cranial epidural hematomas in children with SCD from three different institutions is considered, along with a literature review of cranial epidural hematomas in this population.

**Results:** Seven children with SCD with cranial epidural hematomas were identified from three different institutions. All patients were male and the age at presentation ranged from 10 to 18 years. Two patients presented with headache (28.6%), while the rest had no neurologic symptoms at presentation. Four patients required urgent neurosurgical intervention (57.1%) and one patient died (14.3%). A literature review identified 18 additional cases of cranial epidural hematomas in children with SCD. Of these, treatment ranged from supportive care to neurosurgical intervention. Twelve patients completely recovered (66.7%), one patient had long-term cognitive impairment (5.6%), and four patients died (22.2%). Combined with our data, cranial epidural hematomas have a mortality rate of 20.0%.

**Conclusions:** Although rare, cranial epidural hematoma can be fatal and should be considered in patients with acute neurological symptoms.

## KEYWORDS

epidural hematoma, pediatric, sickle cell disease, stroke

## 1 | INTRODUCTION

Sickle cell disease (SCD) affects approximately 119,000 adults and children in the United States and can lead to numerous clinical complications.<sup>1,2</sup> A significant proportion of SCD morbidity and mortality results from central nervous system (CNS) complications, mainly strokes, both infarctive and hemorrhagic.<sup>3,4</sup> In addition to symptomatic stroke, silent cerebral infarcts are found in at least 30% of the children with SCD-SS.<sup>5,6</sup> The morbidity and mortality of overt stroke

and silent infarcts have led to multiple clinical trials assessing the appropriate monitoring and treatment.<sup>6-8</sup>

In addition to infarctive and hemorrhagic strokes, extradural hematomas can occur in children with SCD. However, relative to available data on strokes in SCD, there is a paucity of literature describing the epidemiology and outcomes for extradural hemorrhagic events.<sup>9-23</sup> A case series of seven patients who developed cranial epidural hematomas from three different pediatric sickle cell centers is presented. In addition, a literature review was performed to provide a comprehensive analysis of all reported cases. As cranial epidural hematomas may require immediate intervention, the objective of this case series and literature review was to better understand the clinical presentation, interventions, and outcomes for this rare occurrence in SCD.

Abbreviations: CNS, central nervous system; CSSCD, Cooperative Study of Sickle Cell Disease; CT, computerized tomography; Hb, hemoglobin; MRI, magnetic resonance imaging; SCD, sickle cell disease

## 2 | METHODS

An Institutional Review Board exempt retrospective review of the charts of seven children with SCD known to have cranial epidural hematomas from three different sickle cell centers was conducted. The time frame for case ascertainment varied by site: Children's Hospital of Philadelphia (2013–2015), Children's National Health System (2005–2014), and University of Alabama at Birmingham (2005–2015). Data were abstracted from chart review by the local hematologist using a standardized data collection form. Data included basic demographic information (age, race, gender, sickle cell genotype), laboratory data (complete blood count, hemoglobin [Hb] electrophoresis, and coagulation studies), treatments, neuroimaging studies, hospital course, and clinical outcomes.

A literature review was performed using PubMed with several combinations of the following key terms, "sickle cell, pediatric, intracranial hematoma, and epidural hematoma" to further identify children with SCD reported to have cranial epidural hematomas. Eighteen cases were identified in the English language that reported cranial epidural hematomas in patients with SCD aged 0–21 years. Based upon these criteria, no literature cases were excluded. Mortality rate was calculated using any death that resulted within 14 days of the cranial epidural hematoma, the time frame used in the Cooperative Study of Sickle Cell Disease (CSSCD).<sup>4</sup>

## 3 | RESULTS

Eight children with SCD who had cranial epidural hematomas were identified at the three different institutions. One, 2-year-old male with known head trauma was then excluded from the analysis. A summary of the seven cases, including laboratory values is shown in Table 1, with additional details described below.

