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Varied Presentation Of Hereditary Spherocytosis In The Family: Unmasked By A Stroke In Young

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• **ABSTRACT:** Hereditary spherocytosis (HS) is due to alterations in genes that encode for proteins such as spectrin and ankyrin involved in vertical associations that tie the membrane skeleton to the lipid bilayer. Moya Moya disease is defined as severe bilateral stenosis of the arteries around circle of Willis with prominent collateral circulation. Hereditary spherocytosis causes decreased deformability of RBCs. Decreased deformability of RBC along with increased blood flow associated with anemia contribute to endothelial proliferation which progresses slowly and produces stenosis followed by occlusion. Here we present a young patient presenting with stroke who was diagnosed with hereditary spherocytosis associated with Moya Moya disease. Consider the possibility of Moya Moya disease in patient with HS presenting with stroke.

• **KEY WORDS:** Hereditary spherocytosis, Moya Moya disease, young stroke.

INTRODUCTION:

Hereditary spherocytosis (HS) is the genetically transmitted disease as a result of heterogeneous alterations in one of the six genes that encode for proteins such as spectrin and ankyrin involved in vertical associations that tie the membrane skeleton to the lipid bilayer. It causes autohemolytic anemia characterized by the production of sphere-shaped RBC rather than biconcave disc and therefore more prone for hemolysis. Cerebrovascular accidents are major complications of sickle cell disease, accompanied by narrowing and occlusion of the internal carotid arteries. It is rare for HS to be associated with cerebrovascular event secondary to moya moya. HS is usually not associated with thrombotic risk. However rare cases of both arterial and venous thrombosis have been described(1–3). Very few case reports reveal the association of HS with moya moya(4,5). Moya moya is the chronic progressive non atherosclerotic non inflammatory and non-amyloid cerebrovascular disorder, defined by progressive stenosis of intracranial vessels.

CASE REPORT

23-year-old male presented to the hospital with complaints of weakness involving left upper and lower limbs which was insidious in onset after patient got up from the bed and was getting ready for day-to-day activities. In the next few hours patient was completely bed bound but there was no loss of sensorium. Patient also complained of mild slurring of speech due to deviation of angle of mouth to right side. He did not have associated bowel and bladder incontinence. Patient had no family history of consanguinity or cerebrovascular accidents, seizure or cancer. He was born to the healthy mother via the full term normal vaginal delivery. Socially he was employed in a pharmaceutical shop and was good with his work responsibilities and behavior toward his fellows. He is nonsmoker, does not use alcohol or drugs.

His examination revealed no skin anomalies suggestive of phacomatosis and no dysmorphic features. Psychomotor development was within normal limits.
He was fully conscious and oriented. His B.P was 106/78 mm hg. On neurological examination the cranial nerves were normal. Power was decreased in left upper and lower limb (0/5) with decreased tone, superficial reflexes were absent and deep tendon reflexes were exaggerated in both left upper

and lower limbs. And left planter was mute. Right sided neurological examination was normal and there were no signs of sensory or cerebellar dysfunction.

Results of a complete blood test revealed anemia Hb 7.0gm/dl, MCV 65.2 fl, MCHC 28 gm/dl, MCH 18.3 pg. Peripheral smear showed marked anisopoikilocytosis with predominantly microcytic hypochromic RBCs along with numerous elliptocytes and few polychromatophills and pencils cells. Platelet count was raised up to 9 lakhs.
Biochemistry indicated hemolysis; total bilirubin of 4.47 mg/dl, and unconjugated bilirubin being 3.89 mg/dl with raised LDH. Corrected reticulocyte count was 4%. Iron profile was within normal limits. There was no evidence of inflammation as ESR and CRP was within normal limits.
Based on above results further investigations were planned to search for the cause of hemolysis. Autoimmune work up was negative (ANA –ve). Direct and indirect coombs test was negative. Sickling test was negative with normal G 6 PD levels. Patient's osmotic fragility was increased. 2D Echocardiography and ECG was absolutely normal; so, possibility of cardioembolic stroke was out. So was the abdomen ultrasonography report with no evidence of organomegaly. Coagulation studies and chest radiograph was unremarkable. NCCT head revealed acute infarct in right fronto parietal region (Figure1). CT angiography revealed significant stenosis of supraclinoid segment of right ICA with reformatting of ACA and MCA via collaterals. Similar stenosis in left ICA, proxiamal A1 segment of left ACA and M1 segment of left MCA. Distal MCA and ACA are reformatted via collaterals. Multiple collaterals are noted in bilateral sylvian fissures along course of MCA (Figure2). MR angiographic findings are suggestive of moya moya syndrome. Compiling all the reports and findings it was diagnosed as moya moya associated with hereditary spherocytosis presenting as a stroke in young patient. Further testing for family members was done which not to our surprise revealed anemia with elliptocytosis and raised osmotic fragility, although mother was asymptomatic with only finding of pallor on examination. Siblings blood testing was within normal limits. Patient was started on dual antiplatelet drugs with pentoxiphylline. Prevention of anemia was crucial so he was transfused with 2 units of whole blood; with target Hb to be in the range between 10 and 12 gm/dl. Gradually during hospital stay by the end of 1 month power improved 3/5 left upper and lower limb at all range of movements at all joints. Splenectomy was not done as there was risk of post splenectomy thrombocytosis. Patient was discharged in stable condition with further follow up done after 1 month showed 4/5 power with normalization of Hb and gradually resolving thrombocytosis.

