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Multifocal Intracranial Occlusive Vasculopathy Resulting in Stroke: An Unusual Manifestation of Williams Syndrome

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Summary: When a 2-year-old child with Williams syndrome had a stroke, he was found to have extensive occlusive cerebrovascular arteriopathy.

Index terms: Arteries, cerebral; Arteries, diseases; Brain, infarction; Children, diseases

The syndrome of supravalvular aortic stenosis, mental retardation, and distinctive elfin facial features, described by Williams et al (1), has been expanded to include a systemic vasculopathy. We report a 2-year-old child with Williams syndrome who had a stroke and was found to have extensive occlusive cerebrovascular arteriopathy.

Case Report

A 2-year-old boy diagnosed with Williams syndrome as an infant presented to the hospital after 4 days of decreased activity and speech, left hand weakness, facial asymmetry, and refusal to walk. The patient's medical history was notable for infantile irritability, decreased physical growth, developmental delay, transient hypercalcemia, mild peripheral pulmonary artery stenosis, and possible mild supravalvular aortic stenosis by echocardiography.

His neurologic examination showed a left homonymous hemianopia, mild left hemiparesis, and a central left facial nerve palsy. Computed tomography of the brain (not shown) showed low attenuation in the right putamen associated with mild mass effect consistent with an acute cerebral infarction. Magnetic resonance imaging showed abnormal high signal intensity on long-repetition-time/long-echo-time sequences within the right basal ganglia, centrum semiovale, and optic radiation compatible with infarction (Fig 1A).

Cerebral and brachiocephalic angiography showed several abnormalities. There were long, segmental stenoses of the right supraclinoid internal carotid artery, right M-1 and M-2 segments of the middle cerebral artery, and right A-1 segment of the anterior cerebral artery, which were nearly occlusive (Fig 1B). Two additional tandem focal stenoses of the basilar artery were seen (Fig 1C). There was extensive pial-pial collateralization to the right middle cerebral territory by the ipsilateral anterior and posterior cerebral arteries. No stenotic disease was shown in the extracranial carotid or vertebral arteries or within the supravalvular portion of the aortic arch.

The patient's left hemiparesis slowly improved over the next 3 months, although he was left with some residual weakness and spasticity. A 6-month follow-up magnetic resonance image showed no change in the appearance of the regions of subcortical brain infarction.

Discussion

Williams syndrome is an uncommon hereditary disorder occurring in approximately 1 in 10 000 births. The constellation of supravalvular aortic stenosis, mental retardation, and distinctive elfin facial features was described approximately 30 years ago (1). The syndrome since has been expanded to include multiple peripheral pulmonary artery stenosis, dental anomalies, peripheral and visceral arterial stenosis, infantile hypercalcemia, growth retardation, transient hypercalcemia, and large arterial anomalies (2).

The pathogenesis of the syndrome is unknown. Early investigators suggested an environmental disturbance attributable to maternal or infantile overingestion of vitamin D, although after removal of this supplementation, the syndrome has persisted (3). Interestingly, administration of high-dose vitamin D to pregnant rabbits has been used to create a model in offspring of the craniofacial anomalies and aortic anomalies found in Williams syndrome (4). Recent studies have demonstrated various abnormali-

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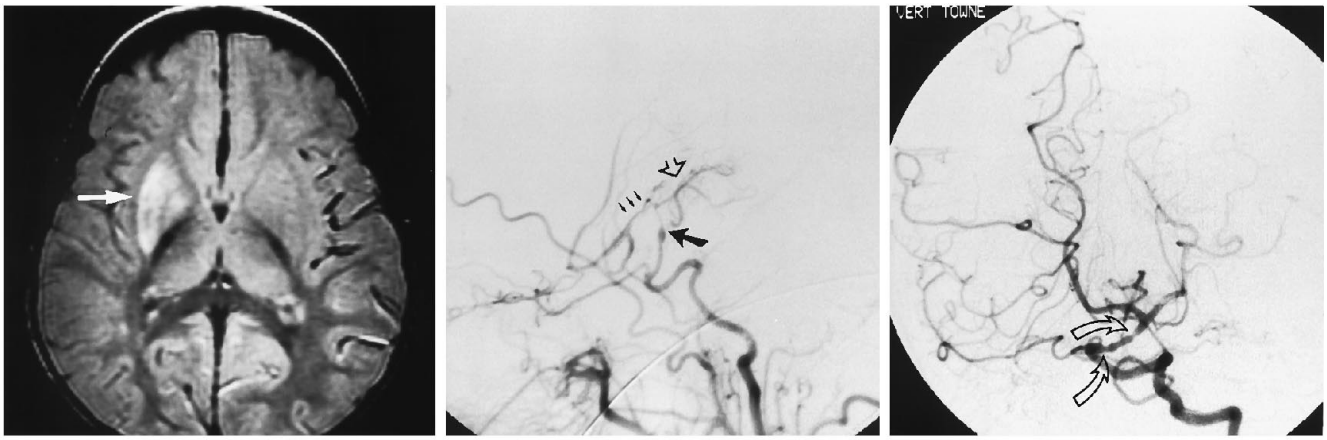

Fig 1. *A*, Axial magnetic resonance image (2000/80/1) of the brain shows increased signal within the right putamen and globus pallidus compatible with infarction (*arrow*).

B, Selected image in the right anterior oblique projection from the arterial phase of a cerebral angiogram via a right common carotid injection shows a long segmental stenosis of the right supraclinoid internal carotid artery (*large arrow*), right M-1 segment of the middle cerebral artery (*open arrow*), and right A-1 segment of the anterior cerebral artery (*small arrows*).

