Moyamoya Syndrome in a Child with HbEβ-Thalassemia

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Abstract

Moyamoya is a progressive cerebrovascular disease associated with stenosis or occlusion of the arteries of the Circle of Willis, especially the supraclinoid internal carotid arteries (ICA), with consequent multiple collaterals. While it is common in sickle cell disease, it is rare in thalassemia. We present a 9-year-old, with HbEβ-thalassemia, who presented with headache, vomiting and episodes of transient hemiparesis. Initial imaging studies showed bilateral frontal old lacunar infarcts and narrowing of the ICA, which progressed to complete occlusion with compensatory dilatation of the basilar and vertebral arteries. She is maintained on anti-platelet therapy and is being evaluated for bypass surgery.

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Abbreviations Key

ICA Internal carotid artery

Hb Hemoglobin

TDT Transfusion dependent thalassemia

NTDT Non-transfusion-dependent thalassemia

SCI Silent cerebral infarct

MMS Moyamoya syndrome

SCD Sickle cell disease

HU Hydroxyurea

OPD Outpatient department

MRI Magnetic resonance imaging

MRA Magnetic resonance angiography

EEG Electroencephalogram

ACA Anterior cerebral artery

MCA Middle cerebral artery

ICA Internal carotid artery

TIA Transient ischemic attack

Mg Milligram

Kg Kilogram

Abstract

Moyamoya is a progressive cerebrovascular disease associated with stenosis or occlusion of the arteries of the Circle of Willis, especially the supraclinoid internal carotid arteries (ICA), with consequent multiple collaterals. While it is common in sickle cell disease, it is rare in thalassemia. We present a 9-year-old, with HbEβ-thalassemia, who presented with headache, vomiting and episodes of transient hemiparesis. Initial imaging studies showed bilateral frontal old lacunar infarcts and narrowing of the ICA, which progressed to complete occlusion with compensatory dilatation of the basilar and vertebral arteries. She is maintained on anti-platelet therapy and is being evaluated for bypass surgery.

Introduction

Patients with transfusion- or non-transfusion-dependent thalassemia (TDT or NTDT), suffer from a hypercoagulable state and often present with thromboembolism [1-3]. NTDT is more than 4 times likely to be associated with thromboembolic events than TDT. In the former, the events are mostly venous and relatively rare in the pediatric age group. On the contrary, arterial strokes are more common in TDT than in NTDT (28% vs 9% respectively). The risk factors in TDT are the higher rate of iron overload-mediated morbidities like diabetes mellitus, cardiac dysfunction and arrythmias [4-6]. Silent cerebral infarcts (SCI) are common in both groups[3-7].

Moyamoya is an idiopathic, progressive cerebrovascular disease, characterized by bilateral stenosis or occlusion of the arteries of the circle of Willis, typically the supraclinoid internal carotid arteries, followed by extensive collateralization. The patients are prone to thrombosis, aneurysm, and hemorrhage. It presents

an angiographic appearance of tangled, tiny, collateral vasculature, that has been compared to a puff of smoke[8,9].

Moyamoya syndrome (MMS), occurs in a wide range of clinical conditions including hemoglobinopathies, especially sickle cell disease (SCD)[10,11]. Few reports of MMS have been reported in TDT [12,13], but more commonly in NTDT[14-16], and rarely in Eβ-thalassemia[17,18].

Case Report

A.O., an Indian girl, first presented at the age of 15 months with pallor, jaundice and dark urine. She was otherwise well and her development was satisfactory. Apart from jaundice and pallor, the only other positive findings were enlarged liver and spleen (2 cm below the costal margin). There were no skeletal changes. Her initial CBC showed WBC 5 x10^9/l, Hb 7gm/dl, MCV 59fl, platelets 414 x10^9/l and reticulocytes 5%. G6PD was normal; HPLC showed HbA 36.3%, Hb A_2 5.8%, HbF 27.5%, HbE 30.3%. β-globin gene study revealed compound heterozygosity for Codon 41-42 del CTTT and E 26 K (c.79 G > A), thus confirming the diagnosis of Eβ-thalassemia. She was managed as NTDT and maintained on folic acid, with transfusion only for severe anemia. Over the next one year, her Hb was ˜7.5 g/dl and she required transfusion only once. At age 3 years, she was commenced on 20 mg/kg of hydroxyurea (HU) daily, to which she showed modest response. However, after about one year on HU, she started to develop skeletal changes. She was therefore commenced on transfusion every 2 months.