Patient 1 is a 10-year-old with SCD-SS on hydroxyurea admitted with bilateral upper and lower extremity pain crisis. He was initially treated with nonsteroidal anti-inflammatory medications (NSAIDs) and opiates. During day 1 of hospitalization, he developed acute chest syndrome and antibiotics were initiated. At that time, his Hb fell from 6.3 g/dl at admission to 4.7 g/dl and his platelet count fell from 187,000 to 92,000  $\mu\text{l}^{-1}$ . He was given a packed red blood cell transfusion, and 7 hr later, he developed bradycardia, hypertension, left upper extremity weakness, and a fixed, dilated right pupil. A head computerized tomography (CT) scan demonstrated a right temporoparietal epidural hematoma with a 1.3-cm midline shift resulting in subfalcine and right uncal herniation. He underwent neurosurgical intervention; at which time, his overlying skull was found to be "moth-eaten," likely related to a bone infarction. Upon transfer to a rehabilitation center 16 days later, he continued to have mild residual left-sided weakness and expressive aphasia, which later resolved.

Patient 2 is a 10-year-old with SCD-SS admitted with pain crisis of the back and bilateral lower extremities. In addition, he complained of previously having a mild headache that had resolved at the time of admission. His presenting Hb was 8.4g/dl. He was treated with

opiate medications and acutely became hypertensive and unresponsive on day 2 of admission. His left pupil became fixed and dilated and he had decerebrate posturing. A head CT revealed a left-sided 2.5-cm diameter cranial epidural hematoma with midline shift, cortical sulci effacement, and an inferior transtentorial herniation without evidence of trauma or overlying bone infarction. He underwent emergent evacuation by neurosurgery and made a full recovery.

Patient 3 is a 13-year-old with SCD-SC on hydroxyurea evaluated in the emergency department three times over a 4-day period for a pain crisis of his knee and a mild headache treated with NSAIDs and oral opiates. At the second visit, he had developed mild, tender right scalp swelling, which progressed to bilateral parietal scalp swelling at the third visit. He was well appearing with a normal neurological examination at all three visits. At the third visit, his Hb was 11.1 g/dl, platelet count was 122,000  $\mu\text{l}^{-1}$ , prothrombin time was mildly prolonged at 14.3 sec, and a partial prothromboplastin time was normal. He was discharged home, instructed to discontinue NSAIDs, and given three doses of vitamin K. Six days later, he returned with headache, emesis, and decreased appetite. He had bilateral parietal scalp boggy but continued to have a normal neurologic examination. His blood pressure was 129/77 mmHg and Hb was 12.9 g/dl, with a platelet count of 278,000  $\mu\text{l}^{-1}$ . A head CT demonstrated a left cerebral convexity extra-axial collection of both acute and chronic appearing blood resulting in a 12-mm rightward midline shift without certain overlying bone infarction. Additionally, scalp hematomas measuring 12 mm in depth on the right and 4 mm on the left were visualized. After evacuation of the hematoma by neurosurgery, he fully recovered.

Patient 4 is a 17-year-old with SCD-SS, who initially presented with a tender, enlarged cervical lymph node and was diagnosed with lymphadenitis. Hb was 7.6 g/dl and the platelet count was 355,000  $\mu\text{l}^{-1}$  at that time. He returned 3 days later with fever and pain in his back and bilateral knees and arms. He was found to have Epstein–Barr viral infection with associated direct antiglobulin positive hemolytic anemia (Hb of 5.8 g/dl), hepatic transaminitis (alanine aminotransferase 2,589 units/l), coagulopathy (prothrombin time 24.4 sec and partial thromboplastin time 50.5 sec), and thrombocytopenia (58,000  $\mu\text{l}^{-1}$ ). Initially, he was administered one dose of NSAID, which was held after noting his thrombocytopenia, and then continued on opiates, steroids, and antibiotics. During a packed red blood cell transfusion on hospital day 2, he developed bradycardia, hypertension, hypoxia, new onset severe frontal headache, and lethargy. Head CT showed a right posterior fossa epidural hematoma with mass effect and tonsillar herniation; therefore, he had an emergent posterior fossa craniectomy with evacuation of the hematoma. A postoperative magnetic resonance imaging (MRI) showed patchy heterogeneous T1 and T2 hyperintensity through the calvarial bone marrow consistent with scattered skull infarctions in the proximity of the hematoma. Five days later, he developed new bilateral sixth nerve palsy along with mental status changes. CT imaging demonstrated re-accumulation of the epidural hematoma, which was managed conservatively. Ultimately, he had a complete recovery.