DISCUSSION

Moya moya disease (MMD) though first reported in Japan, since then been reported worldwide. The disease has a particularly high incidence in eastern Asia, especially in Japan. The male to female ratio was 1.8: 1 and a family history was noted in 10% of cases(6). MMD is rarely associated with HS.
MMD is a cerebrovascular disorder defined as a severe bilateral stenosis or occlusion of the arteries around circle of willis with prominent collateral circulation. Moya is a Japanese word that means puffy and is used to describe the peculiar angiographic appearance of the collateral vascular network(7).

Stroke-like signs represent a common clinical expression in adulthood as well as childhood, but the clinical presentation may be atypical in younger populations, with migraine-like headaches and involuntary movements(8,9).

Moya Moya occurs in patients with brain tumors, vascular malformations, neurofibromatosis, primary and secondary vasculitis after irradiation, infections, and head trauma. Holz et al reported the first association of hereditary spherocytosis and Moya Moya syndrome(10). Severe hemolysis may trigger endothelial injury and contribute to oxidative damage through nitric oxide scavenging. In addition, less deformability of the red blood cells (RBCs) and increased blood flow associated with anemia contribute to endothelial proliferation, which progresses slowly and produces stenosis followed by

occlusion. Increased hemolysis can also lead to chronic hypoxia and abnormal vasculature. As Moya Moya syndrome is well known to be associated with sickle cell disease and other prothrombotic states, Moya Moya syndrome in this child is in all likelihood related to spherocytosis. Splenectomy with maintenance blood transfusions to prevent anemia are the main components of treatment in HS, which is even more important in patients with associated MMD. Prevention of anemia is crucial because it is an important risk factor for ischemic events.

Both the abnormal rheology of spherocytes and chronic anemia led to the formation and progression of cerebral vasculopathy. In our patient preventive role of transfusions in stroke reflect the critical role of anemic hypoxia in the progression of cerebral vasculopathy. Thrombocytosis after splenectomy might be the predisposing factor for cerebrovascular events. Splenectomy will prevent the destruction of RBCs, prevent anemia, and increase the survival of RBCs.
Although rare, it is important to consider the possibility of MMD in a patient with HS presenting with stroke.

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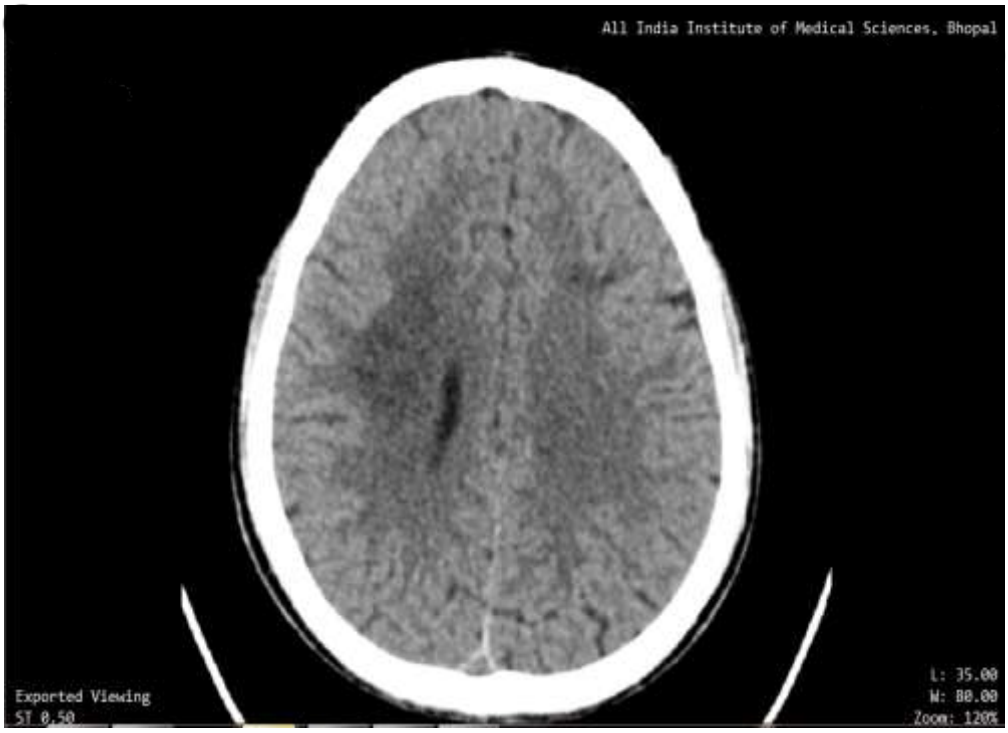

