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Unusual presentations of sickle cell disease in India – A case series

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Abstract

India is listed to have one of the highest national burdens of sickle cell disease (SCD) in the world. The clinical presentation of SCD may not follow a defined pattern in all cases. A wide variation in the severity as well as features has been noted in published data and clinical experience. However, published literature on unusual presentations of SCD from India is scarce. Present case series describes three unusual clinical presentations of SCD which we came across at a tertiary care Indian hospital - Moyamoya disease, cardiac arrhythmia, and nephropathy.

Keywords: Sickle Cell Disease, Moyamoya Disease, Cardiac Arrhythmia, Nephropathy, Sickle Cell Anemia

Introduction

Sickle Cell Disease (SCD) is a point mutation in the beta-globin chain, that results in the substitution of valine for glutamic acid at position 6. Hemoglobin S is the name given to this hemoglobin, whose deoxygenation results in polymerization, reducing red blood cell flexibility and increasing red blood cell rigidity.[1] The clinical course of SCD does not follow a single pattern; some patients have mild symptoms, while others have very severe symptoms.

India, home to more than 20 million SCD sufferers, has the greatest disease prevalence in South Asia.[2] With 42,016 babies projected to have been born with sickle cell anaemia in 2010 [interquartile range (IQR): 35,347-50,919], India has been listed as the nation with the second-highest predicted SCD births.[3] SCD is characterized by considerable variability in clinical severity, with some rare clinical presentations noted across various pediatric clinics across the world. Present case series describes three unusual clinical presentations of SCD which we came across at a tertiary care Indian hospital in Western India.

Case descriptions

Case 1: A 10-year-old female child presented with hypertensive crisis as a first symptom of the disease in november 2018. At first, she presented with progressively increasing generalised oedema, decreased urine output and macroscopic hematuria over 4 days, along with severe pallor. Child developed hypertensive emergency with blood pressure more than 95th centiles for age, gender, and height; along with 2 episodes of generalized seizures. She was given antiepileptics, packed red cell transfusions and labetalol drip. Initial impression of acute glomerulonephritis was made, Serum C3 levels, C-ANCA, P-ANCA and anti-GBM antibodies level were within normal limits. Peripheral smear was suggestive of sickle cells, target cells, hypochromia and microcytosis. MRI brain and Renal Doppler were also noted to be normal.Urine protein creat ratio was raised (>2). Child required blood transfusion in view of severe anemia (hemoglobin: 6.9 g/dl, MCV: 58.9 fL ,MCH- 31.8pg, TLC:9670 PLT: 5 lakhs) . High-performance liquid chromatography (HPLC) report was suggestive of Sickle-Beta Thalassemia. A diagnosis of sickle B thalassemia with sickle nephropathy with nephrotic syndrome was made. Once stable she was discharged on oral Hydroxyurea (15mg/kg/day) and anti-hypertensives and is on regular follow up for the same.

Case 2: An 8-year-old female child, a known case of SCD was admitted with pallor and icterus (January 2021). On examination, incidentally, child was found to have bradycardia (60beats /minute) with irregularly irregular pulse with no radio-femoral or radio-radial delay and no pulse apex deficit. Her blood pressure was normal. On cardiac examination, the second heart sound was wide and fixed split, ejection systolic murmur at pulmonary area. A diagnosis of cardiac arrhythmia in a sickle cell disease was considered and the child was further investigated. Her chest x-ray showed cardiomegaly with LA prominence. ECG showed features with signs of sick sinus syndrome (Image 2) and this was confirmed on Holter monitoring. Child was given packed red cell transfusions and started on oral orciprenaline (2mg /kg/ day QID). Her heart rhythm became regular though bradycardia persisted. She was advised to continue the same medication. As the child was asymptomatic and the stress test was normal, pacemaker was not advised. Child is now 10 years old, doing well and following up with us.

