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Cerebral Infarction and Recovery in a 12-Year-Old Child With Intracranial Fibromuscular Dysplasia

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HIGHLIGHTS

- FMD should be considered as a potential cause of pediatric stroke although the incidence of stroke arising from FMD is very rare in children.

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Conceptualization: Yang SS; Data curation:

ABSTRACT

Fibromuscular dysplasia (FMD) is a congenital vascular anomaly resulting in arterial stenosis and weakening of typically medium-sized arteries. It is a noninflammatory, nonatherosclerotic arterial disease that affects most commonly the renal and internal carotid arteries, but intracranial FMD in the pediatric population is very rare. We report a young age-onset ischemic stroke patient with FMD affecting the middle cerebral artery (MCA). A 14-year-old boy was admitted with left-side weakness during physical education at school. The brain magnetic resonance (MR) imaging revealed an acute ischemic stroke in the right basal ganglia and internal capsule, while the MR angiogram showed segmental intraluminal stenosis in the left proximal MCA. The transfemoral angiography revealed the pathognomonic sign of a “string of beads” at the proximal MCA area. The clinical course was stable, and the boy gradually recovered from the motor weakness of his arm and leg. FMD should be considered as a potential cause of pediatric stroke.

Keywords: Fibromuscular Dysplasia; Ischemic Stroke; Neurological Rehabilitation, Pediatrics

INTRODUCTION

Fibromuscular dysplasia (FMD) is a condition that affects the small and medium-sized arteries without being linked to atherosclerosis or inflammation. While it is more common in adult women but rare in children [1].

Originally observed in the renal arteries, FMD has also been found in the cervical arteries, though it rarely impacts intracranial arteries. Harrison and McCormick classified FMD pathologically in 1971. The most frequently observed type of FMD is medial fibroplasia. This type is recognized by its "string of beads" appearance in angiographic images, where the bead size exceeds the artery's usual diameter. This beading effect arises from alternating regions of narrowing due to fibrous webs and dilation after the narrowing. Other less prevalent FMD types include intimal, perimedial, and adventitial fibroplasia [2].

Cervicocephalic FMD can sometimes present without symptoms, but when they do occur, they might include events like stroke, seizures, or the bursting of an intracranial aneurysm.

Kim MH, Lee JI; Investigation: Yang SS, Lee JI; Supervision: Yang SS; Writing - original draft: Yang SS, Lee JI; Writing - review & editing: Yang SS.

The article highlights the case of a child who exhibited stroke symptoms and was uniquely diagnosed with intracranial FMD using magnetic resonance (MR) radiography and traditional angiography. While it is uncommon for intracranial arteries to show clinical signs in any age group [3,4], there are only a few documented cases in the pediatric group [5]. Kirton et al. [6] reported that childhood arterial ischemic stroke was associated with FMD in less than 1% of cases and with an incidence rate of 1:3,000,000 children per year.

Therefore, we would like to report a case of ischemic pediatric stroke owing to FMD with clinical improvement after intensive rehabilitation program.

CASE DESCRIPTION

A 14-year-old boy was admitted to the emergency room of our hospital with sudden onset of generalized tonic-clonic type seizure lasting 5 minutes with eyeball deviation, followed by complete left hemiplegia occurring at school. At the time of hospitalization, the patient's level of consciousness was alert, and the initial vital signs were as follows: a blood pressure of 146/79 mmHg, a body temperature of 37.1°C, a pulse rate of 95 beats per minute, and a respiratory rate of 16 beats per minutes. He had no specific medical history except for Kawasaki disease at nine months old, nor did his family.

In the neurological examination performed in the emergency room, he showed weakness of the left upper and lower extremities with Medical Research Council (MRC) scale 1/5, left facial palsy and mild dysarthria. The deep tendon reflex was hyperactive on the left side, and the Babinski reflex was present on the left. National Institutes of Health Stroke Scale was observed with a score of 9, and the modified Rankin scale scored 5. His language and cognitive function were in the normal range, but the K-Modified Barthel Index (MBI) was 22 with the maximal assist.

Laboratory findings including hemoglobin, white blood cell, platelet count, coagulation profile (prothrombin time, activated partial thromboplastin time), blood sugar and lipid were in normal range. No abnormal findings were obtained from plain chest X-ray and electrocardiography.

