Case Report

A case series of hemorrhagic neurological complications of sickle cell disease: Multiple faces of an underestimated problem!

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ABSTRACT

Sickle cell disease (SCD) is a group of hemoglobinopathies that vary in severity, the most severe form, homozygous sickle cell anemia, is often associated with neurologic complications. The incidence of various neurologic complications in SCD ranges from 6% to 30% in different series. Although the incidence of acute ischemic stroke and chronic cerebral ischemia is higher in SCD, about 20–30% of the neurological complications may be hemorrhagic in nature. Complications such as spontaneous subarachnoid hemorrhage, hemorrhagic stroke, extradural, and subdural hematomas have been described in the literature. The aim of this article was to report uncommon spontaneous hemorrhagic neurological manifestations of SCD. We have described three uncommon hemorrhagic neurological complications of SCD. One case had a parenchymal (intracerebral) bleed and presented with acute onset of parkinsonism, while two cases had an extradural hematoma (EDH), of which one patient had recurrent EDH at the same site which is hitherto not reported in the literature. Two patients survived, while one with recurrent EDH succumbed. Hemorrhagic neurological complications should be included in the list of differential diagnoses of neurological presentations in patients of SCD. EDH is an uncommon complication of SCD, while recurrent EDH is extremely rare. The condition should be suspected early in patients with SCD, as timely treatment often reduces the mortality.

KEY WORDS: Sickling; Anemia; Hemorrhage; Neurological; Stroke

INTRODUCTION

Sickle cell disease (SCD) is an autosomal recessive hemoglobinopathy characterized by the sickled red blood cells causing obstruction to the microcirculation resulting in tissue hypoxia.[1] Neurological complications in SCD can cause sequelae, impaired cognition, thus contributing significantly to the morbidity and disease mortality. These are attributed to the vaso-occlusion and micro-obstruction in the circulation of the central nervous system (CNS). The commonly reported complications in the literature include silent cerebral infarction, ischemic stroke, transient ischemic attacks, headaches, seizures, and neurocognitive impairment. Although hemorrhagic complications also occur, they are rarely thought of. We present a series of three rare cases of SCD, who had hemorrhagic CNS manifestations.

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CASE REPORT 1

A 34-year-old lady, unmarried, was admitted with severe headache, giddiness, and weakness of 2 days duration. There was no history of vomiting, fever, double vision, or convulsions. She refused a history of head trauma. She was a diagnosed case of SCD and had undergone cholecystectomy at the age of 7 years for cholelithiasis, splenectomy at 10 years of age, and total hip replacement for chronic arthritis of the right hip joint secondary to avascular necrosis of femur neck

in 2013. She had last received blood transfusion 2 years back for anemia. She did not have a history of any other significant medical ailments. She did not consume alcohol and tobacco. She was the second affected sibling in the family.

On admission, she was lean, had mild pallor and icterus, no pedal edema, and cyanosis. She was afebrile, with a pulse rate of 106/min, blood pressure 110/70 mm Hg, and respiratory rate of 18/ min, regular and abdominothoracic type. Examination of CNS revealed awake person, apathetic, Glasgow coma scale (GCS) E4 (vacant), and M6V2 – 12/15, pupils were normal size and reacting to light, preferential left-sided gaze, and left hemiparesis with left up-going plantar. The neck was soft. Examination of other systems such as cardiovascular, respiratory, and gastrointestinal was within normal limits. Considering the possibility of a cerebrovascular accident (CVA), an urgent non-contrast computed tomography (NCCT) brain was done, which showed acute bleed in the right parietal lobe with surrounding edema and mass effect. Basal cisterns were open. There was no midline shift [Figure 1a and b].

Her hemoglobin, on admission, was 6.9 g/dl, total white blood cell (WBC) count 10,200 cu mm with 35% neutrophils, 53% lymphocytes, 8% monocytes, mean corpuscular volume (MCV) 74.9 fl, and platelet count 1.5 lakhs/cu mm. Her liver function tests (LFT) revealed total bilirubin 3.96 mg/dl, direct fraction 0.98 mg/dl, indirect fraction 2.98 mg/l, alanine transaminase 17.9 U/L, aspartate transaminase 52.6 U/L, alkaline phosphatase 82.6 U/L, total serum proteins 7.01 g/dl, serum albumin 4.01 g/dl, globulin 3.0 g/dl, activated partial thromboplastin time (APTT) 12.4 s, control 14 s, prothrombin time (PT) 19 s, control 11 s, and PT (international normalization ratio [INR]) 0.99. Renal function tests showed blood urea 17.2 mg/dl and serum creatinine 0.56 mg/dl. Serum iron was 70.5 mcg/dl, and serum ferritin was 1444.8 ng/ml. Her hemoglobin electrophoresis showed fetal hemoglobin (HbF) 11%, HbA_2 3.7%, sickle hemoglobin (HbS) 85.3%, and no adult hemoglobin (HbA).

