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A case of bilateral Moyamoya disease associated with Williams syndrome

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Abstract

Bilateral Moyamoya disease manifesting as ischemic stroke in a patient with Williams syndrome has not been previously reported. Williams syndrome is a genetic disorder characterized by infantile hypercalcemia, elfin facial features, an outgoing personality, and cardiovascular abnormalities. It has been found to be related to elastin gene defect. Cerebrovascular abnormalities with associated strokes in Williams syndrome have been described only recently and rarely. Moyamoya disease is a cerebrovascular disorder characterized by progressive occlusion of the supraclinoid internal carotid artery. The pathogenesis of Moyamoya disease is unclear. Only a single report of Moyamoya disease associated with Williams syndrome manifesting as an intracerebral hemorrhage has been published. We report the first case of bilateral Moyamoya disease manifesting as ischemic stroke in a patient with Williams syndrome. We propose that inherited moyamoya disease is also related to elastin gene defect.

INTRODUCTION

Williams syndrome is characterized by infantile hypercalcemia, elfin facial features, an outgoing personality, and cardiovascular abnormalities. The cardiovascular disorders include hypertension and structural heart diseases, including supravalvular aortic or pulmonic stenosis, ventricular septal defects, patent ductus arteriosus, and mitral valve prolapsed.[1,2]

Moyamoya disease is a cerebrovascular disorder characterized by progressive occlusion of the supraclinoid internal carotid artery (ICA).[3] Some researchers believe that genetic factors contribute to the development of the disease[4,5] and several studies have described Moyamoya syndrome associated with congenital heart disease.[6,7] We postulated that a relationship exists between Moyamoya disease and Williams syndrome and that the same pathogenesis could be involved in both. Here, we present a case of bilateral Moyamoya disease associated with Williams syndrome and suggest a possible pathogenesis of Moyamoya disease based on our case and a literature review.

CASE REPORT

The patient was born after a normal pregnancy and delivery. At the age of 2 months, he was evaluated for facial features characteristic of Williams syndrome (a broad forehead and long smooth philtrum) and a heart murmur. An echocardiogram performed at that time revealed supravalvular aortic stenosis and mild coarctation of the aorta. When he was 2 years old, the patient underwent a supravalvular aortic stenosis patch dilatation operation, at which time he showed mild mental retardation and developmental delay. His intelligence quotient (IQ) was only 49 at the age of 6 years. A genetic consultation established a diagnosis of Williams syndrome based on his facial features, cardiovascular disorder, and mental retardation. At the age of 9 years, he was admitted for repeat surgery to treat coarctation of the aorta due to an impaired blood supply to the lower extremities and resultant muscle weakness (Figure 1). On the third postoperative day, he suddenly presented with right-side weakness and was referred to the department of neurology.

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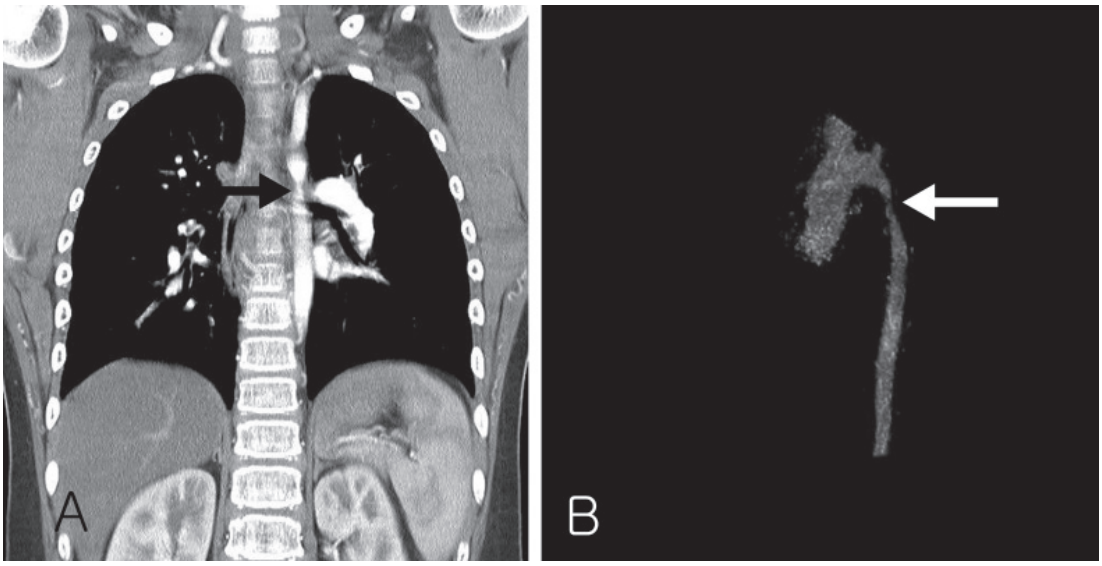

Figure 1: Chest computed tomography(A) and three-dimensional reconstruction(B) images show coarctation of the aorta (arrows).