Brain MR imaging showed diffusion restriction in the right striatocapsular area and revealed cerebral infarction findings spanning the right basal ganglia and internal capsule (**Fig. 1**). MR angiography demonstrated the diffuse narrowing stenosis of the right distal internal carotid artery (ICA) and proximal MCA. The patient was started on antiplatelet therapy with aspirin and was admitted to the pediatric neurology department.

Transfemoral cerebral angiography confirmed the diagnosis of FMD, revealing a diffuse string-of-beads appearance in the right distal ICA (A1) and proximal MCA arteries (M1), as well as occlusion of several branches of the right MCA and increased leptomeningeal collaterals from the right posterior cerebral artery to the MCA territory (**Fig. 2**). Additionally, through computed tomography angiography, we could confirm that his aorta and renal vessels were normal. Initially, the patient showed complete paralysis of the affected limbs. He could not stand or walk and needed maximal support for sitting, transfers, and bedside mobility. He slowly regained muscle power in his left arm and leg 7 days after the onset of stroke.

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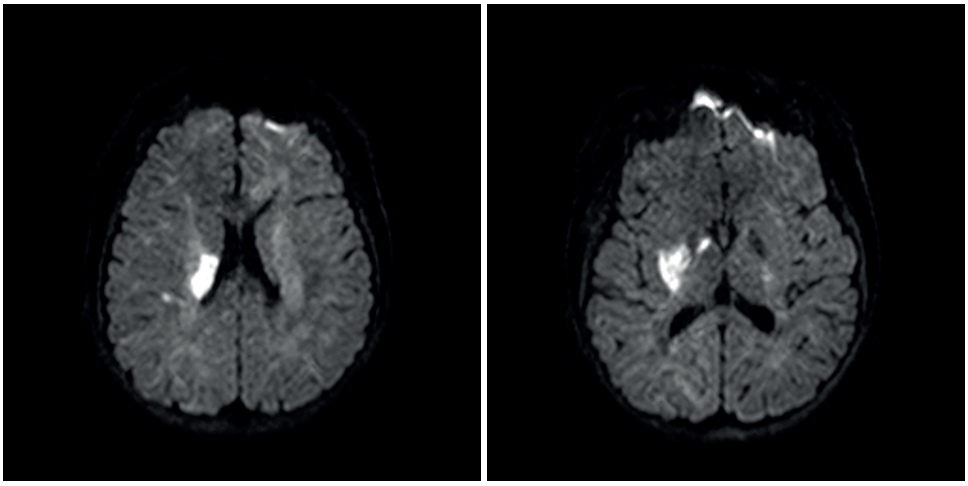

Fig. 1. Initial axial diffusion-weighted imaging shows high signal-intensity in the right striatocapsular area.

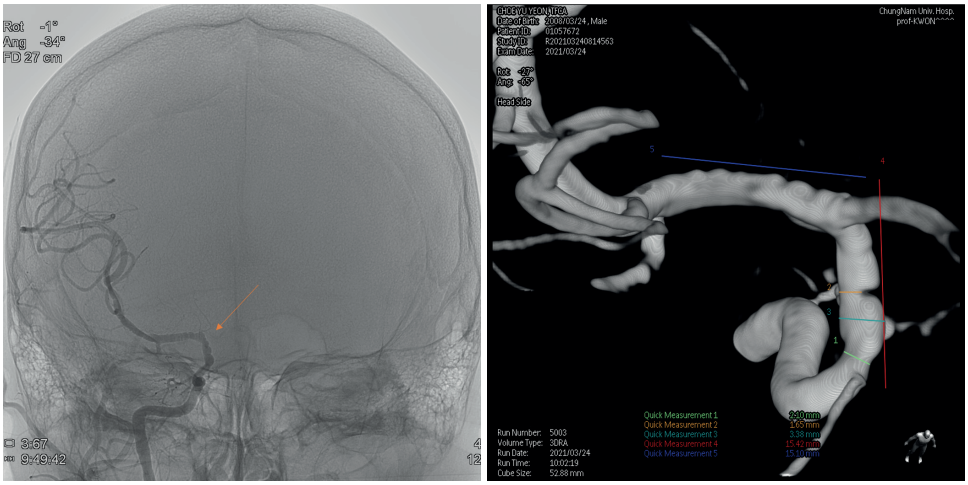

Fig. 2. Transfemoral cerebral angiography reveals "a string of beads" in the right distal internal carotid artery and proximal middle cerebral artery (marked by an arrow).