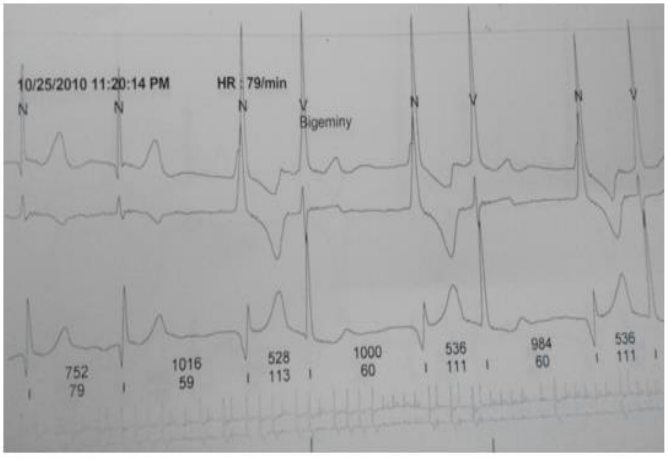

Figure 1: ECG showing features of sick sinus syndrome (Case 2)

Case 3: A 9-year-old male child was referred to our Pediatric Department of LTMGH with pallor and hepatosplenomegaly in December 2020. At that time, the child was diagnosed to have HbSD disease. Parents were counseled and child was given packed cell transfusions and discharged on hydroxyurea and other supportive care. Child was doing well, maintaining hemoglobin around 9 to 10 gm% till August 2021 following which he came back with multiple episodes of unconsciousness (off and on) for 6 months and inability to speak since a day. There was no other significant neurologic history. On examination, he was well nourished, drowsy with stable vital parameters. He had no pallor or icterus but had hepatosplenomegaly. On CNS examination, child was conscious at that time, however, his speech was impaired with good comprehension and sign of motor aphasia. His deep tendon reflexes were brisk with a positive Babinski's sign. Child was given supportive care and MR Angiography brain was done, which was suggestive of Moyamoya disease (Image 3). Patient was referred for surgical revascularization.

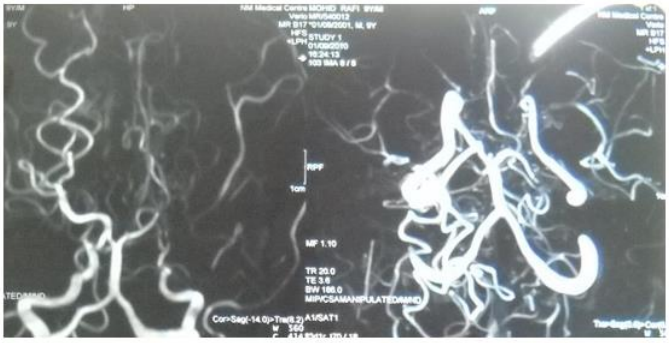

Figure 2: MR Angiography suggestive of MoyaMoya Disease (Case 3)

Discussion

Sickle cell disease may present uniquely to the clinician many times, and here we present a case series of three unusual presentations – Moyamoya disease, arrhythmia, and nephropathy.

Two key characteristics of Moyamoya disease, a rare chronic occlusive cerebrovascular condition, include the development of tiny capillary-sized capillaries that supply collateral blood flow and bilaterally increasing stenosis of the Circle of Willis arteries.[4] The angiographical appearance of these aberrant reticular arteries is hazy, or Moyamoya (literally "misty" in Japanese), giving the impression of a puff of smoke. Both ischemic strokes in children and brain hemorrhages in adults are frequently brought on by these vascular alterations.[5] Today, continuous transfusion treatment is used to manage sickle cell anemia patients who have had a cerebrovascular accident or who have shown signs of large artery vasculopathy by transcranial Doppler ultrasonography.[6] Nonetheless, the use of chronic transfusion treatment carries some risk. Potential adverse effects include hemosiderosis and iron overload, which may necessitate stopping therapy.[7] Many ischemic symptoms in patients with idiopathic Moyamoya disease who have substantiation of diminished perfusion reserve by positron emission tomography or single-photon emission computed tomography scan are relieved by surgical interventions, including direct and indirect vascularization procedures.[8,9] There are very few case reports of a sickle cell disease patient receiving an encephaloduroarteriosynangiosis (EDAS) surgery, despite the fact that there have been several documented cases of surgical revascularization in idiopathic Moyamoya disease.[10] The case mentioned in present series underwent EDAS surgical intervention.