The physical examination showed prominent ears, a long smooth philtrum, full cheeks, and prominent lips (Figure 2). The neurologic examination found right central-type facial palsy, tongue deviation to the right, and Medical Research Council (MRC) grade 4 right hemiparesis affecting the arm worse than the leg. The other neurological results were normal.

Initial computed tomography (CT) of the cranium performed without intravenous contrast showed a discrete hypodense area lateral to the left internal capsule and adjacent to the left putamen. Magnetic resonance imaging (MRI) of the head showed an area of abnormally increased signal intensity in the left frontal lobe and putamen, consistent with anterior border zone infarction

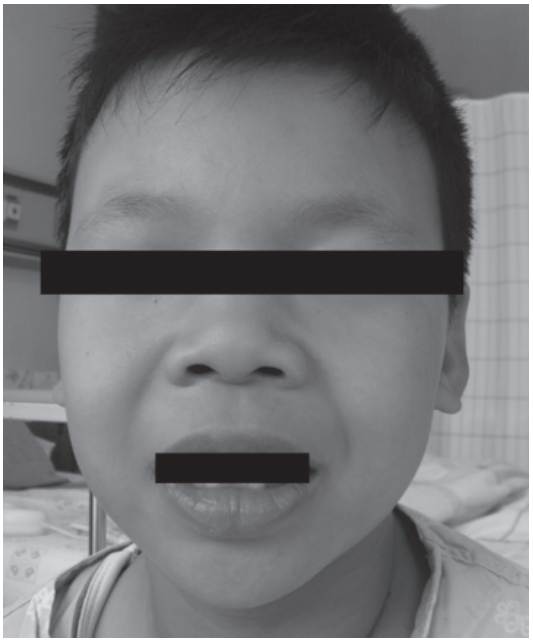

Figure 2: The patient's face has prominent ears, a long smooth philtrum, full cheeks, and prominent lips, features characteristic of Williams syndrome.

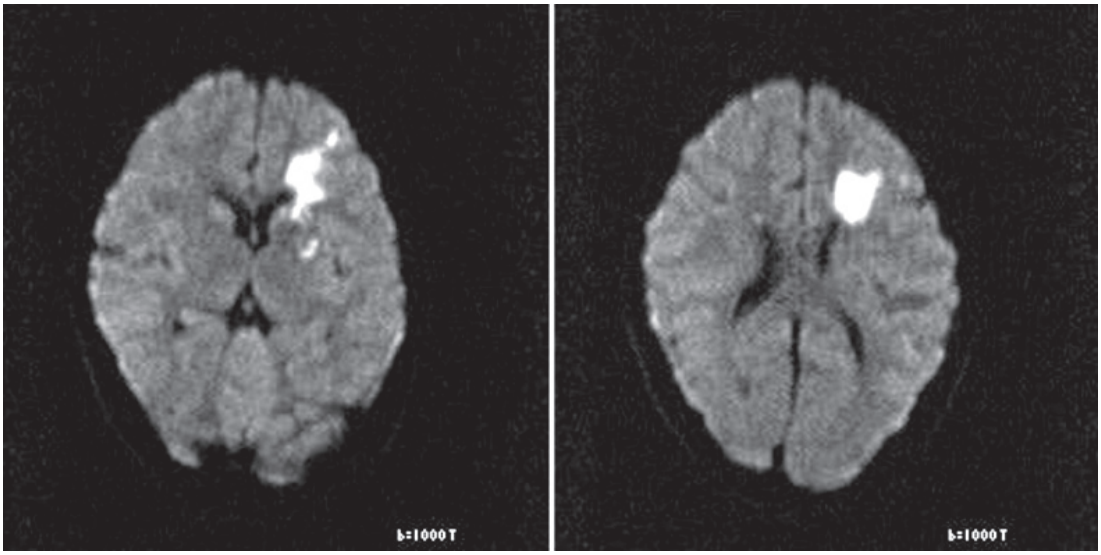

Figure 3: Diffusion-weighted magnetic resonance imaging shows an area of abnormally increased signal intensity in the left frontal lobe, consistent with anterior border zone infarction.

