Intracranial Fibromuscular Dysplasia in a Six-Year-Old Child: A Rare Cause of Childhood Stroke

ABSTRACT

Intracranial fibromuscular dysplasia is a nonatheromatous angiopathy that most commonly affects adult women and is rarely recognized in children. Symptoms include stroke and headache, although the vasculopathy may be asymptomatic. Diagnosis is based on angiographic appearance, commonly described as a "string of beads." The etiology of intracranial fibromuscular dysplasia is not known, although possible causes include genetic predisposition, trauma, and underlying connective tissue disease. Treatment of intracranial fibromuscular dysplasia is largely supportive once symptoms become manifest. We report a 6-year-old girl who presented to our center for further evaluation of a large left middle cerebral artery distribution infarction. The patient was previously healthy, without known risk factors for stroke. Initial symptoms consisted of a dense global aphasia and a right hemiparesis. On arrival, the patient's aphasia had improved but she continued to have significant deficits in both receptive and expressive language as well as residual right hemiparesis. Magnetic resonance imaging and conventional angiographic studies demonstrated characteristic beading of the distal portion of the left internal carotid artery, as well as the proximal middle cerebral artery. Laboratory evaluation, echocardiogram, and renal ultrasound were normal. The renal vasculature did not demonstrate evidence of intracranial fibromuscular dysplasia. In conclusion, intracranial fibromuscular dysplasia should be considered in the differential diagnosis of childhood stroke. When recognized, other sites of vascular involvement should be sought, and consideration of underlying disorders is important, as connective tissue disorders have been associated with a propensity to develop this vascular abnormality. Careful follow-up is warranted, due to possible progression of disease. (J Child Neurol 2000;15:559-562).

Fibromuscular dysplasia, a nonatheromatous angiopathy, is commonly encountered in adult women but rarely seen in children.^{1,2} Initially described in the renal vasculature, subsequent reports have identified fibromuscular dysplasia in the cervical arteries.^{3,4} Symptoms of cervicocephalic fibromuscular dysplasia may be absent or may include stroke, seizure, or rupture of an intracranial aneurysm.³ Diagnosis is confirmed by appearance during arteriography or, occasionally, on histopathologic manifestations of surgical specimens.³ This article describes a child with the clinical presentation of stroke, for whom the unusual diagnosis of intracranial fibromuscular dysplasia was made with conventional arteriography. Clinical manifestations due to involvement of intracranial arteries is rare in any age group; in children, only isolated reports exist.^{5–13} Despite its rarity, differential diagnosis of stroke in childhood should include intracranial fibromuscular dysplasia.

Case Report

K.B. is a 6-year-old white girl who presented to Walter Reed Army Medical Center for further evaluation following a complete left middle cerebral

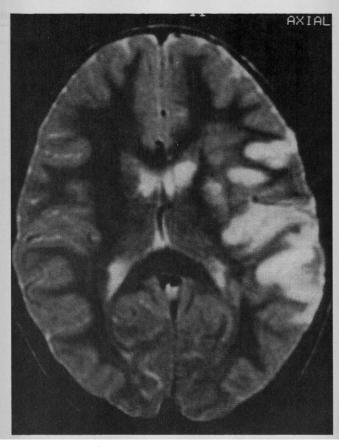


Figure 1. MRI of patient's head. T_2 -weighted image is consistent with a left middle cerebral artery distribution ischemia and early infarction.

artery stroke. At the time of the event, the patient had no significant medical history and her family history was unremarkable. The patient was well until 2 weeks prior to admission, when she complained of new onset bitemporal headache while at a friend's home. The patient was given acetaminophen and went to sleep. Upon awakening, the father believed she had influenza, because she was somnolent and not speaking. The father states that after approximately 36 hours, the patient had a continued lack of spontaneous speech and right-sided weakness. She was subsequently brought to her physician for evaluation. Physical examination by her family practitioner demonstrated a right hemiparesis and a presumed global aphasia, although some preservation of receptive language function remained. The patient was transferred to a local hospital and underwent an evaluation for stroke. Initial laboratory studies were normal; the patient underwent an angiogram 48 hours after presentation or about 4 days after initial symptoms. The findings of T2-weighted images of the initial magnetic resonance imaging of the patient's head were compatible with ischemia and early infarction in the middle cerebral artery territory (Figure 1). Conventional angiography of the cranial vessels was performed, and a tentative diagnosis of moyamoya disease was made (Figures 2 and 3). The patient was then transferred to the authors' center.