FIGURE 1: NCCT head revealed acute infarct in right fronto parietal region.

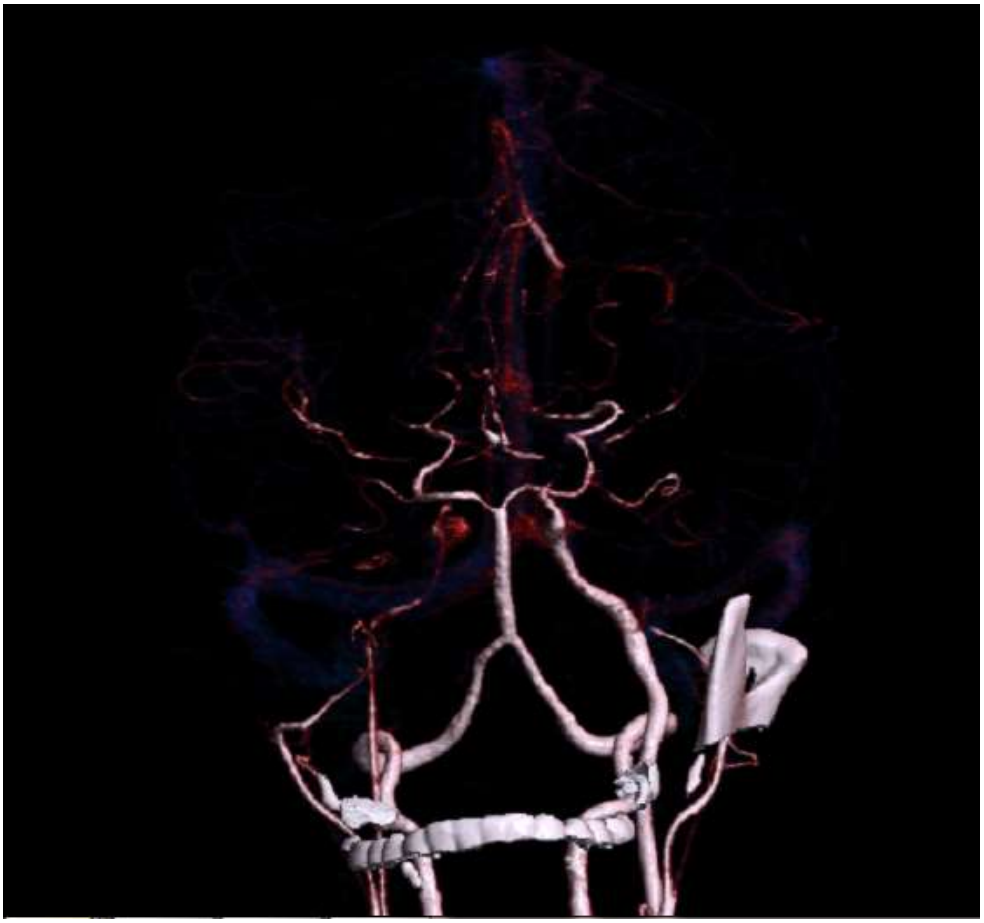

FIGURE 2: CT angiography revealed significant stenosis of supraclinoid segment of right ICA with reformatting of ACA and MCA via collaterals. Similar stenosis in left ICA, proxiamal A1 segment of left ACA and M1 segment of left MCA. Distal MCA and ACA are reformatted via collaterals. Multiple collaterals are noted in bilateral sylvian fissures along course of MCA.