Spontaneous Internal Carotid Artery Dissection Secondary to Fibromuscular Dysplasia: A Case Report

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Abstract

Fibromuscular dysplasia is not well understood by practitioners, and as a result is often under-diagnosed. Although the etiology of fibromuscular dysplasia is unknown, this disease is frequently associated with stroke and vascular dissections. Approximately 12-15% of spontaneous carotid artery dissections can be attributed to the presence of fibromuscular dysplasia. This article will discuss symptoms and presentations that mask an early diagnosis of fibromuscular dysplasia, and will highlight the vulnerable populations often affected. Advanced practice providers must be aware of the complexity of symptoms and presentations of patients with an underlying diagnosis of fibromuscular dysplasia. Early diagnosis and intervention are required to minimize catastrophic events and long-term deficits.

INTRODUCTION

Fibromuscular dysplasia (FMD) is classified as a nonatherosclerotic, noninflammatory vascular disease. Anomalies are frequently seen in the renal, carotid, and vertebral arteries. To a lesser extent, the visceral arteries and arteries of the extremities may be affected [12345]. FMD lesions weaken arterial walls and predispose the craniocervical arteries to dissection. This disease is a predisposing factor in 10-20% of carotid artery dissections [1].

FMD primarily affects women of child-bearing age, and occurs up to four times as often in women than in men [4]. Clinically, researchers are considering whether hormonal factors are involved [45]. However, current research is limited and samples are small, leading to no conclusive causative links to the disease. Diagnosis to date has typically been made by the classic angiographic finding of the “string of beads”

(Figure 1) [1234]. Although rarely attained, the pathologic specimen is diagnostic [14].

CLINICAL MANIFESTATIONS OF CEREBROVASCULAR FIBROMUSCULAR DYSPLASIA

Clinical manifestations of symptoms are determined by the arteries affected and the cerebral territory the vessels supply. Hypertension can be attributed to the renal artery (RA), while facial palsies, Horner’s Syndrome, and transient ischemic attacks (TIAs) can be attributed to either the carotid artery (CA) or vertebral artery (VA) [2]. For a detailed classification of symptoms based on the vascular territories affected after an ischemic or hemorrhagic stroke refer to Table 1 [6].

Figure 1

Table 1: Cerebral Territories and Stroke Related Symptoms

TERRITORY	ARTERIES INVOLVED	SYMPTOMS
Anterior Circulation	Internal Carotid	TIAs, unilateral symptoms such as hemiparesis, facial droop
	Middle Cerebral	Contralateral hemiparesis worse in the arm & face, dysarthria, aphasia , homonymous hemianopia
	Anterior Cerebral	Contralateral hemiparesis which is worse in the leg, memory loss, confusion
Posterior Circulation	Posterior Cerebral	Hemiplegia, pure hemi-sensory loss, unilateral infarction produces homonymous hemianopia, unilateral 3rd cranial nerve palsy, bilateral infarctions may cause cortical blindness, visual agnosia, memory loss
Vertebrobasilar System	Vertebral Basilar	Gait disturbances, ataxia, dysarthria, dysphagia, vertigo, diplopia or visual loss

To further complicate the clinical presentation, 26% of these patients will have the disease diagnosed in more than one vascular bed [4]. Clinicians must be aware that symptoms

alone may not provide adequate guidance in the diagnosis of FMD. Past medical history and unusual symptoms for an age group, accompanied with laboratory and angiographic images, will assist in the diagnosis.

Within the central nervous system (CNS), headaches, vascular dissections, and stroke are the most common clinical presentations [12]. However, symptoms such as vertigo, tinnitus, or syncope may be the primary presenting problem [4]. In some cases, headache and neck pain may be the only presenting complaints prior to a spontaneous internal carotid artery (ICA) dissection [7]. Physical examination may reveal a carotid bruit, leading to an incidental finding of FMD [45].

For some time, neurologists have known FMD to be an important cause of stroke in young adults [8]. The presentation of a carotid or vertebral dissection with an accompanying anterior circulation ischemic stroke affects 10-25% of all ischemic strokes in young adults [910]. Ninety-five percent of diagnoses of FMD involve the ICA, followed by the VA 60-85% of the time [4]. FMD is associated with single or multiple aneurysms found most frequently along the ICA and middle cerebral artery (MCA) [4]. To gain a better understanding of the angiographic diagnosis of FMD, a description of a classification system will be discussed.

