Int J Clin Exp Med 2019;12(2):2020-2024
www.ijcem.com /ISSN:1940-5901/IJCEM0075222

Case Report

Childhood stroke associated with Takayasu arteritis: a case study

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Received March 1, 2018; Accepted July 13, 2018; Epub February 15, 2019; Published February 28, 2019

Abstract: Purpose: This present study reports a case of a child with Takayasu arteritis, with onset of stroke as the primary symptom. This case illustrates that Takayasu arteritis is dangerous in children patients and is related to acute recurrence that can cause catastrophic complications within six months. Methods: A diagnosis of multiple Takayasu arteritis, with a primary manifestation of cerebral stroke, was established for a 12-year-old male patient, through reviewing patient disease history, clinical manifestations, physical examination results, laboratory examination, limbs vascular ultrasound, head magnetic resonance imaging, and cranial magnetic resonance angiography imaging. Results: The patient developed Takayasu arteritis that initiated upon onset of cerebral infarction, in contrast with the common process of Takayasu arteritis. Conclusion: This case illustrates that multiple Takayasu arteritis is dangerous in children patients, may cause cerebral infarction in early stages, and may present repeated acute recurrence, causing catastrophic complications within six months.

Keywords: Takayasu arteritis, associated stroke, children

Introduction

Takayasu arteritis (TA) is a kind of chronic inflammatory arteriopathy commonly affecting the aorta and its major branches. It has been reported that 20% of TA patients have symptoms in the central nervous system, usually manifesting as cerebral ischemia or strokes [1]. Childhood stroke is a rare event, with an incidence of approximately 2.5-2.7% cases per 1,000,000 per year [2]. The present study reports a case of TA in a child with sudden onset of ischemic stroke. This case demonstrates that TA is related to acute recurrence, causing catastrophic complications within six months.

Case report

In July 2007, a 12-year-old male patient was admitted to a local hospital with weakness in his left side, dysarthria, and deviation of angle of the mouth towards the right side. This lasted for over 24 hours. Brain magnetic resonance imaging (MRI) revealed multiple areas of infarctions in the right frontal and temporal lobes (**Figure 1A**). Digital subtraction angiography (DSA) did not reveal any abnormal findings in bilateral internal carotid arteries (**Figure 1B**, **1C**). Results of the above examinations indicated that the patient was suffering from the disease of moyamoya. Accordingly, the patient was treated with ceftriaxone (1 g every 12 hours) and aspirin (150 mg/day). After 10 days, the patient's speech returned to normal and he could walk unaided. The left-sided facial palsy recovered. Upon discharge, muscle power in his left limb was found to be 4/5. However, his parents stated that the child had wild mental retardation, even though he was able to return to school two months after the stroke.

In October 2007, the patient was admitted with relapsing dysphasia, hearing loss, and tinnitus over the previous two days. Symptoms of fever, headache, seizures, and altered sensorium were absent. There was no history of trauma or cardiac disorders. He had no family history of inherited cerebrovascular disease. He was the only child of non-consanguineous parents.

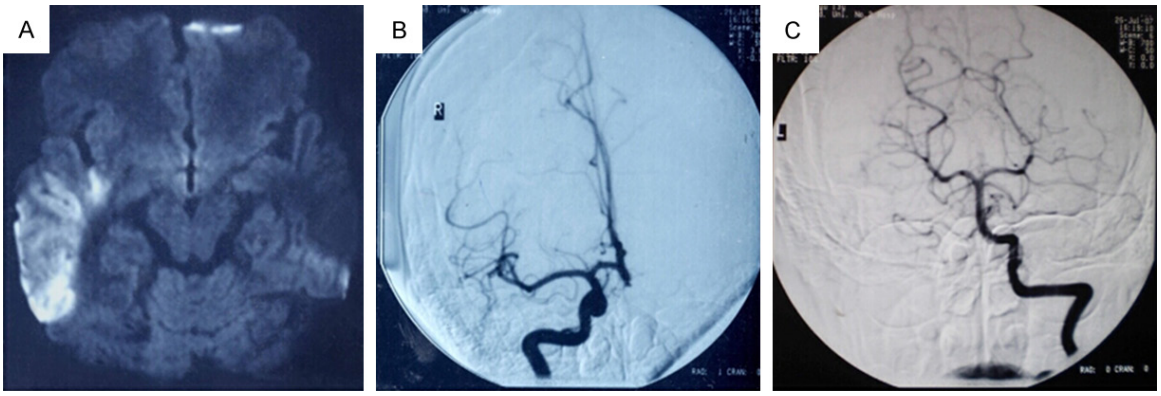

Figure 1. Brain MRI (A) demonstrated multiple hyperintense signals in the right frontotemporal region. The right temporal lobe swelled. DSA revealed no abnormal findings in right (B) and left (C) internal carotid arteries.