On arrival 2 weeks after the ictus, the patient was medically stable and normotensive, and had normal data on medical examination. The neurologic examination was characterized by a subtle right-sided hemiparesis, a dense expressive aphasia, and hyperreflexia and a Babinski reflex on the right side. There was no Horner's sign. Evaluation of the tests done prior to transfer indicated that the patient had intracranial fibromuscular dysplasia, affecting the right distal internal carotid artery, with portions of the ipsilateral middle cerebral artery affected as well (Figure 2). Results of repeated laboratory studies were normal except for the lipid profile, which indicated a total serum cholesterol level of 266 mg/dL (Table 1). The serum alpha-1-antitrypsin

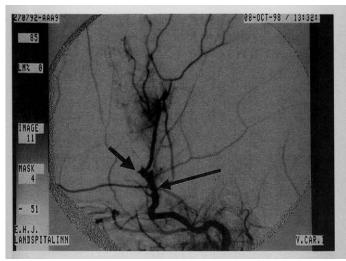


Figure 2. Conventional angiogram of the cranial vessels (lateral view, common carotid artery injections), demonstrates beading and irregularity of the distal cavernous and supraclinoid internal carotid artery (long arrow). Abrupt interruption of flow is noted at the origin of the anterior cerebral and middle cerebral arteries (short arrow). The apparent blush present around the perfusion portion of the middle cerebral artery is likely luxury perfusion related to the infarct.

level was 127 mg/dL (normal range, 90 to 200 mg/dL); the ophthalmologic examination was normal, as were the Doppler ultrasound studies of the renal vasculature. The kidneys appeared normal. The patient was started on aspirin at a dosage of 81 mg/day, and begun on an aggressive rehabilitation program. There were no further complaints of headache or other systemic symptoms, and her neurologic status slowly improved, although a significant residue of expressive language deficit remains. The patient had a follow-up magnetic resonance imaging and a magnetic resonance angiogram $3\frac{1}{2}$ months after her stroke; they showed persistent abnormalities in the left middle cerebral artery (Figure 4).

Discussion

Fibromuscular dysplasia is a well-recognized cause of stroke and transient ischemic attacks in adults. It is found most often in young to middle-age women, and Caucasians have an an apparent racial predisposition.² In children, fibromuscular dysplasia is a rare but recognized cause of stroke; the first reported case of fibromuscu-

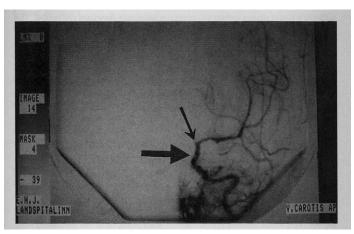


Figure 3. Anteroposterior angiographic view of vessels demonstrates beading of supraclinoid internal carotid artery (thick arrow), with absence of flow in the anterior cerebral artery (thin arrow).

lar dysplasia was in a child.³ Although commonly seen in the renal arteries, fibromuscular dysplasia has been demonstrated throughout most of the vasculature, including the splanchnic, aortic, carotid, vertebral, and, rarely, intracranial vasculature.^{1,3,14} Ophthalmologic findings in fibromuscular dysplasia have also been reported, although they were not demonstrated in the current patient.¹⁵ Pathologic manifestations of this angiopathy are well described, and include four major subtypes:^{16–18}

- 1. *Medial fibroplasia*. Most common, and characterized by accumulation of dysplastic fibrous tissue within the media, but can also involve the external elastic lamina.
- 2. *Intimal fibroplasia*. Subendothelial mesenchymal cells accumulate within fibrous tissue.
- 3. *Perimedial dysplasia*. Also described as subadventitial hyperplasia, this subtype is characterized by an abnormal increase in elastic tissue underlying the adventitial layer.
- 4. *Medial muscular hyperplasia*. Characterized by smooth muscle hyperplasia without fibrosis within the media.

