Moyamoya syndrome with ruptured aneurysm in α-thalassemia: A case report

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Abstract. Moyamoya syndrome (MMS) refers to the moyamoya vascular disease associated with various systemic diseases and conditions, including sickle cell anemia, Fanconi anemia and iron deficiency anemia. However, the association between MMS and other hemoglobinopathies is less frequently observed. MMS, like moyamoya disease, is a cerebrovascular condition that is characterized by chronic progressive stenosis or occlusion at the ends of the bilateral internal carotid arteries, anterior cerebral arteries and the beginning of the middle cerebral arteries, and is secondary to the formation of an abnormal vascular network at the base of the skull. Patients with MMS are prone to thrombosis, aneurysm and bleeding. The present study reports the case of a 43-year-old man with α-thalassemia who presented with moyamoya vessels with a ruptured aneurysm bleeding into the ventricle. α-thalassemia is considered as an extremely rare but potential cause of MMS. Since MMS is a progressive disease, early diagnosis and treatment is vital to prevent the disease from worsening.

Introduction

Moyamoya syndrome (MMS) is a moyamoya vascular disease that occurs in patients with a number of underlying diseases, including sickle cell anemia (1), Fanconi anemia (2) and iron deficiency anemia (3). Among all the blood disorders, MMS is more commonly associated with sickle cell anemia. Non-deformable erythrocytes, especially sickle cells, obstruct the blood flow in the *vasa vasorum*, thus leading to vessel wall

ischemia and subsequent intimal proliferation of the internal carotid artery, thereby leading to occlusion (4). The reduction in blood flow from anemia, along with fewer deformed blood cells, may also lead to progressive endothelial proliferation and subsequent vascular occlusion (5). Symptom progression has been reported in most patients with MMS within 5 years and may lead to transient ischemic attack (TIA), ischemic stroke or cerebral hemorrhage (6). Without appropriate treatment, the prognosis of patients with MMS is poor (7). Therefore, identifying the etiology of MMS along with prompt diagnosis and treatment is essential to improve patient outcomes. Although a variety of hematological disorders have been identified as causes of MMS (1-3), it is unclear whether thalassemia is a cause of MMS. The present study describes the case of a 43-year-old man with α-thalassemia who manifested moyamoya vessels with a ruptured aneurysm bleeding into the ventricle.

Case report

A 43-year-old male was admitted to the Xiaolan People's Hospital of Zhongshan (Zhongshan, China) due to the sudden manifestation of headache, dizziness and nausea. The patient was generally healthy, with a family history of anemia, no family history of spontaneous intracerebral hemorrhage or aneurysm, and no any history of hypertension, diabetes or any other chronic disease. Physical examination was unremarkable except for a stiff neck, an overgrown maxilla and a prominent forehead. Routine blood analysis revealed a hemoglobin level of 94 g/l (normal range, 110-160 g/l), a mean corpuscular volume of 63 fl (normal range, 82-92 fl) and a mean corpuscular hemoglobin content of 18.2 pg (normal range, 27-31 pg). All remaining laboratory examinations were normal. Head computed tomography (CT) revealed a hemorrhage from the ventricular system and localized white matter hypodensity in the left frontal lobe (Fig. 1A and B). CT angiography indicated bilateral internal carotid artery terminal segments, bilateral anterior cerebral arteries, bilateral middle cerebral artery stenosis with moyamoya vessels and subependymal nodular dense opacities in the posterior horn of the left lateral ventricle (Fig. 1C and D). Other disorders associated with MMS, such as vasculitis (8), autoimmune disease (9), infection (10) and thrombophilia (11), were excluded through medical history, physical examination and relevant blood tests. The patient was duly diagnosed with moyamoya disease (MMD) with

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aneurysm rupture and bleeding. The cause of the anemia was unknown.

Digital subtraction angiography was performed on the day of admission (Fig. 2) followed by cerebral aneurysm embolization. During surgery, a Marathon microcatheter was used to superselect the origin of the left posterolateral choroidal artery. The aneurysm and parent artery were then occluded with Glubran glue. Postoperative angiography showed that the aneurysm and the left posterolateral choroidal artery were completely occluded and no longer visualized (Fig. 3).