Patient 5 is an 18-year-old with SCD-S $\beta^0$ -thalassemia on hydroxyurea therapy admitted to a community hospital for pain crisis of his back and bilateral lower extremities. His initial Hb was 9 g/dl and initial platelet count was reported as normal. He was managed with

**TABLE 1** Case descriptions—current series and literature review

Patient/[Ref]	Age (years)	Sex	SCD type	Presenting symptoms <sup>a</sup>	Time from presentation to diagnosis of hematoma	Location of hematoma	Evidence of skull bone infarction	Midline shift or herniation	Neurosurgical intervention	Outcome
1	10	Male	SS	Pain crisis	About 24 hr	Right temporo-parietal	Yes—right temporo-parietal	Midline shift with uncal and subfalcine herniation	Yes	Complete recovery
2	10	Male	SS	Pain crisis	24–48 hr	Left side	No	No	Yes	Complete recovery
3	13	Male	SC	Headache, pain crisis, scalp swelling	At second ED presentation over 6 days	Left side	No	Midline shift	Yes	Complete recovery
4	17	Male	SS	Fever, pain, transaminitis, coagulopathy, cytopenias	24–48 hr	Right posterior fossa	Yes—scattered over the hematoma	Tonsillar herniation	Yes	Complete recovery
5	18	Male	S $\beta^0$	Pain crisis	About 72 hr	Left parietal	No	Midline shift	No	Death
6	18	Male	SS	Pain crisis	About 96 hr	Right parietal	Yes—right parietal bone	No	No	Complete recovery
7	18	Male	SS	Headache, photophobia	24–48 hr	Bilateral parietal	Yes—bilateral parietal	No	No	Complete recovery
9	20	Male	SS	Pain crisis	72 hr	Left frontal	Yes	No	No	Complete recovery <sup>b</sup>
9	7	Female	SS	Pain crisis	Unk	Right temporal	Yes	Midline shift	Yes	Long-term neurologic complications
9	12	Male	Unk	Confusion after liver biopsy	Unk	Unk	Yes	Herniation	No	Death/DIC
12	18	Male	Unk	Pain crisis	24 hr	Right frontal, right parietal, left parietal	No	Unk	Yes	Complete recovery
11	11	Male	SS	Scalp and periorbital edema	0 hr	Adjacent to right orbital wall, bifrontal	Yes	Unk	Yes	Complete recovery
10	15	Male	SS	Periorbital edema and headache	48 hr	Right frontal	Yes—orbital bone, right frontal bone	Unk	No	Complete recovery

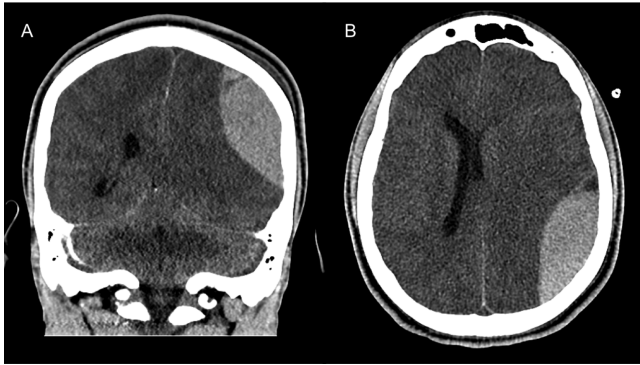
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TABLE 1 (Continued)

Patient/[Ref]	Age (years)	Sex	SCD type	Presenting symptoms <sup>a</sup>	Time from presentation to diagnosis of hematoma	Location of hematoma	Evidence of skull bone infarction	Midline shift or herniation	Neurosurgical intervention	Outcome
13	2	Male	SS	Palpebral edema	<24 hr	Right frontotemporal,	No	Midline shift	Yes	Death
13	12	Male	SS	Headache	Within the first 2 weeks	Left sided	Yes—left frontoparietal bone	Unk	No	Death 6 months later secondary to infection related to initial bone infarction
14	19	Male	SC	Headache	6 days	Right parietal	Yes	Unk	No	Complete recovery
15	13	Male	SS	Periorbital edema, proptosis, limited EOM	Unk	Right retro-orbital, bifrontal	Yes	Unk	Yes	Complete recovery
16	18	Male	SS	Headache	0 hr	Right frontal	No	Unk	Yes	Complete recovery
17	16	Male	Unk	Headache, periorbital edema	0 hr	Left frontalorbital	Yes—left orbital	No	No	Complete recovery
19	9	Male	SS	Fever, Pain Crisis	Within 24 hr	Bifrontal	No	Unk	No	Death
20	14	Male	SS	Pain Crisis, Headache	About 48 hr	Right frontal	Yes—bilateral frontal, right parietal	Unk	No	Complete recovery
18	15	Male	Unk	Pain Crisis, Headache	11 hr	Bifrontal	No	Uncal and subfalciine herniation	Yes	Death
22	19	Male	SS	Pain Crisis	About 48 hr	Left frontal, adjacent to orbital lateral walls bilaterally	No	No	No	Complete recovery
21	10	Male	Unk	Headache	0 hr	Unk	Yes	Unk	No	Complete recovery
23	19	Male	SC	Headache, Parietal scalp swelling	0 hr	Occipital	No	Unk	No	Complete recovery