It is these pathologic changes that account for the characteristic radiographic findings that are most important to diagnosis. Conventional angiography is the gold standard for demonstration of fibromuscular dysplasia, with the "string of beads" being the most common radiographic appearance (Figure 2).¹⁶ This is characterized by areas of stenosis alternating with abnormally wide poststenotic luminal ectasia. Less common manifestations include tubular stenosis and diverticular outpouching of one part of an arterial wall.¹⁶ Although magnetic resonance angiography is a less invasive means of following the radiographic findings in fibromuscular dysplasia, artifacts encountered with its use may mimic fibromuscular dysplasia; therefore, conventional arteriography is recommended for equivocal cases.¹⁹

The etiology of the pathologic process is unclear. Suggestions include postinfectious injury, hormonal effects, trauma, toxic injury to the endothelium, and congenital propensity to vascular injury.^{1,2,12,20} Recent reports of the characteristic findings of fibromuscular dysplasia in children and adolescents with alpha-1-antitrypsin deficiency indicate that the cause could be an underlying congenital connective tissue disorder. The high association (20% to 50%) of intracranial aneurysms in patients with fibromuscular dysplasia supports this.² The alpha-1-antitrypsin levels in most children reported in the literature are not available, so it is unclear whether this contributed to these cases. Given the heterogeneity of the affected population, it is probable that a variety of potential injuries superimposed on a pre-existing genetic tendency results in the characteristic histopathologic and subsequent radiographic findings.²

Patients with cervicocephalic fibromuscular dysplasia range from asymptomatic individuals to those with epilepsy, headache, and stroke. Subarachnoid hemorrhage due to rupture of associated intracranial aneurysms is also seen.² Although the exact pathophysiology of the most serious manifestations remains unclear, dissection and embolic phenomenon from sources in ectatic regions are the most commonly invoked etiologies.^{16,21–23} Symptoms in children are similar, and it is important to consider fibromuscular dysplasia in the evaluation of infantile and childhood hemiplegic

Table 1.	Laboratory	and Radiographic	Test Results
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Test	Patient's Results	Normal Values
Prothrombin time	12.1 sec	11.9-14.5 sec
Partial prothrombin time	32.9 sec	24.6-34.6 sec
Fibrinogen	232 mg/dL	182–410 mg/dL
11	17.6 sec	14.6–19.0 sec
Homocysteine	8.6 μmol/L	2.8–13.5 μmol/L
Methylmalonic acid	119 nmol/L	60–2 50 nmol/L
Urine organic acids	No evidence of inherited disease	
Hemoglobin electrophoresis	Hemoglobin AA	
Sickledex	Negative	Negative
Erythrocyte sedimentation rate	13 mm/H	0–20 mm/H
C creative protein	<0.4 mg/dL	0.0–0.8 mg/dL
Protein S	77%	50–112%
Protein C	180%	71–170%
ATIII	109%	91–129%
Activated protein C resistance	Negative	
Lupus anticoagulant	Negative	
RVVT	Negative	
Antinuclear antibody	Negative	
Antidouble-stranded DNA	Negative	
Anti-Smith antibody	Negative	
Anti-RNP antibody	Negative	
Anti-SSA antibody	Negative	
Anti-SSB antibody	Negative	
Anti-cardiolipin antibodies	Negative	
Alpha-1-antitrypsin	127 mg/dL	90–200 mg/dL
Venereal disease research laboratory (cerebrospinal fluid)	Nonreactive	
Venereal disease research laboratory (serum)	Nonreactive	
Lyme (cerebrospinal fluid)	Negative	
Lyme (serum)	Negative	
Human immunodeficiency virus	Negative	
Thyroid-stimulating hormone	2.450 μIU/mL	0.27–4.20 μIU/mL
Cholesterol	230 mg/dL	50–200 mg/dL
Triglycerides	146 mg/dL	35–250 mg/dL
High-density lipoprotein	37 mg/dL	35–82 mg/dL
Very-low-density lipoprotein	29 mg/dL	2–49 mg/dL
Low-density lipoprotein	164 mg/dL	0–129 mg/dL
Urinalysis	Within normal limits	Within normal limit
Kidney magnetic resonance angiogram	No evidence of fibromuscular dysplasia	
Renal ultrasound	Within normal limits	