(Figure 3). Magnetic resonance angiography (MRA) suggested near-total narrowing of both distal ICAs, so conventional angiography was performed, which showed near-total occlusion of both ICAs just proximal to the bifurcation, together with numerous Moyamoya vessels (Figure 4). Brain single-photon emission computed tomography (SPECT) showed hypoperfusion of the bilateral frontal lobes and no vascular reservoir (Figure 5). Aspirin therapy was initiated, and the patient recovered to a nearly normal state within 2 weeks after his onset of symptoms and was transferred to a rehabilitation facility, where he continued to improve. In view of the SPECT finding, we thought that the etiology of the stroke is hemodynamic dysfunction rather than cardioembolic causes. Given his diagnosis of Moyamoya disease and the presence of compromised cerebral perfusion, he will ultimately require bypass surgery (encephaloduroarteriosynangiosis).

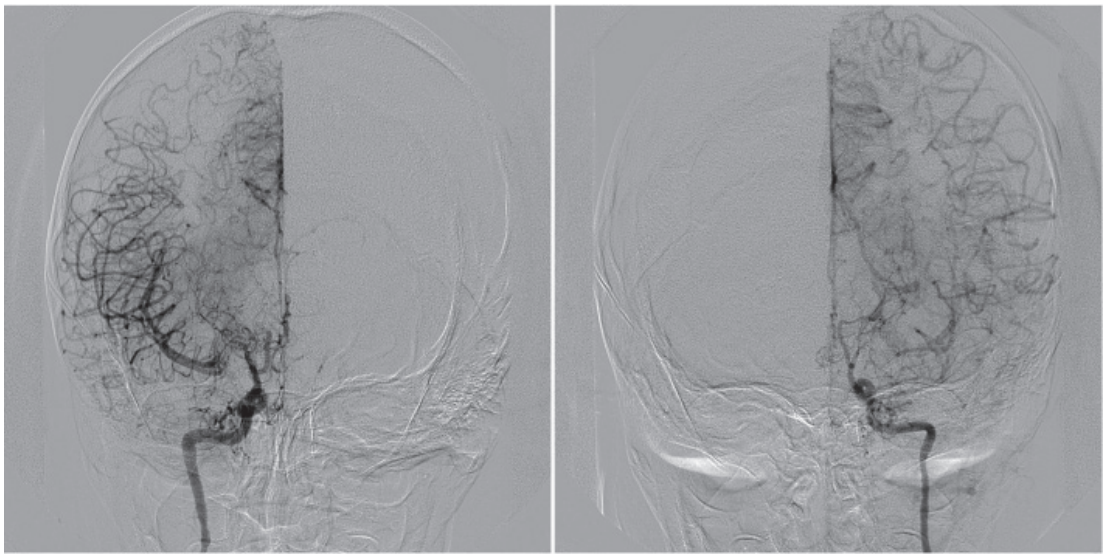

Figure 4: Transfemoral cerebral angiography shows near total occlusion of both supraclinoid internal carotid arteries, just proximal to the bifurcation and numerous Moyamoya vessels.