<sup>a</sup>Pain crisis denotes pain in areas other than the head.

<sup>b</sup>EOM, extraocular movements; Ref, reference; Unk, unknown.



**FIGURE 1** CT scan for patient 5. Coronal (A) and transverse (B) views demonstrate cranial epidural hematoma with midline shift

opiate therapy and antibiotics were added when he developed fever. On hospital day 3, his pain had improved and he was preparing for discharge; however, he was abruptly found by staff to be unresponsive, seizing, and in decorticate positioning without known trauma. He was intubated and transferred to the Sickle Cell Center, where a head CT revealed an 8 cm × 3.1 cm × 7.1 cm left-sided epidural hematoma with herniation but no evidence of overlying bone infarction (Fig. 1). He was declared brain dead and life-supportive measures were withdrawn.

Patient 6 is an 18-year-old with SCD-SS, who was admitted with pain crisis of the back, abdomen, and bilateral lower extremities for which he was managed with opiate therapy. His presenting Hb was 9.2 g/dl. On hospital day 4, he became disoriented and began having hallucinations. An emergent head CT revealed a 3.2 cm × 0.9 cm epidural hematoma along the inner table of the right parietal bone without the midline shift. He was treated with supportive care and made a full recovery.

Patient 7 is an 18-year-old with SCD-SS, who presented with a 2-day history of severe occipital headache with photophobia. Initial work-up demonstrated an Hb of 9.5 g/dl, a platelet count of 181,000  $\mu\text{l}^{-1}$ , and a head CT that was negative for intracranial bleeding. He was admitted and started on an NSAID and opiate therapy. His symptoms progressed on day 2 of the admission to include tender, boggy bilateral parietal areas of scalp swelling and hypertension. At that time, an MRI demonstrated extensive acute calvarial infarctions of the frontal, occipital, and parietal bones with bilateral subperiosteal and epidural hematomas associated with the parietal infarcts. There was no evidence of mass effect. He was managed conservatively and had a full recovery.

In summary, all patients in the case series were male with a mean age of 14.9 years (range 10–18 years) at presentation. Two patients (28.6%) presented with headache, four (57.1%) presented with a pain crisis at other bone sites, and five (71.4%) had no neurologic symptoms at the presentation. Although recent transcranial Doppler ultrasound results were not available for all patients, the results were normal for the three patients studied within the year prior to presentation. On imaging, five patients (71.4%) had evidence of mass effect with midline shift or herniation; four of these underwent successful urgent neurosurgical intervention and one patient died.

**TABLE 2** Characteristics of patients with cranial epidural hematoma—current series and literature combined (N = 25)

Characteristic	N (%)
Sex (male)	24 (96.0)
SCD genotype	
SCD-SS	17 (68.0)
SCD-S $\beta^0$ -thalassemia	1 (4.0)
SCD-SC	2 (8.0)
Unknown	5 (20.0)
Initial clinical presentation <sup>a</sup>	
Headache	11 (44.0)
Scalp/periorbital edema	7 (28.0)
Pain crisis	13 (52.0)
Acute illness	1 (4.0)
Evidence of skull infarction	15 (60.0)
Treatment	
Neurosurgical intervention	11 (44.0)
Supportive management	14 (56.0)
Outcome	
Complete recovery	19 (76.0) <sup>b</sup>
Recovery but with neurological sequelae	1 (4.0)
Death (within 14 days)	5 (20.0) <sup>c</sup>

<sup>a</sup>Some patients presented with more than one symptom.

<sup>b</sup>One patient in this group died 6 months later secondary to a wound infection.

<sup>c</sup>One patient in this group had liver failure and disseminated intravascular coagulation.