She was treated conservatively with 20% Mannitol 100 ml for 3 days intravenously, 3 units of compatible packed red blood cells transfusion, pantoprazole 40 mg OD, Ryle's tube feed of 1.8 l/day, and other supportive measures. She developed features of acute parkinsonism in the form of mask-like face, hypertonia, and cogwheel rigidity on day 4 of admission. Her contrast-enhanced computed tomography brain done after 10 days showed resolving hemorrhage with surrounding edema with effacement of the right lateral ventricle and midline shift [Figure 2a and b]. She did not worsen neurologically and was given injection dexamethasone 8 mg 3 times a day intravenously for 5 days and subsequently discharged with advice to continue physiotherapy and follow-up in outpatient department.

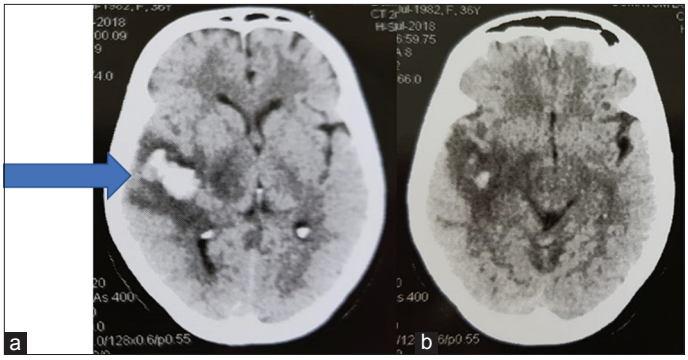

Figure 1: (a and b) Non-contrast computed tomography brain showing acute bleed in the right parietal lobe with surrounding edema and mass effect (arrow)

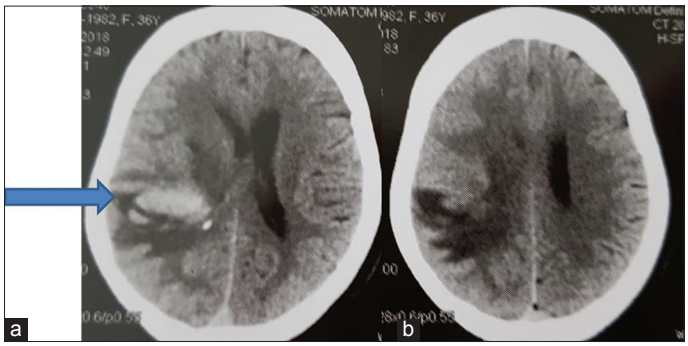

Figure 2: (a and b) Non-contrast computed tomography brain showing resolving bleed in the right parietal lobe with surrounding edema extending into basal ganglia and mass effect (arrow)

CASE REPORT 2

A 18-year-old male, case of sickle cell anemia (SCA), was admitted with chest, lower back pain for 3 days, and frontal headache of 1 day duration. He had a previous history of several vaso-occlusive crises needing simple analgesia. He was not on hydroxyurea. He was born at full term and was the first affected sibling. On admission, he was afebrile, had significant pallor, icterus, tachycardia, and normal blood pressure. Examination of CNS revealed restless, irritable, and confused patient with GCS of 9/15 (E3M4V2). There was mild right hemiparesis with upgoing plantar. The rest of the systemic examination did not reveal any abnormality.