In May 2016, at the age of 5 years, she had haploidentical bone marrow transplantation, with the mother as the donor. However, there was no engraftment and her Hb rapidly dropped to the baseline value. Since September 2016, she has been on regular transfusion every 5-6 weeks and 30 mg/kg/day deferasirox.

She was admitted to the hospital in December 2019 with acute liver injury: elevated transaminases and direct bilirubin, along with abdominal pain and vomiting. Blood-borne virology and hepatitis screen were negative. Deferasirox was discontinued; she gradually improved with supportive therapy and was discharged after 1 week.

At the OPD visit in March 2020, she complained of repeated attacks of early morning headache and non-projectile vomiting of recent onset. She reported two episodes of transient right-sided weakness and numbness that lasted for a few minutes. There was no neurologic deficit, the sensorium was unaffected and cranial nerves were normal. The weakness was not progressive. There was no prior history of focal neurological deficit, seizures, cognitive or psychiatric manifestations and no pertinent family history.

MRI showed multiple old lacunar infarcts in both cerebral hemispheres, while MRA revealed normal intracranial arteries. The distal segments of both ICAs were small in caliber. MRA of the neck showed small calibers of both ICAs, with compensatory dilatation of both vertebral arteries.

EEG showed no specific abnormalities and echocardiography was normal. Serum ferritin was not elevated and there was no evidence of iron accumulation in the liver or heart. Thrombophilia screening, inflammatory markers and antibody studies were all normal.

She was on regular transfusion, low-dose deferasirox (10 mg/kg/day) and prophylactic aspirin. Despite this, 4 months later, she complained of more frequent and more prolonged episodes of weakness in both hands and feet, with associated dysarthria but no loss of consciousness or spatial perception. These were suspected to be partial seizures and she was treated with carbamazepine, after which the episodes ceased. She was neurologically normal in-between attacks.

Repeat MRI showed no evidence of new ischemic or inflammatory changes; the previously seen cerebral infarcts were evident. However, MRA now showed complete occlusion of both ICAs as they enter the intracranial cavity (Fig 1). The ACA and MCA showed good flow, being supplied from posterior cerebral arteries through communicating arteries bilaterally. The calibers of the vertebral and basilar arteries and communicating arteries were more than double to compensate for the ICA occlusion (Fig. 2).

Three weeks after the imaging studies, the patient had no more morning headache or vomiting, there was reduced frequency of TIAs and no weakness.

Discussion

Eβ-thalassemia spans the spectrum of NTDT to TDT and our patient was initially managed as NTDT, but eventually became transfusion dependent. She could therefore, present with complications associated with the 2 phenotypes. Indeed, she presented with TIA and was eventually found to have several old lacunar infarcts. Therefore, an initial impression of SCI was made but, because of extension of her symptoms, repeat imaging confirmed complete occlusion of both ICAs, with increased collaterals, consistent with MMS[8] . She had also shown evidence of deferasirox hepatotoxicity.

MMS may be asymptomatic but could present with TIA, ischemic or hemorrhagic stroke, and epilepsy. Rarely, patients may develop dystonia, chorea, or dyskinesia[19,20]. Our patient presented with morning headache and transient brief unilateral weakness, which became more frequent and lasted for longer periods of time. She later developed focal seizures, accompanied by dysarthria. Other common causes of abnormal movements such as drug side effects, Sydenham's chorea, and neurodegenerative conditions, vasculitis, autoimmune conditions, infections, thrombophilias, and connective tissue disorders were all ruled out.

She had been on regular transfusion for at least 5 years before her neurological symptoms. This supports the premise that, while transfusion dependency reduces the effect of chronic tissue hypoxia, patients are still at risk of arterial thrombosis [4,13,21] . Moreover, MMS is not uncommon among patients with HbE-β-thalassemia. In one study, three of four beta thalassemia patients with MMS were NTDT and one of them was HbE-β-thalassemia [22]. In another recent study among 13 patients of MMS with thalassemia, 6 were TDT and 3 had HbE-β-thalassemia [13]. Our patient is, however, much younger than those in the literature.

The complete occlusion of both ICAs in our patient probably prevented the appearance of new vessel formation and the appearance of the classic puff of smoke, especially given the good compensation by communicating vertebral and basilar arteries. This is consistent with stage II of the Suzuki MMS staging system [8].

There is no curative treatment for MMS; it is therefore imperative to search for and treat any underlying condition. The vascular occlusion tends to continue despite any known medical management[13] as in our patient, who was on aspirin therapy and regular transfusions. She is currently being considered for bypass surgery [23].

Conflict of Interest

The authors have no conflict of interest to declare.

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