A literature review identified 18 additional cases of cranial epidural hematomas in pediatric patients with SCD (Table 1).<sup>9–23</sup> In these cases, the age at the presentation ranged from 2 to 20 years, with a mean of 13.8 years. Nine patients presented with headache (50.0%), seven with a pain crisis (38.9%), and seven required urgent neurosurgical intervention (38.9%). Twelve patients completely recovered (66.7%), one had long-term cognitive impairment (5.6%), and four died (22.2%).

From the combined data, eight (32.0%) patients had evidence of midline shift or herniation. Of those, six patients had neurosurgical intervention (75.0%). Of the six patients without the evidence of midline shift or herniation, only one received neurosurgical intervention and all made complete recoveries. Although subject to publication bias, data from the literature review combined with our case series show a 20% mortality rate from cranial epidural hematomas in children with SCD (Table 2).

## 4 | DISCUSSION

A number of acute complications with resultant morbidity and mortality can develop in patients with SCD, including stroke, acute chest syndrome, splenic sequestration, aplastic crisis, and sepsis.<sup>24</sup> In the CSSCD, the overall mortality rate for patients with SCD who are younger than 20 years of age was 2.6% (0.5 deaths per 100

person years), with infection and stroke being the two most common causes.<sup>25,26</sup> Mortality rates of 10.6% for stroke and 3% for acute chest syndrome have been reported in adults and children with SCD.<sup>4,25,26</sup> In the CSSCD, there were no deaths at presentation with infarctive stroke, but the mortality rate was 24% for hemorrhagic stroke.<sup>26</sup> In the current report, we found a relatively high mortality rate of 20% for cranial epidural hematoma. In comparison, cranial epidural hematomas in the general population have a reported mortality rate of 7%.<sup>27</sup> Our study may overestimate the true mortality rate in children with SCD, as milder cases may go unrecognized; nonetheless, cranial epidural hematoma is a serious, life-threatening complication of which clinicians should be aware. The incidence of cranial epidural hematomas in patients with SCD is currently unknown, but one small case series showed epidural hematoma in 21% of the children with SCD who presented with an orbital infarction.<sup>11</sup>

The pathophysiology of cranial epidural hematomas in SCD is not well understood, and a number of theories have been postulated. Most theories involve an underlying bone infarction and some involve venous congestion and thrombosis.<sup>9,12,28</sup> Sickling in the marrow causes stasis, hypoxia, and eventual infarction. Outside of infancy, sickling occurs most commonly in the long bones of the humerus, followed by the tibia, and then the femur, but it can also occur less commonly in skull bones.<sup>29</sup> Because of the increased intramedullary hematopoiesis leading to cortical expansion and thinning of skull bones in SCD, these bones may be particularly vulnerable to bleeding associated with infarctions.<sup>30</sup> Evidence of bone infarction can be seen on MRI, but the number of infarctions may be underestimated because not all patients in this report had an MRI. Nonetheless, 15 patients (60.0%), including four of the five patients who presented with periorbital edema, had clear evidence of skull bone infarction. Another theory is that cortical bone expansion due to chronic medullary hematopoiesis is exacerbated in the setting of acute anemia leading to disruption of the skull cortex.<sup>12</sup> Hb levels were not available at the time of the epidural bleed for all subjects; however, worsening anemia was noted in two of the seven patients from our case series.

Outside of the sickle cell patient population, cranial epidural hematomas are most often the result of trauma, but less common causes include paracranial infection, coagulopathy, underlying vascular malformations, and malignancy.<sup>31</sup> In this report, cranial epidural hematoma developed in the setting of liver dysfunction with coagulopathy and thrombocytopenia in two patients, a third child was receiving anticoagulation, and the four additional patients had thrombocytopenia.<sup>9</sup> As such, close attention to the correction of coagulation defects is warranted in this population. No paracranial infections, vascular malformations, or malignancies were present in our case series and none were reported in the literature review. However, pain was an initial complaint in 21 of the 25 cases (84.0%), with either headache or a pain crisis at another site. Inflammatory markers are elevated in the setting of pain crises, thus inflammatory mediators could plausibly influence the development of cranial epidural hematomas in children with SCD.<sup>32</sup> Given the numerous different clinical presentations in this paper, it is likely that the underlying pathophysiology of cranial epidural hematomas in SCD is multifactorial.