He was transferred to the rehabilitation department on the 10th day post-onset. We first planned an intensive rehabilitation program with the goal of independent walking on flat ground with orthosis and independent activities of daily living with modified bimanual hand activity. He participated in intensive rehabilitation program composed of various therapeutic exercise, occupational therapy, whole-body pool therapy, and robot-assisted walking training for more than 4 hours a day, five times a week.

To predict the possibility of motor recovery via the viability of the corticospinal tract, we carefully measured the motor evoked potential (MEP) on bilateral abductor pollicis brevis and tibialis anterior muscles despite the heightened risk of seizures [7]. After four weeks of rehabilitation, follow-up MEP tests proved the improvements from absent response to newly formed responses with significant amplitude in the left upper and lower limbs (**Fig. 3**). Diffusion tensor imaging at this time revealed the improved white matter tract integrity in the infarction lesion (**Fig. 4**, **Table 1**).

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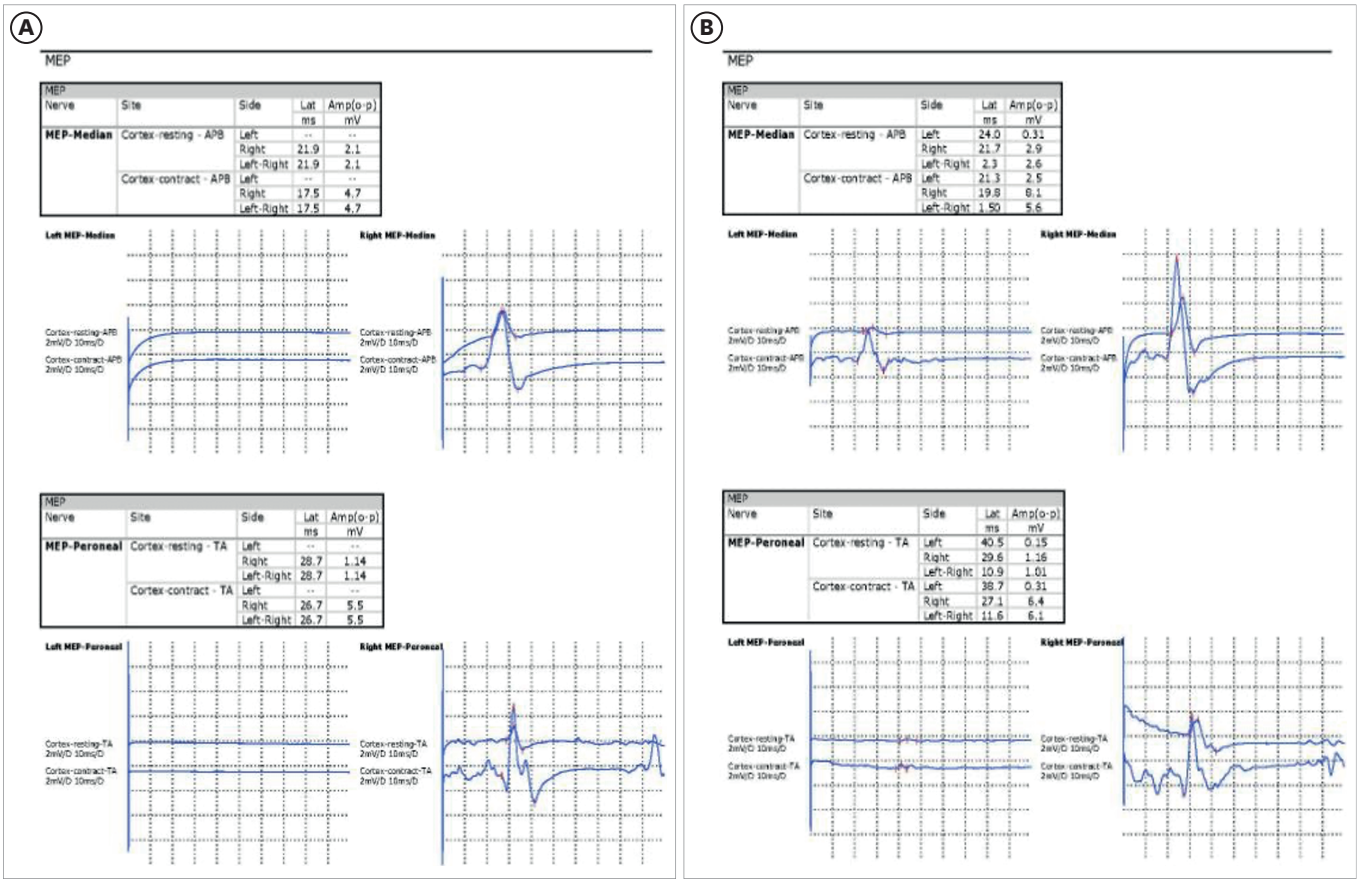

Fig. 3. Motor evoked potential was recorded at bilateral abductor pollicis brevis and tibialis anterior muscles on the 10th day post-stroke (A) and the 6th week post-stroke (B) to assess the viability of the corticospinal tract.
MEP, motor evoked potential.