Laboratory values on admission showed hemoglobin (Hb) 6.7 g/dl, hematocrit 20.1%, total WBC count 12,200 cu mm with 65% neutrophils, 53% lymphocytes, 35% monocytes, MCV 78.9fl, and platelet count 75,000/cu mm. LFT was normal. PT (INR) and APTT were normal. His hemoglobin electrophoresis showed HbF 14%, HbA_2 3.7%, HbS 82.8%, and no HbA. His serum 1actate dehydrogenase (LDH) was 1025 U/L. His Hb 3 months before this admission was 7.4 g/dl. His headache intensified the next day requiring escalation of pain analgesia to opiates. In view of the focal neurological deficit and headache, he underwent an urgent NCCT brain which showed an extradural hematoma

(EDH) overlying the left frontal-parietal lobe with mass effect, midline shift to the right [Figure 3a and b]. The neurosurgical opinion was sought, and he underwent emergency left-sided craniotomy for draining of the hematoma. Subsequently, he was treated with analgesia, packed red cell transfusions, antibiotics, anti-epileptic (levetiracetam), and other supportive measures. He made a significant recovery with rehabilitation and was discharged after 20 days.

This patient was readmitted 1 year later with body aches, severe headache of 2 days duration, and one episode of generalized convulsion. On admission, he had pallor and icterus and was restless with GCS of 7/15. Pupils were asymmetric; the right pupil was dilated (4 mm), sluggishly reactive to light and the left pupil (2 mm) showed a normal reaction. There was a right hemiparesis with positive Babinski's sign. Laboratory values showed Hb 6.2 g/dl, hematocrit 18.6%, total WBC count 13,200 cu mm with 75% neutrophils, and 23% lymphocytes. LFT revealed that total bilirubin 6.9 mg/dl, direct fraction 0.9 mg/dl, indirect fraction 6 mg/l, and liver enzymes were normal. His NCCT brain showed a large left frontal EDH with midline shift to the right. He underwent an emergency left-sided craniotomy. The EDH was evacuated, and dural arterial bleeding was controlled. He was managed postoperatively in the intensive care unit with 3 units of packed cell transfusions, antibiotics, and mechanical ventilation. Two days post-surgery, he had a sudden cardiac arrest and could not be revived. There was no time to repeat computed tomography (CT) scan of the brain. The cause of death was probably, re-accumulation of hematoma with herniation of the brain.

CASE REPORT 3

A 26-year-old male, known case of SCD, was admitted with the severe headache involving the whole head with pain in the small joints of the body with low backache of 2 days duration. There was no fever, vomiting, altered sensorium, visual disturbance, or epileptic seizure. No history of head trauma was found. He had one episode of acute chest syndrome 2 years back. Examination of the central nervous system showed normal orientation to time, place, and person and no focal neurological deficit. The rest of the systemic examination was normal except for mild hepatomegaly. His blood tests revealed Hb 7.7 g/dl, hematocrit 23.1%, total WBC count 13,200 cu mm with 75% neutrophils, 23% lymphocytes, 2% monocytes, MCV 76.9 fl, and platelets 1.25 lakh/cu mm. LFT revealed total bilirubin 8.32 mg/dl, direct fraction 1.12 mg/dl, indirect fraction 6.8 mg/l, while liver enzymes were normal. Coagulation parameters such as PT, APTT, and serum fibrinogen were normal. His hemoglobin electrophoresis showed an HbS level of 76.8% and no HbA. His serum LDH was 925U/L. NCCT brain

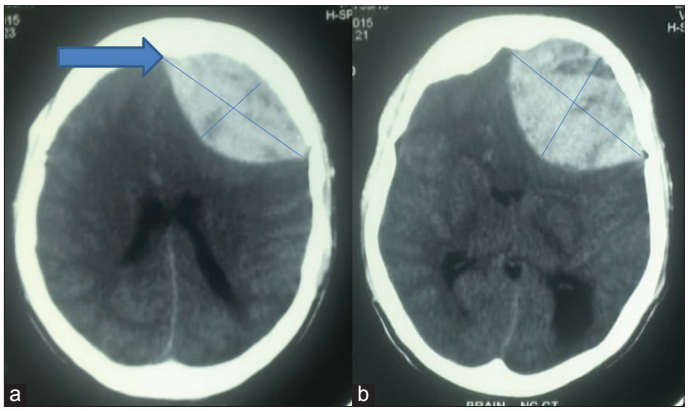

Figure 3: (a and b) Axial views of non-contrast computed tomography brain showing left extradural hematoma