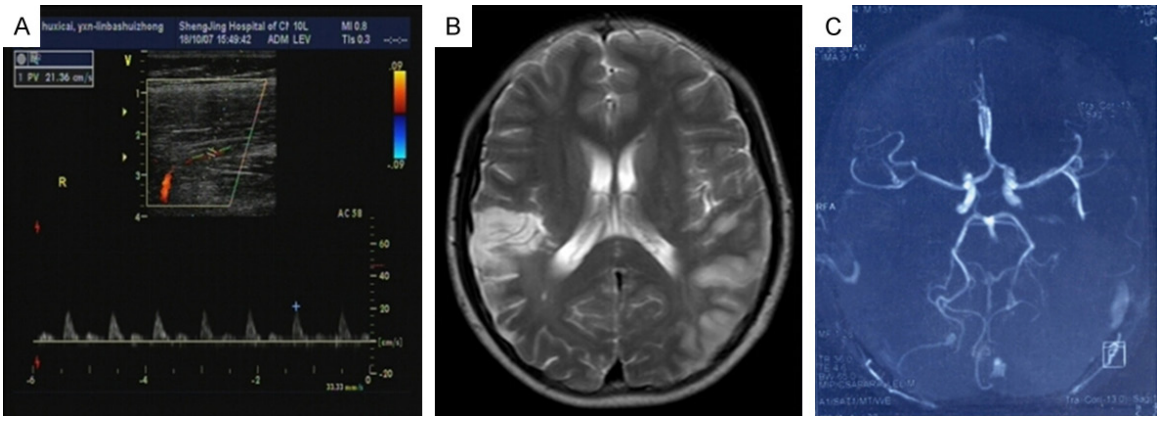

Figure 2. Ultrasonography (A) demonstrated that internal diameter was 3.3 mm in the right anterior tibia artery and 2.8 mm in the left ones. The velocity of bloodstream bilaterally was non-measurable. It revealed stenosis in the anterior artery of the right and left tibia. Brain T2-weighted MRI (B) revealed high-intensity lesions in right temporal lobes. The gyrus in the left temporal and occipital lobes widens and the white matter of the subcortical area were high intensity. Brain MRA (C) revealed that the stem of the bilateral middle cerebral arteries was normal and its distal branches were rare. The right MCA was more severe than the left ones. There were no abnormal findings of the basilar artery and posterior.

General examination revealed a blood pressure of 105/80 mmHg on his right arm and 148/80 mmHg on his left arm, as well as a bruit over the aorta abdominalis. After neurological examination, he was alert, conscious, and oriented. There was no facial palsy. Muscle power in the left upper limb was 4/5 and 3/5 in the lower limb. Deep tendon reflexes were exaggerated on the left side and the left plantar reflex was extensor. Laboratory data revealed a white blood cell count of 6.8×10^9/L. Erythrocyte sedimentation rate (ESR) was 10 mm/hr. C-reactive protein (CRP) concentration was 3.16 mg/L (normal: 0-8 mg/L). Investigations for autoimmunity (ANA, dsDNA, anticardiolipin antibodies, antiplatelet antibodies, and rheumatoid factor) were negative. Cerebrospinal fluid normal display: white blood cell count was 25/mm^3, a protein level of 0.4 g/L, and a glucose level of 3.07 mmol/L. Tuberculin test of 1:2,000 was negative. Electroencephalogram of all leads showed a relatively large number of scattered medium θ waves. Both electrocardiogram and color Doppler examinations of the heart were normal. Ultrasonography for major peripheral arteries revealed stenosis and occlusion in the right and left anterior tibia artery (**Figure 2A**), as well as in the distal portion of the left brachial artery. Electroencephalography revealed that the diffusing background was slow with no epileptiform activity. Furthermore, T2-weighted MRI revealed high-intensity lesions in the left