Table 1. Number of tracts and FA values of the CST and CRT

Variable	No. of tracts		Tract volume		FA	
	Right	Left	Right	Left	Right	Left
CST	1,097	1,516	7,066	13,844	0.45 ± 0.13	0.59 ± 0.15
CRT	191	1,081	1,562	7,634	0.38 ± 0.11	0.53 ± 0.14

Values are presented as means ± standard deviations.
FA, fractional anisotropy; CST, corticospinal tract; CRT, corticorubral tract.

By the ninth week of rehabilitation, the patient's motor power had significantly improved to MRC scale 4 excluding distal finger extension (MRC scale 2) with an improvement of Berg Balance Score from 5 to 55 enabling independent and symmetrical gait as well as achieving 420 meter in the 6-minute walking test. He could carry out tasks of daily living independently showing an enhanced MBI score of 100. His fine motor skills also improved as evidenced by the Box & Block Test score increasing from 43/0 to 61/49.

After six months of rehabilitation, the patient's motor strength had utterly recovered to MRC scale 5. The patient is currently independent with a slower pace when using the left hand. We obtained written and signed consent from the patient's parent to publish this case report and approval by the Institutional Review Board (IRB) of Chungnam National University Hospital.

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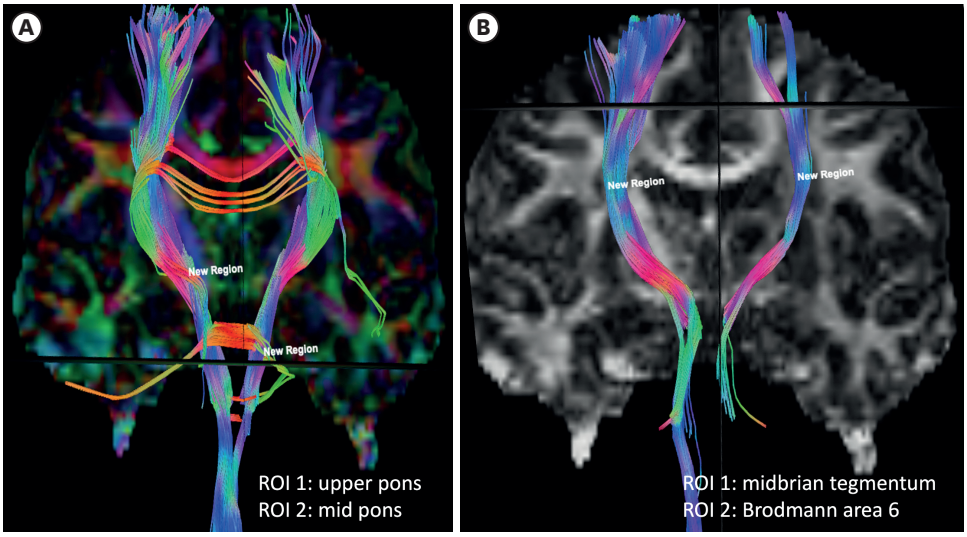

Fig. 4. The tractography was reconstructed to visualize the motor fiber connectivity of (A) CST and (B) CRT by selecting ROIs. The ROI was drawn at the CST portion of the anterior mid-pons and at the CRT portion of midbrain tegmentum and Broadman area 6.
CST, corticospinal tract; CRT, corticorubral tract; ROI, region of interest.

DISCUSSION

The incidence rate for all ischemic strokes in all children was 2.09 per 100,000 person-year and arterial ischemic stroke emerged as the predominant subtype of ischemic stroke with a yearly rate of 1.28 per 100,000 person [8]. Numerous conditions correlate with strokes in children but among them, vasculopathies, infections, cardiac issues, and coagulopathies stand out as the most significant risk factors for pediatric strokes. In one Korean study, an analysis of 65 pediatric ischemic stroke cases over a decade revealed that 35% were of vascular origin. Only one case was found to be associated with FMD [9].