TT = Thrombin time; ATIII = antithrombin III; RVVT = Russell's viper venom time; Anti-RNP = anti-ribonucleoprotein; Anti-SSA = anti-Sjogren's syndrome A; Anti-SSB = anti-Sjogren's syndrome B.

syndromes.¹⁰ The patient reported here did not show evidence of ongoing inflammatory or infectious processes, and evaluations for coagulation or autoimmune disorders were negative. The only laboratory abnormality was her lipid profile, perhaps indicating a susceptibility to accelerated microscopic atherosclerotic endothelial injury.

The natural history of this disorder is variable, and progression has been demonstrated in most adult patients.² Rare reports exist of spontaneous resolution of renovascular fibromuscular dysplasia. Because of the relative paucity of reports, the disease course in children is more difficult to predict. One case report indicated a progression of apparently systemic disease, with renal and mesenteric artery involvement after 5 years.⁷ Because of the possibility of progression, imaging of the patient in this case was repeated 3 months after her stroke using magnetic resonance angiogram. This revealed persistent beading of the left proximal middle cerebral artery, without progression of disease.

Treatment of cervicocephalic fibromuscular dysplasia has not been systematically employed, though long-term therapy to prevent complications seems prudent. Due to her age and the severity of her stroke, antiplatelet therapy with aspirin was initiated in this patient. Another option is long-term anticoagulation with heparin or warfarin. This approach might be especially appropriate if dissection is considered to be the etiology of the patient's stroke.²⁴ Surgical treatments for renal and other arterial disease have also been employed with some long-term success.²⁵

Complication rates were low, and follow-up has not found a reappearance of fibromuscular dysplasia in the affected vessels. Surgical correction of cervicocephalic disease has not been reported in children. However, bypass procedures for arterial disease like moyamoya has been used with success in children, and may be a consideration for those with fibromuscular dysplasia affected by recurrent or severe bilateral disease.²⁶

In summary, a case of childhood stroke due to intracranial fibromuscular dysplasia was presented. Stroke is a rare complication of this disease, and it is likely an acquired abnormality of vascular connective tissue integrity with variable pathologic findings. Extracranial fibromuscular dysplasia is most commonly encountered; intracranial manifestations are rarely reported in children. These manifestations are best seen by conventional angiographic techniques, and often have a characteristic radiographic appearance known as the "string of beads." Evidence for fibromuscular dysplasia found during evaluation of childhood stroke should prompt evaluation for other affected vessels, and the patient should be followed closely for progressive disease. Treatment should be based on the individual, since there are no current data supporting a particular regimen that improves long-term outcome. Indications that some patients with known connective tissue disorders can have a propensity to develop similar vascular lesions might provide a clue to the underlying etiology of this abnormality, and should encourage research in this area.

> Marc DiFazio, MD Sidney R. Hinds II, MD

Department of Child and Adolescent Neurology Mark Depper, MD Department of Neuroradiology Bryony Tom Ronald Davis, MD Department of Child and Adolescent Neurology Walter Reed Army Medical Center Washington, DC

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Address correspondence to Dr Marc DiFazio, Department of Child and Adolescent Neurology, Walter Reed Army Medical Center, Washington, DC 20307-5001.

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