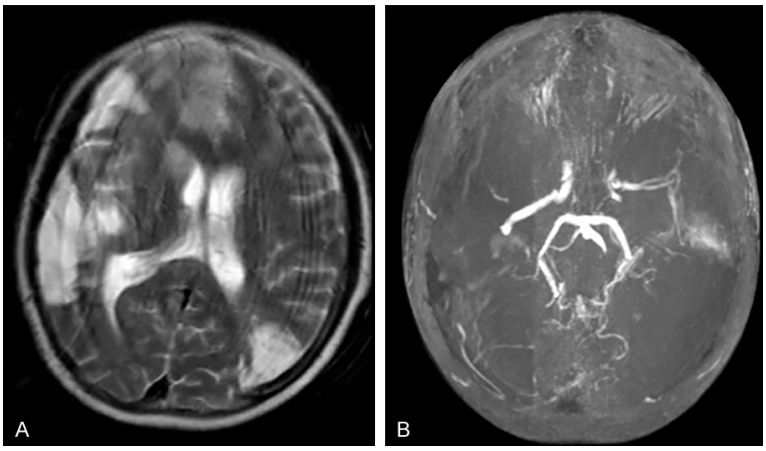

Figure 3. Brain T2-weighted MRI (A) revealed multiple high intensity in the right frontal, left temporal, and occipital lobes. Gyrus of the right frontal lobe widened and showed the hyperintense signal. MRA (B) showed occlusion of both distal middle cerebral arteries, anterior cerebral artery bilaterally, and communicating artery. Also, there was narrowing in left internal carotid arteries.

temporal cortical area and subcortical area of the white matter. In addition, it revealed cortical atrophy and white matter hyperplasia in the postmedian of the right temporal lobe and in the cortex of the parietal lobe (**Figure 2B**). Magnetic resonance angiography (MRA) of cerebral vessels revealed multiple stenosis of the branches of the right middle cerebral arteries (**Figure 2C**). Three-dimensional MRA of the aorta and its proximal branches were suggested, but not performed, as the patient left the hospital against medical advice.

He was readmitted three months later with fever, seizures, and becoming unconscious, with stiffness with trembling in his left side. Blood pressure was 140/110 mmHg in his left upper extremity. Brachial artery pulses were not measurable. Accordingly, his radial and tibial pulses were also undetectable. As a result, his feet were cold and hands were cyanotic. Blood analysis revealed a 16.2×10^9/L white blood cell count. ESR was elevated to 65 mm/hr, CRP was elevated to 10.8 mg/L, prothrombin time was 14.7 seconds (normal: 10.5-13.5 seconds), partial thromboplastin time was 41 seconds (normal: 21-37 seconds), fibrinogen was 4.186 g/L (normal: 2-4 g/L), and D-dimeride was 1,861 μg/L (normal: 0-252 μg/L). Brain MRI revealed multiple infarcts in the right frontal and temporal lobes and in the left temporal and occipital lobes (**Figure 3A**). MRA revealed an occlusion of both distal middle cerebral arteries, anterior cerebral artery bilaterally, and communicating artery. In addition, there was narrowing in the left internal carotid arteries (**Figure 3B**). After two days, although aggressive management was taken, the patient had a massive intracerebral edema. The family agreed to discontinue medical support considering the poor prognosis. The patient progressed to herniation and expired.

Discussion

TA is a rare idiopathic systemic and chronic inflammatory disease of unknown etiology, commonly involving large arteries such as the aorta and its primary branches [3, 4]. It is the most frequent pediatric large-vessel childhood vasculitis worldwide [5]. Most pediatric patients with TA present during adolescence [6]. It has been reported that 20% of TA patients have symptoms in the central nervous system, usually manifesting as cerebral ischemia or strokes[1]. Furthermore, strokes are the most serious symptom of TA, with TA mortality ranging from 8% to 35% over five years in adults [7]. Childhood stroke is rare, with an incidence of approximately 2.5-2.7% of cases per 1,000,000 per year [2]. Transient ischemic attacks or strokes may occur in TA due to occlusion or embolic material [8]. For example, Ringleb et al. reported that middle cerebral artery (MCA) involvement was most common [9]. Girls are affected more than boys [10]. In the present study, a 12-year-old boy with sudden onset of ischemic stroke was reported. There was no evidence of infection diseases or inherited factors in the patient, after extensive investigations, including all kinds of encephalitis, systemic lupus erythematosus, and other vasculitides.