The patient was subsequently diagnosed with α-thalassemia with a $-^{SEA}/-\alpha^{3.7}$ genotype by genetic testing. The patient was given intermittent lumbar puncture, analgesic (0.3 g/bid ibuprofen) and fluid infusion (normal saline and 5% glucose solution). At 18 days after surgery, CT scans revealed that the ventricles were unobstructed, whereas strip-like and nodular dense opacities were newly evident in the left ventricle, which were consistent with the postoperative changes (Fig. 4). The condition of the patient improved and they were discharged from the hospital. According to the usual MMS treatment procedures of the Xiaolan People's Hospital of Zhongshan, long-term strict follow-up was planned, and left superficial temporal artery and middle cerebral artery bypass will be performed at 3 months post-surgery. Before bypass surgery, whole-brain CT perfusion (CTP) will be performed to evaluate whether to adjust the surgical plan. During follow-up, if the patient has a rapid decrease in hemoglobin or rapid enlargement of the spleen, a blood transfusion or splenectomy will be performed after a comprehensive evaluation. At 1 month post-discharge, CT confirmed that each ventricle was unobstructed, the intraventricular hemorrhage had been completely absorbed and an embolic glue artifact appeared in the left ventricle (Fig. S1).

Discussion

α-thalassemia is a single-gene genetic disease with a high global incidence. Approximately 5% of the global population carry mutations in the α-globin gene (12). High incidence areas include tropical and subtropical regions such as southern China, Southeast Asia, the Mediterranean region, India, the Middle East and Africa (13,14). In China, epidemiological surveys show that the highest rates of α-thalassemia mutation occur in the Guangdong (12.70%), Guangxi (19.11%) and Hainan (45.04%) provinces (15). In China, Japan and South Korea, the annual incidence of newly diagnosed cases can be as high as 6.03 per 100,000 individuals (16). To the best of our knowledge, there is no report of any demographic research on MMD in the Guangxi and Guangdong provinces. MMS manifests in a variety of ways, including TIA, reversible ischemic neurological deficit, ischemic stroke, hemorrhagic stroke, epilepsy, cognitive impairment, involuntary movements and headache (17,18). The present patient was born in Guangxi, China, which is an area with a high incidence of α-thalassemia. Causes of MMS such as atherosclerosis, neurofibromatosis (multiple), intracranial tumors, radiation injury and hyperthyroidism were excluded through examination of the patient's medical history, laboratory tests and radiographic imaging. To the

best of our knowledge, there are few reports relating to MMS associated with α-thalassemia.

Thalassemia is a common and autosomal recessive genetic disease with a high incidence (19). According to the type of globin synthesis disorder, thalassemia can be divided into α-thalassemia and β-thalassemia (19). Mutations or deletions of the globin gene in thalassemia result in an imbalance in globin synthesis, premature destruction of erythrocyte precursors in the bone marrow, hemolysis of erythrocytes in the peripheral blood and the appearance of abnormal erythrocytes (20). Endothelial damage, platelet activation, increased plasma microparticles, impaired nitric oxide bioavailability, increased blood oxidants, loss of erythrocyte deformability and phosphatidylserine exposure on the outer leaflet of the red blood cell membrane lead to a hypercoagulable state (21-23). Anemia and hypercoagulability may lead to tissue hypoxia, endothelial hypertrophy and microvascular stenosis (23,24). MMS is occasionally reported in β-thalassemia. In a previous study, among 13 patients with β-thalassemia and MMS, 7 patients had non-transfusion-dependent thalassemia, whereas 3 patients had hemoglobin E (HbE)-β thalassemia (4). In another recent study, a patient with HbE-β-thalassemia was diagnosed with MMS at the age of 9 years, and magnetic resonance imaging showed the presence of multiple old lacunar infarcts in both cerebral hemispheres (25). The patient's age at onset was much younger than previously reported (25). Several studies have shown that multiple cerebral infarction and large artery occlusion in β-thalassemia-related MMS are associated with a chronic hypercoagulable state (4,24,25). As α-thalassemia and β-thalassemia share similar pathogenesis, we hypothesize that the left frontal cerebral infarction and large artery occlusion in the present study were related to the anemia and hypercoagulable state. The establishment of an α-thalassemia animal model is expected to further clarify the mechanism of α-thalassemia-induced MMS and provide a theoretical basis for the clinical diagnosis and treatment of α-thalassemia-related MMS.