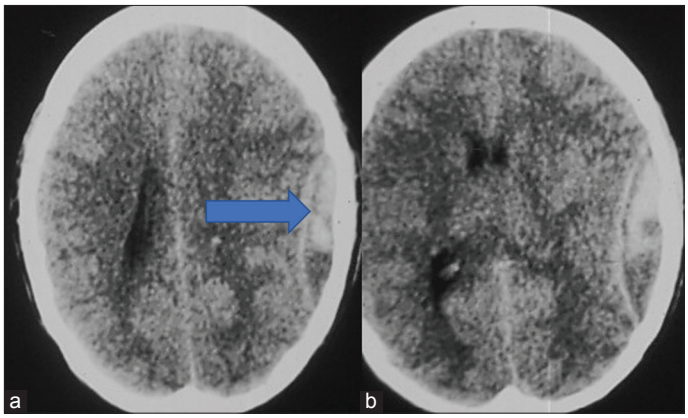

Figure 4: (a and b) Axial views of non-contrast computed tomography brain showing left parietal extradural hematoma (arrow)

done, which showed an EDH overlying the left parietal lobe [Figure 4a and b]. He was managed conservatively (in view of small EDH) with analgesia, blood transfusion, antibiotics, and other supportive measures. CT brain repeated after 1 month showed near-complete resolution of the hematoma.

DISCUSSION

SCD is a qualitative hereditary hemoglobinopathy characterized by the presence of Hb S (sickle Hb).[2] The amino acid glutamine is substituted by valine in the sixth position of beta-globin chain. Its incidence is high among the people of African, Arabian, and Indian origin. SCD in India is prevalent in the Western, Central, and Eastern regions and pockets of South. In the Eastern regions, it is common in Odisha, Jharkhand, and Bengal.[3] SCD is characterized by hemoglobin S polymerization, erythrocyte stiffening with loss of deformability, and subsequent vaso-occlusion.[1] These changes lead to obstruction to the microcirculation, consequent ischemia of the tissues, and infarction in various organ systems, including the cerebrovascular system. All three patients in our series had

homozygous form (HbSS), thus representing a severe form of the disease.

Patients of SCD have a higher incidence of cerebrovascular events. The incidence of various neurologic complications in SCD ranges from 6% to 30% in the literature. The neurologic complications of SCD include silent cerebral infarcts (39% by the age of 18 years), acute and chronic headache (36% in children), neurocognitive impairment (25%), seizures (7–10%), ischemic stroke (1% in children with screening and prophylaxis, but about 11% in children without screening), and hemorrhagic stroke (3% in children vs. 10% in adults).[1,4-6] Approximately 70–80% of all strokes in SCD are ischemic, while 20–30% are hemorrhagic in nature.[1,7]

Primary hemorrhagic stroke has a reported mortality of 24–65%.[8,9] Ischemic strokes are relatively more common in children than in adults, while hemorrhagic strokes are more common in adults than in children.[8] As per the Cooperative Study of SCD (CSSCD) report, 5 (9.6%) of 52 first strokes in SCD-SS in patients <20 years were hemorrhagic, while 14 (52%) of 27 first stroke in those over 20 years of age were hemorrhagic.[8,9] Hemorrhagic complications recognized in SCD include intracerebral hemorrhage, intraventricular bleed, subarachnoid hemorrhage (SAH), subdural, and epidural hematoma. A study of neurological complications in 325 patients with SCD done at the University of Illinois between 1975 and 1989 revealed 11 cases of SAH, of which ten had aneurysms.[6,10]

Our first patient had hemorrhagic acute CVA. CVA is a devastating complication of SCD and a common cause of death in both children and adults. It is more common in the HbSS genotype with an incidence of 0.61/100 patient-years.[11] The CSSCD followed up 4000 patients for 10 years from 1978 to 1988 and found that the prevalence of stroke was 5% in those with homozygous SCD (SCD-SS).[12] The incidence of hemorrhagic stroke (0.44/100 – patient years) was highest in patients aged 20–29 years.[13] It was associated with low steady-state Hb and a high total leukocyte count. Subarachnoid hemorrhages were less common, while extradural bleeds were rare.[14] The risk factors identified for the development of hemorrhagic stroke in adults included hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, and renal disease.[6,11] Hemorrhagic strokes in SCD could also be due to advanced sickle cell hepatopathy, resulting in impaired coagulation profile.[15] However, none of these factors was present in our patient.