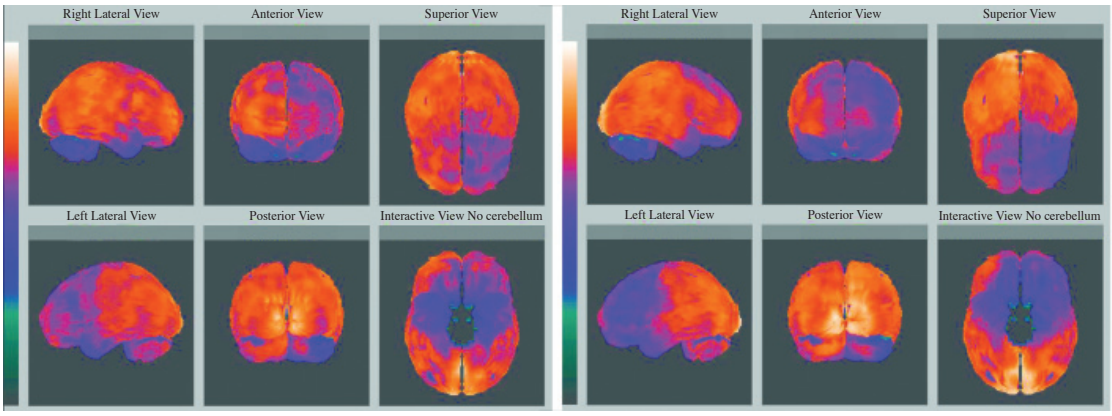

Figure 5: The brain single-photon emission computed tomography images show areas with hypoperfusion in the frontal lobes bilaterally (left). Images after Diamox infusion reveal no significant perfusion changes (right).

DISCUSSION

Williams syndrome is a genetic disorder that results from a submicroscopic deletion of chromosome 7q11.23. This region is 1–2 Mb in length and includes the elastin gene, the deletion of which results in an autosomal dominant disorder.[8] The classic Williams syndrome is described in all textbooks on dysmorphology: typical facies, cardiovascular disorders, and variable mental retardation with a friendly, outgoing personality. The key facial features are a broad forehead, medial eyebrow flare, periorbital fullness, strabismus, stellate iris pattern, flat nasal bridge, malar flattening, full cheeks and lips, long smooth philtrum, and wide mouth. Intellectual development varies widely, with most cases falling in the mild to moderately retarded range of the spectrum. The characteristic cardiovascular abnormalities are supravalvular aortic stenosis and peripheral pulmonary artery stenosis, with other muscular arteries involved less often.[1,2] These features may be related to deletions of the elastin gene, which occur in about 90% of cases.[8]

Cerebrovascular incidents have rarely been described in Williams syndrome and only recently.[9,10] It may be related to the cardiovascular abnormalities that can be seen in Williams syndrome, which are risk factors for stroke, including hypertension, cardiac disease, and arterial stenosis. Although stenoses within the cerebral vasculature may also be major determinant of stroke in these patients, because patients with Williams syndrome do not commonly undergo cerebral angiography, the true incidence of asymptomatic cerebrovascular stenosis is not known.[10]

One autopsy report has described Moyamoya disease associated with Williams syndrome.[11] This is the only a single report of Moyamoya disease associated with Williams syndrome manifesting as an intracerebral hemorrhage. In that case, the autopsy revealed vascular abnormalities, with supravalvular aortic stenosis, and an abnormally complicated cerebrovascular network in the cerebral arteries.[11] The arterial wall of the supravalvular aortic stenosis lesion consisted of thickened medial tissue exhibiting elastic disorganization, along with prominent smooth muscle cells.[11] The carotid artery wall was also abnormally distensible and thick, and major ultrastructural abnormalities of elastic fibers were observed in conjunction with smooth muscle cell dedifferentiation.[11] A previous study found that the elastin gene defect in patients with Williams syndrome leads to abnormal elastic fiber assembly within the media.[12] Arterial wall hypertrophy associated with a defect in the elastin gene may be a major factor in increased distensibility, suggesting that an increased proliferative response and the associated dedifferentiation process represent two important mechanisms underlying matrix accumulation and the development of arterial stenosis.

Moyamoya disease is a cerebrovascular disorder that is characterized by progressive occlusion of the supraclinoid ICA and its main branches within the circle of Willis.[3] This occlusion results in the formation of a fine vascular network (the Moyamoya vessels) at the base of the brain. However, the pathogenesis of Moyamoya disease is unclear. Some researchers believe that genetic factors contribute to the development of the disease.[3–5]

The predominant feature in the pathology of Moyamoya disease is now considered to be progressive stenosis of the carotid artery terminations, and the Moyamoya vessels evolve into dilated perforating arteries that function as collateral pathways.[3] The histopathological findings in the carotid terminations include fibro-cellular thickening of the intima, irregular undulation of the internal elastic lamina, and attenuation of the media, similar to what is seen in the Moyamoya vessels in Williams syndrome.[3,13]

We report here a case of bilateral Moyamoya disease associated with Williams syndrome. This is the first case of Moyamoya disease with Williams syndrome manifesting as ischemic stroke. In view of the similarity of the carotid artery pathology between Moyamoya disease and Williams syndrome noted in previous studies[11,12], we suggest that inherited Moyamoya disease is also related to an elastin gene defect.

ACKNOWLEDGEMENT

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