In SCD patients, scientific reports have mentioned about electrocardiographic abnormalities, but such published data is rare from India.[11,12] QT prolongation, ventricular arrhythmias, first-degree AV blocks, atrial premature contractions, and ventricular premature

contractions are among the arrhythmias associated with SCD and crisis that have been observed.[13] In research conducted in the USA by Patel et al., concurrent arrhythmias were seen in roughly 6% of all hospitalizations attributable to SCD. In SCD-related hospitalizations from 2010 to 2014, rising trends in arrhythmia were seen in the reference study.[14] In the study by Gupta et al., it is mentioned that I nterleukin-18 (IL-18), arrhythmic load, and cardiac fibrosis were all found to be causally related to the cardiomyopathy associated with SCD.[15] Cell sickling in SCD may be the underlying cause which culminates in myocardial ischemia and inflammation, diffuse myocardial fibrosis, diastolic dysfunction, and cardiomyopathy.[16,17] Blood transfusions used to treat SCD may worsen cardiac dysfunction due to an uptick in inflammation, with a reduced risk of iron-mediated harm due to an increase in non-transferrin bound iron and labile plasma iron. In animal studies, iron-mediated damage causes cardiac fibrosis, increased oxidative stress, and diastolic and systolic dysfunction.[18] Therefore, persistent anemia, microvascular illness, systemic inflammatory disease, and iron-mediated damage are the main causes of cardiac disease linked with SCD. These patients need to be followed-up adequately.

It has been shown that blood pressure in people with sickle cell disease is lower than recommended normal ranges. Potential explanations for the lower blood pressure in SCD patients include lower body mass index in SCD patients, lower arterial stiffness, obstruction of the vasa recta in the kidney, repeated ischemia to the renal medulla, which results in a distal renal tubular concentrating defect and hyposthenuria.[19-21] A frequent but little-known consequence of SCD is renal damage, often known as sickle cell nephropathy (SCN). Despite the fact that most individuals do not experience symptoms of kidney disease, those who advance to severe chronic kidney disease (CKD) have a considerable morbidity rate.[22-24] The pathophysiology of SCN is connected to the kidney's vascular supply, which supports its clinical manifestations of hyposthenuria, hyperfiltration, tubular abnormalities, and haematuria.[22] Proteinuria, which can vary from microalbuminuria to unselective proteinuria, is fairly common and can occasionally progress to nephrotic levels over time.[22] A particularly bad prognosis is linked to full nephrotic syndrome in children, which affects about 4% of cases.[25] The ideal method for stopping kidney damage progression in SCD patients has not yet been identified. Early on, one should consider administering hydroxyurea and an anti-ACE inhibitor (ACEi).[26,27] There are currently no known early indicators for SCN in children.[28] Yet, there is a link between albuminuria and a "hemolysis phenotype," which is associated with an increased risk of problems which include pulmonary hypertension, systemic hypertension and severe anemia). There have been very few reports linking SCD with nephrotic syndrome in pediatric population or adolescents. One such case report by Cunha et al. explained an instance of nephropathy in SCD, who had a remarkable recovery after treatment with hydroxyurea and ACEis after an initial treatment failure with corticotherapy.[29] According to research by Gordeuk et al., individuals with sickle cell disease who have systolic SBP 120–139 mm Hg or DBP 70–89 mm Hg fall into the category of relative systemic hypertension, which is linked to an elevated risk of pulmonary hypertension and renal impairment. Clinical studies should be conducted to evaluate if antihypertensive and/or nitric oxide donor

treatment in sickle cell disease patients with relative hypertension avoids these and other problems.

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