C, Single image (Towne view) from the arterial phase from a left vertebral artery injection shows tandem focal stenoses of the basilar artery (*open arrows*).

ties in vitamin D metabolism, calcium clearance deficiency, and impaired secretion of immunoreactive calcitonin (5). Genetic research supports inheritance by autosomal dominance with variable penetrance (6), although identification of a specific enzymatic defect or gene locus has yet to be accomplished.

Extracranial arterial stenotic disease has been widely reported since the initial description of Williams syndrome. Clinically significant stenoses of the aortic arch and its branches, renal, coronary and mesenteric arteries all have been reported (7–10). Aortic stenosis, aortic hypoplasia, and renal artery stenosis appear to have important pathophysiologic significance, because they frequently produce systemic hypertension and its sequelae (7–10). Associated coronary artery stenotic disease in Williams syndrome may produce acute myocardial ischemia and sudden death (9).

Until Kawai et al (11) reported a patient with Williams syndrome and moyamoya disease, no instances of intracranial vasculopathy have been previously described, to our knowledge. Stroke in children with Williams syndrome has been described occasionally, although these events usually have been attributed to thromboembolic and hypertensive complications of systemic vascular occlusive disease (including stenotic disease of the origins of the brachiocephalic arteries) (7, 12).

The histopathology of arterial stenosis associated with Williams syndrome is distinctive. These lesions are characterized by a prominent medial hyperplasia with variable degrees of intimal hyperplasia (13). The medial elements display alterations in ultrastructural arrangement by electron microscopy, suggestive of disordered regional growth (ie, localized dysplasia) (14). Studies of the supravalvular aortic stenosis of Williams syndrome typically have shown a circumferential, haphazard medial arrangement by light microscopy (14). These histopathologic findings are considered representative of the arteriopathy occurring at other sites (13).

In the only previously reported case of associated intracranial cerebrovascular disease, histological examination showed a prominent intimal hyperplasia quite distinct from the typical histopathology of extracranial stenosis in Williams syndrome. The discordance in features raises the question of coincidental occurrence of moyamoya disease in a patient with Williams syndrome.

In the present case, it is likely that the patient's stroke was attributable to an occlusive arteriopathy affecting the internal carotid and middle cerebral arteries. This supposition is based upon the combined findings of segmental stenotic lesions on cerebral angiography and the absence of thromboembolic sources from

the heart, aortic arch, and extracranial carotid or vertebral arteries shown on echocardiography and angiography. This raises the interesting consideration of whether the observed intracranial stenoses in our case may be the result of the same medial hyperplastic vasculopathy commonly described in extracranial vascular lesions associated with Williams syndrome (13). Pathologic substantiation of this supposition, however, is lacking.

In conclusion, ischemic neurologic deficits occurring in patients with Williams syndrome should be evaluated for possible intracranial occlusive vasculopathy in addition to other previously described etiologic factors, such as thromboembolic phenomena and hypertension occurring from systemic vascular occlusive disease.

References

1. Williams JCP, Barratt-Boyes BG, Lowe JB. Supravalvular aortic stenosis. *Circulation* 1961;24:1311–1318
2. Burn J. Williams syndrome. *J Med Genet* 1986;23:389–395
3. Oppe TE. Infantile hypercalcemia, nutritional rickets and infantile scurvy in Great Britain. *Br Med J* 1964;I:1659–1661
4. Friedman WF, Mills LF. The relationship between vitamin D and the craniofacial and dental anomalies of the supravalvular aortic stenosis syndrome. *Pediatrics* 1969;43:12–18
5. Culler F, Jones K, Deftos LJ. Impaired calcitonin secretion in patients with Williams syndrome. *J Pediatr* 1985;107:720–723
6. Grimm T, Wesselhoeft H. The genetic aspects of Williams-Beuren syndrome and the isolated form of the supravalvular aortic stenosis: investigation of 128 families. *Z Kardiol* 1980;69:168–172
7. Daniels SR, Loggie JM, Schwartz DC, et al. Systemic hypertension secondary to peripheral vascular anomalies in patients with Williams syndrome. *J Pediatr* 1985;106:249–251
8. Ino T, Nashimoto K, Iwahara M, et al. Progressive vascular lesions in Williams-Beuren syndrome. *Pediatr Cardiol* 1988;9:55–58
9. Conway CE Jr, Noonan J, Marion RW, Steeg CN. Myocardial infarction leading to sudden death in the Williams syndrome: report of three cases. *J Pediatr* 1990;117:593–595
10. Robinson L, Gedroyc W, Reidy J, Jaxton HM. Renal artery stenosis in children. *Clin Radiol* 1991;44:376–382
11. Kawai M, Nishikawa T, Tanaka M, et al. An autopsied case of Williams syndrome complicated by moyamoya. *Acta Paediatr Jpn* 1993;35:63–67
12. Williams RL, Azouz EM. Aortic anomalies in an adolescent with Williams elfin facies syndrome. *Pediatr Radiol* 1984;14:122–124
13. Zalzstein E, Moes CAF, Musewe NN, Freedom RM. Spectrum of cardiovascular anomalies in Williams-Beuren Syndrome. *Pediatr Cardiol* 1991;12:219–223
14. O'connor WN, Davis JB Jr, Greissler R, Cottrill CM, Noonan JA, Todd EP. Supravalvular aortic stenosis: clinical and pathological observations in six patients. *Arch Pathol Lab Med* 1985;109: 179–183