There are three stages to TA. To the best of our knowledge, phase I of TA commonly presents non-specific symptoms, such as fever, dyspnea, weight loss, vomiting, fatigue, and abdominal pain in children [11]. At this stage, arteriographic findings may be minimal and the disease is often unrecognized. Phase II of TA is dominated

by vessel pain and tenderness due to vessel inflammation. Phase III is the fibrotic stage, in which ischemia dominates in many organs [6]. Neurological symptoms in TA may develop in phases II and III. The patient reported in this study was in good physical condition and normal before turning 12 years old. When he revealed the symptoms of stroke, the third stage of TA was evident. The non-specific nature of symptoms at the first stage, combined with the absence of physical signs, resulted in delayed diagnosis and failure to initiate early adequate treatment in the disease course. The patient appeared to have acute symptoms of TA associated with elevated ESR, C-reactive protein, and white blood cell count, when ultimately admitted. Takayasu arteritis appears to be an autoimmune disease with an initial inflammatory response in the vasa vasorum, with cellular infiltration mainly by T-cells, which invade the outer layer of the media and adjacent adventitia [12]. This case demonstrates that TA can cause cerebral strokes in children, activated by an unknown etiology.

Diagnosis of TA in this patient was assessed according to the American College of Rheumatology Criteria for TA [13]. Presence of ≥3 of the six criteria was consistent with the diagnosis of TA: onset age <40 years, claudication, decreased brachial artery pulse, >10 mmHg difference in systolic blood pressure between arms, a bruit over the aorta or subclavian arteries, and arteriographic evidence of narrowing or occlusion of the aorta, as well as its primary branches including the proximal upper and lower extremities. The patient did not fulfill the angiography of the aorta and its branches due to the invasive method of delineating vascular anatomy. However, the patient was given ultrasonographic narrowing arteries of the upper and lower extremities. Ultrasound of the affected artery revealed a characteristic pattern of diffuse homogeneous circumferential thickening of the vessel wall with narrowing of the lumen and dampening of the spatial Doppler waveform [14]. Presentation of this patient highlighted the diagnostic challenges of a young child. TA was not diagnosed, unfortunately, until late in his second hospital visit.

Differential diagnosis of TA in children involves systemic non-inflammatory vasculopathies associated with fibromuscular dysplasia and moyamoya syndrome. This reported case demonstrates the symptoms of stroke at the onset of disease. Accordingly, MRI revealed cerebral ischemia, although the patient did not find any stenosis and occlusion in the cerebral vessels in DSA during the second hospitalization. However, the patient was judged to be suffering from moyamoya disease (MMD), due to cerebral ischemia. When the patient was admitted eventually for multiple cerebrovascular complications of TA, he presented with similar cerebrovascular signs of MMD. Based on a review of the literature, Suzuki's classification divides moyamoya disease into six stages, according to angiographic findings [15]. The carotid arteries in the patient displayed changes typically for only one stage. In addition, patient survival was prolonged. A very dense network was observed at the base of the brain, resembling a "puff of smoke", first described in 1957 [16]. To the best of our knowledge, moyamoya disease, associated with Takayasus arteritis in children, has not been previously described. Although the pathogenesis of moyamoya remains unclear, primary and secondary forms have been recognized. The primary form is characterized by bilateral angiographic lesions [17]. Secondary forms occur in association with other autoimmune diseases, including systemic lupus erythematosus [18] and Behcet's disease [19]. In the present patient, occlusion of intracranial arteries may have resulted from vasculitis caused by autoimmune mechanisms purported to cause TA.

Once the diagnosis of TA is made, treatment becomes challenging. Glucocorticoids remain an effective agent for 60% of patients with TA [20], although more than half of these patients flare with tapering [21]. If the disease relapses, induction with cyclophosphamide and corticosteroids is an effective therapeutic option for childhood TA [22]. The present patient relapsed with platelet and coagulation activities increasing in TA. Therefore, anticoagulation is valuable.

Conclusion

Takayasu arteritis is a chronic inflammatory arterial disease of unknown causes, occurring predominantly in young women. Incidence of stroke in Takayasu arteritis is rarer in children than in adults. It is not a typical symptom during the acute phase of TA. In the present patient, a 12-year boy with a sudden onset of

ischemic stroke did not have acute symptoms of TA. MRI noted stenosis or occlusion at the terminus of bilateral middle cerebral arteries at the beginning. After six months, the pathogenetic condition of the patient was promptly aggravated. He developed extensive cerebral infarction. In such cases, the patient should receive an angiography of the aorta and its branches first.

Disclosure of conflict of interest

None.

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