A few clinical characteristics are striking when reviewing the results of this study. First, all patients in our case series are male and 94% of the cases from the literature review are male. A male predominance for cranial epidural hematoma is also found in the general pediatric population, occurring 1.5–2.5 times more frequently in males.<sup>33–35</sup> Second, the majority of children (88.0%) presented in the second decade of life. Reasons for this are unclear, but analyzing lifestyle changes and pubertal effects as part of a future study could ultimately aid with understanding this finding.

Clinical presentation was variable and most patients initially presented with symptoms that are relatively common in SCD. Approximately half of the patients presented with headache. Headache is a common complaint in children with SCD, making it difficult to determine who needs imaging to evaluate for CNS complications.<sup>36</sup> In a prior study, most CNS events in the setting of acute headache were accompanied by other neurological complaints or abnormalities on physical examination.<sup>37</sup> Only three of the combined 25 patients (12.0%) in our report had neurologic symptoms other than headache at initial presentation, although all patients went on to have acute neurologic changes. Of note, seven of 25 (28.0%) patients had either scalp (two) or periorbital edema (five) and four of the patients with periorbital edema had underlying evidence of bone infarction. Thus, the presence of headache accompanied by neurological symptoms or the presence of scalp or periorbital edema should prompt acute neuroimaging.

Generalized treatment recommendations and prediction of prognosis are difficult to make given the small patient sample size and limitations of retrospective chart reviews. Our results support aggressive intervention when radiologic evidence of increased intracranial pressure (midline shift or herniation) is seen. Only two of the eight patients with radiologic evidence of increased intracranial pressure did not undergo urgent neurosurgical intervention, and both of them died. One, a patient in our case series, had an acute and rapid clinical decline precluding surgical intervention, while the other death occurred in a patient with disseminated intravascular coagulation.<sup>9</sup> Two other patients died despite neurosurgical intervention.<sup>13,18</sup> In total, four of the five patient deaths had radiographic evidence of increased intracranial pressure.

Whether early treatment in the setting of skull infarction can prevent the development or progression of epidural bleeding is unknown. Exchange transfusion to achieve HbS levels of less than 20% has been reported to help alleviate symptoms resulting from skull infarctions.<sup>38</sup> In our series, no patient underwent exchange transfusion. However, simple transfusions had been administered in two of the patients in our case series and in at least three of the patients from the literature review prior to the development of symptomatic epidural hematoma, suggesting this did not prevent progression.<sup>9,13,16</sup> It remains unclear if exchange transfusion would prevent or mitigate this complication. The increasing use of prophylactic hydroxyurea may lead to a reduction in skull infarction and epidural hematoma. Three subjects from our case series were receiving hydroxyurea, two of whom were thought to have good adherence. Hydroxyurea significantly reduces the number of vaso-occlusive pain events in patients with SCD, although these events may still occur, even with good adherence.<sup>39</sup> With such a high mortality rate, prevention and treatment need to be optimized.



Reasons for this high mortality rate in SCD are not clear; however, the presence of underlying morbidity prior to the development of the cranial epidural hematoma may, in part, contribute to this. In the general population, cranial epidural hematomas are often associated with trauma leading to a higher index of suspicion, which prompts earlier imaging and intervention. In children with SCD, that index of suspicion is not as high, which could lead to a relative delay in diagnosis. Further studies are needed to identify mortality risk factors as well as optimize prevention and treatment.

A few limitations of this retrospective review are worth noting. The main limitation is reporting bias. Uniform data such as use of prophylactic hydroxyurea or chronic transfusion, hematological values at the time of the event, and standard neuroimaging were not available for all cases. As noted above, the mortality rate is based on a small number of cases and reports that may be biased toward higher severity. Additionally, long-term follow-up is not available for all of these cases.

Future prospective, multicenter studies are needed to help determine the incidence, pathophysiology, risk factors, prognosis, and potential treatments or interventions. Clinicians should consider this complication in their differential diagnosis and be aware that it occurs in the setting of common sickle cell symptoms, including headache, scalp or periorbital edema, and pain crises. An acute neurologic change, acute development of hypertension and/or bradycardia, or an unexplained drop in Hb level should prompt clinicians to consider urgent neuroimaging. Identification of a cranial epidural hematoma requires immediate neurosurgical consultation for consideration of intervention. Early diagnosis and, if needed, rapid intervention will likely decrease the high mortality rate for patients with SCD and cranial epidural hematoma.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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