To the best of our knowledge, there is currently no definite and effective drug for MMS (26). Cases of MMS complicated by aneurysm rupture should be treated surgically as soon as possible to prevent rebleeding (27). In the present case, the aneurysm was located at the distal end of the posterolateral choroidal artery and had caused hemorrhage in the ventricular system after rupture. Emergency embolization of the aneurysm effectively prevented rebleeding. Intracranial and extracranial revascularization surgery is the main treatment for MMS and can effectively prevent ischemic stroke (28,29). In recent years, the efficacy of extracranial and intracranial revascularization for reducing the risk of bleeding has gradually been confirmed (30,31). Intracranial and extracranial revascularization procedures include direct techniques (e.g., external carotid artery-to-internal carotid artery bypass) and indirect techniques (e.g., encephaloduroarteriosynangiosis, omental-cranial transposition, encephalo-myo-synangiosis and encephaloduroarteriomyosynangiosis) (16). Compared to indirect techniques, direct techniques have the advantage that they can re-establish blood flow immediately once the anastomosis is created. Since the present patient had MMS with a ruptured aneurysm, the left superficial temporal
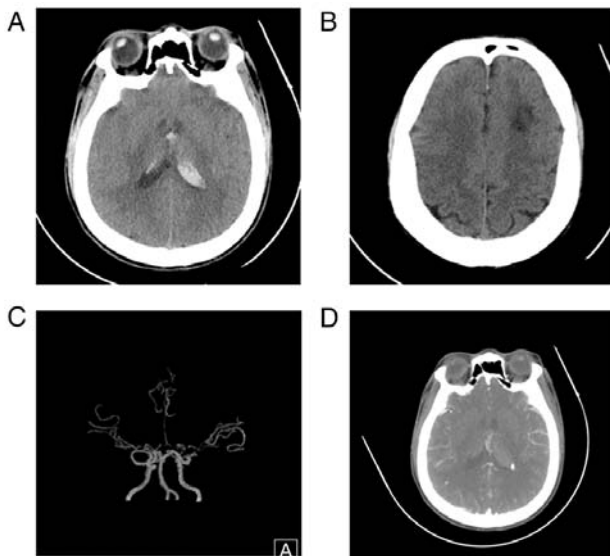
Figure 1. Head CT indicating (A) ventricular system hemorrhage and (B) localized white matter hypodensity in the left frontal lobe. CT angiography revealing (C) bilateral internal carotid artery terminal segments, bilateral anterior cerebral arteries and bilateral middle cerebral artery stenosis with moyamoya vessels. (D) CT angiography revealing subependymal nodular dense opacities in the posterior horn of the left lateral ventricle. A, ahead; CT, computed tomography.
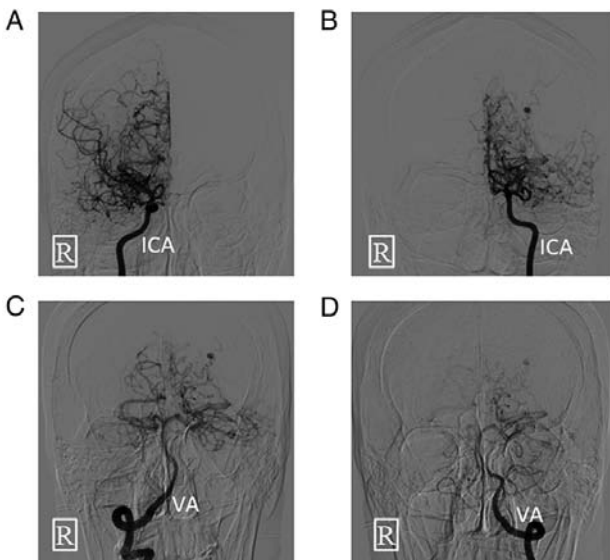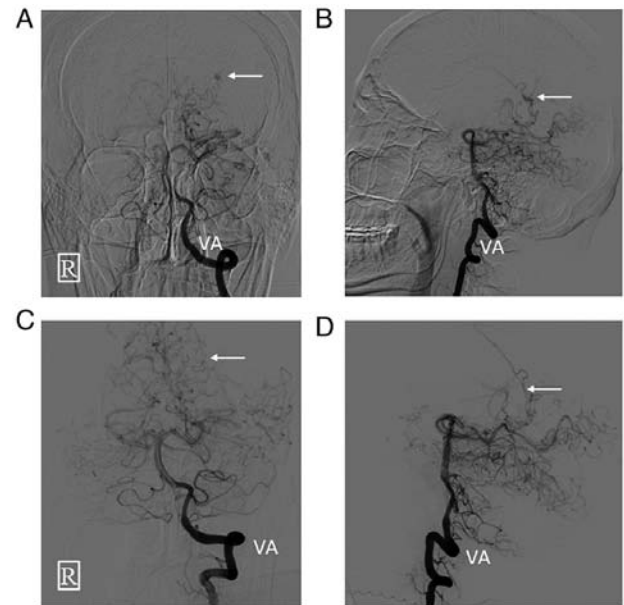

