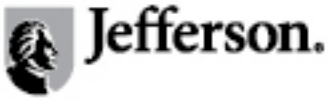

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Primary stroke in a woman with sickle cell anemia responsive to hydroxyurea therapy.

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Primary Stroke In A Woman With Sickle Cell Anemia Responsive To Hydroxyurea

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ABSTRACT

The most common cause of stroke in children with sickle cell anemia is infarction due to ischemia. In adults, however, stroke is most commonly hemorrhagic in nature. Other causes of stroke in patients with sickle cell disease are very rare. In this short communication we describe a woman with sickle cell anemia responsive to therapy with hydroxyurea who had primary stroke due to paradoxical embolization caused by a large atrial septal defect. Successful management of the stroke included surgical closure of the defect with trans-esophageal echocardiographic guidance. To the best of our knowledge this is the first patient with sickle cell anemia and stroke due to congenital heart disease that did not require open heart surgery for successful management.

Key words: sickle cell anemia, stroke, primary stroke, atrial septal defect, patent foramen ovale, paradoxical embolization

Introduction

Stroke is a major complication of sickle cell anemia (SS) in children. Its incidence is about 10% in children with SS less than 10 years of age [1]. Moreover, incidence of silent stroke detected by magnetic resonance imaging (MRI) could be as high as 35% [2]. Pathophysiologically, these strokes are most often infarctive in nature secondary to cerebrovascular occlusion. Stroke due to SS in adults is less common and is usually due to hemorrhage [1]. Risk factors for recurrent stroke in SS include acute chest syndrome, severe anemia, cerebral vasculopathy, previous stroke and transcranial Doppler ultrasound velocity > 200 cm/sec [3]. Other rare causes of recurrent stroke in patients without SS include paradoxical embolization due to patent foramen ovale [4]. In addition, co-existent hyperviscosity or thrombophilia with patent foramen ovale increase the risk of stroke. This scenario was reported in a child with SS and patent foramen ovale [5]. In this communication we describe an adult woman with SS and stroke secondary to paradoxical embolization due to atrial septal defect.

Case Report

A 42-year-old woman with SS has been followed in our adult sickle cell program for 25 years. Complications of her disease included acute chest syndrome, avascular necrosis of hip joints, mitral valve prolapse, migraine headaches and frequent vaso-occlusive crises (VOC). She was enrolled in the multicenter study of hydroxyurea (MSH) when she was 21 years old and has been on 2500 mg of hydroxyurea (HU) per day since then. She had an excellent response to HU with no recurrent episodes of acute chest syndrome and infrequent need for blood transfusion. After starting HU the frequency of VOC requiring hospital admissions decreased from one admission

every 1 to 2 months to less than one admission per year except when HU was discontinued due to pregnancy. Her hematologic parameters before and after HU are shown in Table 1.

At the age of 35 years she presented to the emergency room two days after developing abrupt bilateral blurry vision, left facial numbness and weakness of her left leg. Physical exam was remarkable for left lower extremity weakness which was more pronounced proximally. Vital signs were normal. All cranial nerves were intact and there was normal sensation bilaterally. Computed tomography (CT) scan of the brain showed three foci of hypodensity and magnetic resonance imaging (MRI) of the brain showed increased signal on T2, FLAIR and diffusion weighted images within the fronto-parietal deep white matter consistent with infarction in the border zone of the middle cerebral artery (MCA)-anterior cerebral artery (ACA). Magnetic resonance angiography (MRA) of the intra-cerebral and extra-cerebral vessels demonstrated focal narrowing of the right MCA at the trifurcation suggesting an embolic cause. Common causes of ischemic stroke including hypertension, diabetes, atrial fibrillation, renal disease and hyperlipidemia were ruled out with routine studies. Her hemoglobin electrophoresis after admission but before blood exchange transfusion showed HbS of 55% and HbF of 45%. Transthoracic Doppler echocardiography showed minimal mitral, aortic and tricuspid valves regurgitation with tricuspid regurgitant velocity (TRV) < 2.0 m/second (normal < 2.5 m/second). She underwent exchange transfusion 2 days after admission and was started on chronic blood exchange transfusions with the assumption that she had ischemic stroke due to SS.

Follow-up transesophageal echocardiography after discharge from the hospital showed a secundum atrial septal defect with a defect size of 1.8 cm. Right heart catheterization was performed and the pulmonary flow to systemic flow (Qp/Qs) was 1.7:1 with a mean pulmonary artery pressure of 21 mm Hg. An Amplatzer atrial septal defect (ASD) closure device was

deployed with transesophageal echocardiographic guidance with successful closure of the defect. At the patient's request exchange red cell transfusions were discontinued. The patient continued treatment with HU and aspirin. Repeat MRI of the brain after repair of the atrial septal defect showed no acute infarction; there were discrete areas of encephalomalacia and gliosis in the deep white matter of the frontal lobe corresponding to the areas of infarction identified previously. To date, seven years after percutaneous repair of the atrial septal defect she has had no strokes.

Discussion

The most common cause of stroke in patients with SS is cerebral infarction in children and hemorrhage in adults. The incidence of stroke in adult patients with SS, however, is not well known and more studies are needed in this population [6] . Moreover, patients with SS are prone to other causes of stroke such as cerebral infections, hyperlipidemia, renal disease, congenital heart disease and hyperviscosity [6]. The role of HU in preventing or causing stroke is controversial. Grace et al reported resolution of cerebral artery stenosis in a child with SS treated with HU [7]. On the other hand, Sidani et al reported stroke in a patient with SS on HU and hyperviscosity due to high Hb level after HU therapy [8]. In addition, the SWITCH study was terminated early because of the increase in secondary stroke with HU [9]. Stroke due to paradoxical embolism associated with congenital heart defect has been reported in patients with SS sporadically. Dowling et al described an 11 year-old girl with recurrent bilateral, strokes associated with patent foramen ovale, antiphospholipid antibodies and increased levels of factor VIII and lipoprotein [5]. A combination of pulmonary arterial hypertension (PAH) and patent foramen ovale may cause paradoxical embolization and stroke. However, stroke has been reported in patients with patent foramen ovale in the presence or absence of PAH [10, 11] which

is best defined by right heart catheterization (RHC) showing a mean pulmonary artery pressure ≥ 25 mm Hg [12]. Our patient had a mean pulmonary artery pressure of 21 mm Hg by RHC thus ruling out significant pulmonary hypertension. Moreover, atrial septal defect without stroke was reported in a child with SS associated with successful closure of the defect with open heart surgery [13].To the best of our knowledge , our patient seems to be the first patient with SS and stroke due to paradoxical embolism secondary to atrial septal defect that did not require open heart surgery for successful management.

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Table 1
Haematological parameters before and after hydroxyurea therapy

Parameters	Before Hydroxyurea*	After Hydroxyurea†
Haemoglobin, g/dL	8.0	9.8
Hematocrit, %	22.4	30.2
Mean corpuscular volume, Fl	96	132
Mean corpuscular Hb, pg	34.3	39.1
Mean corpuscular Hb concentration	35.6	32.5
Reticulocyte count, %	15.4	5.3
Reticulocyte count, absolute	358,820/uL	123,500/uL
Fetal Hb, %	6.1	45
White blood cell count,	15,800/uL	8,500/uL
Platelets,	537,000/uL	452,000/uL

*Baseline data before starting HU; †Data when presented with stroke