

## Case Report

# Uncommon neurological manifestations of hemolytic anemia: A report of two cases

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Neurological complications of hemolytic anemias are rather uncommon. We are reporting two cases of hemolytic anemia presenting as chorea and recurrent ischemic stroke. The first one is a case of chorea in a patient with sickle cell trait. Reviewing the literature we could find only one case report of chorea in sickle cell disease. The second is a case of recurrent ischemic stroke in hereditary spherocytosis. We could trace two reports on a Medline search, though their association was less certain.

**Key words:** Chorea, hemolytic anemia, hereditary spherocytosis, ischemic stroke, sickle cell trait

Sickle cell disease (SCD), the homozygous state for sickle cell gene (SS Hb pattern) is an important risk factor in the development of stroke and most strokes occur in subjects under the age of 15 years. By contrast, sickle cell trait (SCT-AS Hb pattern) is considered to be a benign condition. In spite of a number of case reports, it is not widely appreciated that SCT can cause cerebral infarction. Radhakrishnan *et al.*, reported two cases of stroke in young with SCT.<sup>[1]</sup> However, chorea in SCT has not been described in the literature to the best of our knowledge even though a case was reported in HbSC disease.<sup>[2]</sup>

Hereditary spherocytosis (HS) is a common type of hemolytic anemia and till now stroke has been reported only twice in this disorder.<sup>[3]</sup>

We are reporting two patients, the first one being chorea in a patient with SCT and, the second, a case of recurrent ischemic stroke in hereditary spherocytosis.

## Case Reports

### Case 1

A 32-year-old female, who was in apparent good health presented with sudden onset of fever, behavioral abnormalities and generalized choreiform movements. There was no history of drug intake or herbal medication. She had undergone tubectomy five years ago. There was no relevant family history.

General physical examination was unremarkable except for pallor and mild dehydration. Palpation of abdomen showed Grade 1 splenomegaly. Examination of the cardiovascular and respiratory system was normal. She was conscious, oriented and was found to have visual hallucinations. There were continuous choreiform movements involving all four limbs, more on the right side. The rest of the neurological examination was normal.

Oxygen saturation was 97%. Slit-lamp examination for KF ring was negative. An ultrasound scan of the abdomen showed mild splenomegaly. A hemogram revealed microcytic hypochromic anemia (Hb 8 gm/dl) with RBC showing sickling with 2% sodium metabisulphate preparation. Peripheral smear did not show acanthocytes. The fasting blood sugar was 76 mg% and serum creatinine 0.8 mg%. Liver function tests, chest X-ray, ECG, antistreptolysin-O titer and a 2D ECHO were normal. Tests for anti nuclear, anti ds DNA, anti sm, anti RNP, anti Ro, anti la, antiphospholipid, antiplatelet, antihistone, antiribosomal P antibodies were negative. Rheumatoid factor, C reactive protein, Elisa for HIV and screening for malignancy were negative.

Hemoglobin electrophoresis by high performance liquid chromatography showed Hb-S of 26.5% (N = 0), Hb A<sub>2</sub> 4.4% (N = 1.5-3.7), Hb F was 3.1% (N = 0-2) and Hb A was 65% (N = 94-98.5), suggestive of Hb-S trait. Computed tomography and magnetic resonance imaging (MRI) of the brain, magnetic resonance angiogram and venograms were normal. She was treated symptomatically with haloperidol and folic acid. Involuntary movements and behavioral abnormalities remitted completely during the next four weeks. During follow-up after four weeks choreiform movements were completely absent.

### Case 2

A 38-year-old female presented with sudden onset of right hemiparesis since one day. There was no history of headache, vomiting, seizures, hypertension, diabetes

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or heart disease. She was detected to have hereditary spherocytosis five years ago during evaluation for anemia. Her father and son also were found to have a similar problem on screening. The father was asymptomatic, while the son had a history of frequent hospitalizations for unrecognized “hemolytic crises” during minor infections.

General and systemic examinations were normal except for mild pallor. Neurological examination revealed right hemiparesis with 3-4/5 power. The rest of the examination was normal.

Hemoglobin was 10 gm/dl. A peripheral smear showed microcytic hyperchromic spherocytes suggestive of hereditary spherocytosis. A sickling test was negative. An MRI brain showed bilateral thalamic lesions consistent with infarcts [Figure 1]. Results of estimation of coagulation profile, Protein S, Protein C, Homocysteine, Antithrombin III, Cardiopilin and a collagen profile were normal. A 2D Echo of the heart revealed no abnormality. Carotid Doppler showed normal neck vessels. The MR angiography (MRA) including neck vessels showed irregular narrowing of the P1 segment of the left posterior cerebral artery. She was treated with antiplatelets, pentoxifyllin and other supportive measures. She made a complete recovery by the end of two weeks. An MRI of the brain repeated after six months showed complete resolution of the earlier lesions. Two years later, she had a second episode of acute onset of severe truncal ataxia, lasting for 12 h which recovered spontaneously. An MRI brain done on the same day did not show any abnormality.