Figure 3. (A) Anteroposterior and (B) lateral views of the aneurysm. (C) Anteroposterior and (D) lateral view of the aneurysm after cerebral aneurysm embolization. All arrows indicate the location of the aneurysm. R, right; VA, vertebral artery.

Figure 2. (A and B) Angiogram of the bilateral ICAs in the AP view indicating steno-occlusive alteration of the ICA terminus with moyamoya vessels. (C and D) Angiogram of the bilateral VAs in the AP view indicating the presence of an aneurysm to the left lateral posterior choroidal artery. ICA, internal carotid artery; AP, anteroposterior; VA, vertebral artery; R, right.
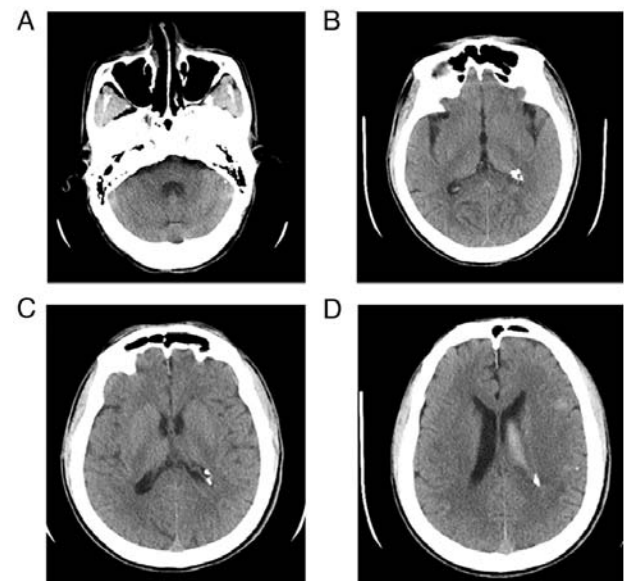

Figure 4. Head computed tomography performed 18 days after surgery indicating that each ventricle is unobstructed, whereas strip-like and nodular dense shadows are newly evident in the left ventricle. The fourth (A) and the third ventricle (B) are unobstructed. (C and D) The lateral ventricle is unobstructed, while the left lateral ventricle shows an artefact caused by embolic glue.

artery was bypassed and a middle cerebral artery bypass was performed after the acute phase of intracranial hemorrhage. Whole-brain CTP can reveal subtle hemodynamic changes that can effectively guide surgery for MMD, evaluate changes in the postoperative cerebral perfusion status and can be used for disease follow-up (32). Whole-brain CTP will be performed on the present patient prior to surgery to assess the cerebral hemodynamic status and thus decide whether to adjust the surgical plan.

In conclusion, α-thalassemia may represent a causative factor for MMS. To the best of our knowledge, there is currently no definite and effective drug for MMS. Patients with MMS should undergo extracranial and intracranial revascularization as soon as possible.

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