The pathogenesis of neurologic complications in sickle cell anemia is not completely understood. Brain CT and magnetic resonance angiography (MRA) have demonstrated large arterial occlusive disease in the terminal intracranial portion of the internal carotid arteries and proximal segments of their main branches but rarely in the vertebrobasilar or extracranial carotid systems.[9,16,17] These changes are referred to as large-vessel cerebral vasculopathy and lead to the formation of a mass of small, friable, and collateral blood vessels in response to severe steno-occlusion of major intracranial vessels. This is called moyamoya phenomenon.[18] Rupture of moyamoya's vessels leads to cerebral hemorrhage. It is seen in 5.5–17% of patients with SCD.[19]

Another cause of cerebral hemorrhage in adults is aneurysm formation. In a study by Nabavizadeh *et al*. involving 709 imaged patients, the prevalence of aneurysm was 10.8% in adults with SCD.[20] Those which ruptured were typically small (2–9 mm) and situated at the bifurcations of major vessels both in the anterior and posterior circulation.[20,21] Histopathology studies have shown degeneration and fragmentation of the internal elastic lamina in the wall of the aneurysms. This is called "elastorrhexis" of the vascular wall.[8,22] Rupture of these aneurysms typically causes SAH but may also cause an intraventricular or parenchymal bleed. Hence, bleeding in any form, except for traumatic subdural hematoma warrants further evaluation for a surgically correctable aneurysm, even if the bleeding appears to be primarily intracerebral. Our first patient presented with acute parkinsonism due to intracerebral bleed. She could not be subjected to MRA due to the metallic implant in the hip joint which was not magnetic resonance compatible. The subarachnoid and intracerebral hemorrhage may also be caused by ischemic changes in the capillaries and arteriolar walls which lead to diapedesis of red blood cells into the subarachnoid space and into the surrounding cerebral tissue.[7]

Since 1978, 15 cases of spontaneous EDHs as a rare complication of SCD have been described in the literature.[23-27] The majority of the extradural hematomas occur due to infarction of the underlying bone, thereby disrupting the cortical bone, thus causing periosteal elevation and subsequent bleeding into the extradural space.[26,27] Another explanation suggested was that the epidural vessels may rupture spontaneously in the vicinity of the infarcted bone and cause EDH.[27] Bone infarct can be visualized on magnetic resonance imaging (MRI) of the skull. We could not demonstrate bone infarcts as both the patients of EDH refused MRI due to financial constraints.

Recently, an alternative mechanism was offered by Dahdaleh. He suggested that patients of SCD have hypervascularity of the skull due to chronic medullary hematopoiesis. This occurs as a response to acute hemolysis. There is rapid proliferation haemopoietic tissue proliferation and expansion, which cause disruption of the skull cortex and precipitates in extravasation of blood and marrow into the epidural spaces.[28] The consequences of acute bone infarction due to vaso-occlusion are not significant in the vertebrae and long bones such as femur, humerus, radius, and ulna, which are surrounded by soft tissues.[26] However, as the skull bones are very thin,

hematomas are likely to be cause compression, especially if they occur on the inner surface of the skull.

The EDH in our patients could be secondary to the acute expansion of hematopoietic tissue or have developed as a periosteal reaction to the infarcted bone. However, as both the patients had a history of vaso-occlusive pain crisis, it is likely that EDH was secondary to skull bone infarct. The fall in hemoglobin and rise in LDH could be due to the development of EDH. Our second patient had recurrent EDH in the same location suggesting some anatomical bone defect. After making an intense literature search, we did not come across a single published report of recurrent EDH in SCD. To the best of our knowledge, this is the first case report of recurrent EDH, that too in the same site in a patient with SCD.

Depending on the location and volume of the hematoma, there could be an alteration of the higher mental functions for the frontal EDH, homonymous hemianopsia in the occipital ones, signs of intracranial hypertension in the frontal and occipital forms, or hemiplegia in the parietal forms.[29] A parietal swelling may develop on the side of the hematoma. EDH is an uncommon cause of neurological symptoms in SCA, and clinicians should suspect this complication even in the absence of focal neurological signs or history of trauma. Small EDH without evidence of cerebral compression or raised intracranial pressure undergo spontaneous resolution and, hence, can be managed conservatively while larger ones require evacuation.

CONCLUSION

These cases highlight the rare neurological hemorrhagic complications of SCD. EDH is an uncommon complication of SCD, while recurrent EDH is extremely rare. Small EDH may not manifest with neurological deficits, while the acute onset of stroke in patients of SCD may not be always related to ischemia. It could be due to intracerebral bleed. There should be a high index of suspicion, as early diagnosis and treatment reduce morbidity and mortality.

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