### Discussion

There is a paucity of literature regarding neurological events in SCT. Sickle cell trait is generally believed to be a benign condition. It may be that SCT becomes a significant risk factor in the setting of other risk factors.



Figure 1: MRI showing bilateral thalamic infarcts

Sickle cell trait can produce sickling manifestations due to vasoocclusive complications under conditions of severe hypoxia. Splenic infarcts and other ischemic sequelae may occur in individuals with SCT as a result of hypoxia associated with general anesthesia and high altitudes.<sup>[4]</sup> Radhakrishnan *et al.*, while reviewing the literature described 12 cases of SCT along with two of their own. The age ranged from 12-38 years (mean 24.8 years). Male to female ratio was 2.7:1. Among the patients, three were due to sinovenous thrombosis and the rest due to arterial occlusions. Two of them were in the posterior circulation territory. Sickling was demonstrated at autopsy at the site of vascular occlusion in autopsied cases. In two, anesthesia and hypoxia were incriminated as the precipitating factors. Unlike the commonly held belief in the pre-angiographic era that small vessels are commonly involved in SCD, large vessel occlusion was demonstrated in six cases internal carotid artery (ICA).<sup>[1]</sup> New data suggest that, in addition to sickle cell disease, other factors, both environmental (e.g. dehydration, hypoxia and inflammation) and genetic (e.g. mutations resulting in thrombogenesis) may contribute to a patient's stroke risk.<sup>[4]</sup> The percentage of hemoglobin in SCT can vary from 25-45%. In carriers who have a high concentration of HbS, the risk of sickling is not much less than in patients with HbSC disease.<sup>[5]</sup> In a study with prospective radiographic imaging of children with SCT, it was demonstrated that children with SCT were more likely to have cerebrovascular tortuosity than controls probably attributable to thrombosis, endothelial activation and platelet activation.<sup>[6]</sup>

Ali *et al.*, reported a seven and a half-year-old black boy with sickle cell disease who developed chorea 17 months after hypertransfusion for a right hemiparesis due to ischemic cerebrovascular disease. They hypothesized that the movement disorder might have been due to the beneficial effect of hypertransfusion therapy on an occult vasculoocclusive lesion in the diencephalons. With improvement in cortical function, the lesion manifested as chorea at a later date.<sup>[2]</sup>

In most of the cases where neurological complications were described in SCT, the hematological condition was diagnosed only at the initial presentation as in our case. Here the hypoxemia appeared global in view of the generalized movement disorder and visual hallucinations. The transitory nature of the event leading to complete recovery and absence of any abnormalities on imaging suggests temporary ischemia as the causative factor. The preexisting anemia and the infection might have precipitated an abnormal hemorheological state which reversed on its own with treatment of infection and improvement in general condition including hydration. The association of SCT and chorea here seems to be more than coincidental. In the absence of more common causes of chorea like rheumatic fever, drugs, SLE, pregnancy,

Wilson's disease, SCT can be incriminated as a possible etiological factor in this patient.

Reports of association of stroke in relation to HS are hard to find in the literature. van Hilten *et al.*, while referring to a single case report of an ischemic stroke in HS in the French literature described two brothers who suffered cerebral infarction in whom they performed hemorheological investigations.<sup>[3,7]</sup> They were aged 65 and 66 and had risk factors like cardiac disease and major intracranial and extracranial occlusive vascular disease on angiography. Though they could demonstrate significant hemorheological abnormalities attributable to HS in both, they expressed skepticism in attributing the stroke to HS in view of the other obvious risk factors.

The second patient described in the present report is a young lady without any conventional risk factors accounting for her bilateral thalamic infarcts. An MRA also demonstrated narrowing of the vessel in the corresponding territory.<sup>[8]</sup> Hereditary spherocytosis can cause distal small vessel occlusion (sludging syndrome) due to increased red cell aggregability, reduced red cell deformity and increased viscosity.<sup>[3]</sup> But large vessel disease in this case is more difficult to explain. The location of the arterial narrowing at a branching point in this case also brings in the contribution by hemodynamic factors. These areas are characterized by low shear stress and oscillatory or turbulent flow. Elevated blood volume secondary to anemia might also

be responsible. These multiple factors may result in endothelial injury, platelet activation and thrombosis. Destruction of the fragile spherocytes may also release prothrombotic substances.<sup>[9]</sup>

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Accepted on 25-09-07

Source of Support: Nil, Conflict of Interest: None declared.