Three types of FMD are recognized based on arterial wall layer involvement: intimal, medial, and adventitial. The most common type in the carotid arteries is medial fibroplasia in 85% of cases in the adult population marked by dense fibrous connective tissue replacing the media's smooth muscle [10]. However, children with FMD exhibit different pathological features compared to adults with FMD. Intimal fibroplasia was the predominant pathologic finding in children, so angiographic findings represented focal, stenotic arteriopathy rather than 'string of beads' of the adult population [6].

Clinically, cerebrovascular FMD has no gender difference, and intracranial FMD is more frequently observed in the pediatric population. It can lead to conditions like acute infantile hemiplegia before the age of 12 months [11,12]. On the other hand, cephalocervical FMD predominantly affects females (more than 90%), and it usually targets the extracranial segment of the ICA in the adult population. A history of hypertension was more prevalent and renal vasculature was more affected in children (63%) than in adults. Also, an additional arterial bed such as a mesenteric artery was more involved, and associated moyamoya syndrome and intracranial aneurysms have also been reported in children [12].

While many patients with FMD show no symptoms, some experience vascular insufficiency symptoms such as transient ischemic attacks, ischemic strokes, and cranial bleeding from

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arterial dissection. In the pediatric population with FMD, ischemic stroke seems to be the primary symptom occurring in 63% of cases and impacting multiple territories in 40% of them. The prognosis is unfavorable, characterized by a significant yearly recurrence of strokes (10%) and a mortality rate of 13% [13]. However, this patient exhibited the finding of 'string of bead' typically seen in adults presented with a focal lesion and had a very favorable prognosis for neurological recovery unlike the pediatric characteristics reported in other studies. So far, he has not shown any recurrence of ischemic stroke.

Catheter-based angiography is the gold standard for diagnosis, but non-invasive imaging techniques like CT angiography and MR angiography are also helpful. It shows the multifocal type representing the classic 'string of beads' pattern with multiple stenosis of the lumen in the affected vessel segment, the tubular type with a long concentric stenosis with or without aneurysmal dilatation and the focal type, with solitary stenosis less than 1 cm in length [14].

The exact cause of FMD remains uncertain, but the hormonal, genetic, and mechanical stress factors are hypnotized as the etiological causes. Several research has been conducted to identify the specific genes that contribute to vascular malformation associated with FMD. FMD is in a genetically diverse condition that presents in both sporadic and familial forms, having at least a partially complex genetic basis. A genetic association study found that phosphatase and actin regulator 1 gene (PHACTR1) was a genetic susceptibility locus for FMD supporting the complex genetic pattern of inheritance. Allele A of a genetic variant (rs9349379) of the PHACTR1 highly prevalent in the general population (~60%) was associated with a 40% increase in relative risk of FMD (OR, 1.39; $p < 7.36 \times 10–10$) [15]. Several genes associated with connective tissue disease (COL3A1, FBN1, PLOD1, TGFβR1, TGFβR2, TGFβ2, SMAD3, ACTA2, and COL5A1) were found to be unrelated to the FMD [16]. However, one recent study reported COL5A1 c.1540G > A was the recurring variant associated with arterial dissections and FMD [17].

Medical therapy includes antiplatelet agents and antihypertensive drugs and, in some cases, endovascular treatment or surgery may be necessary [14,18-20]. It has yet to be determined for how long treatment should be maintained. Antiplatelet treatment is deemed appropriate to avert thromboembolic issues. Endovascular surgery is generally limited to patients who exhibit symptomatic stenosis even after receiving the best medical treatment or those who experience a burst of an intracranial aneurysm. Present guidelines advocate for intervention in instances of carotid/vertebral artery dissections when there's ongoing ischemia despite optimal medical treatment [21]. The standard surgical procedure is angioplasty, but alternatives include endarterectomy, vascular grafting using a saphenous vein segment, and STA-MCA anastomosis [5,22]. This patient was given the antiplatelet drug from the symptom onset.

In conclusion, this is a rare case of FMD in a pediatric patient, resulting in cerebral infarction, highlighting it as a risk factor for young-onset stroke. Our case demonstrated the remarkable recovery through intensive rehabilitation, emphasizing the significance of early rehabilitative therapies in enhancing post-stroke recovery in children. FMD should be considered as the cause of a stroke in younger age groups without cardiovascular risk factors.

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