PATHOLOGIC CLASSIFICATION

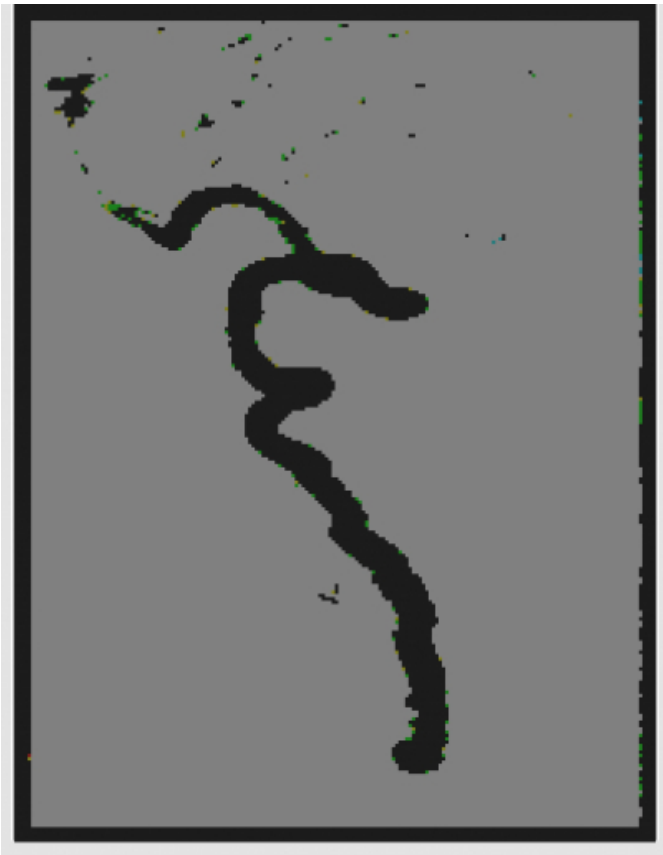
Classification is based on the angiographic appearance of the vessel, which correlates with the dominant arterial wall affected [1]. Therefore, vessels will either be labeled as medial dysplasia, intimal dysplasia, or adventitial fibroplasia [1234]. Subcategories further assist the practitioner in identifying commonalities in symptoms and the types of patients that FMD affects. The “string of beads” is the most common angiographic finding for FMD in both the RA and ICA, followed by concentric stenosis (Figures1&2) [1211].

Figure 2

Figure 1: String of Beads

Figure 3

Figure 2: Concentric Stenosis



Although this classification was originally developed for use in the RAs, the system has been applied successfully to all vascular beds affected by FMD [24]. Dissection was once a subcategory, but has now been referenced as a cause. Refer to Table 2 for the

Angiographic Classification of FMD [124].

Figure 4

Table 2: Angiographic Classification of Fibromuscular Dysplasia

Classification	Frequency	Appearance	Points of Interest
Medial Type			
Medial Fibroplasia	75-80%	"String of beads" Bead diameter is larger than the proximal aspect of the vessel	Usually found in the distal end of the main renal artery (RA) and at the ICA at C 1-2
Perimedial Fibroplasia	10-15%	"String of beads" Lesser amounts More severe stenosis	Most commonly found in young women
Medial Hyperplasia	1-2%	Concentric Smooth stenosis	Found in the ICA Lesser amount in the RA
Intimal Fibroplasia	<10%	Focal Band-like Concentric stenosis Tubular	Can occur in all vascular beds simultaneously, mimicking necrotizing vasculitis
Adventitial Fibroplasia	< 1 %	Localized Tubular stenosis	Diagnosed by pathological specimen only

CASE REPORT

HISTORY

The patient was a fifteen-year-old Caucasian, right-handed, female who presented to the emergency department (ED) with a sudden onset right-sided facial pain and uncontrolled twitching of the right eye and cheek. The patient was reportedly walking off the volleyball court when she collapsed to her knees and was observed having twitching on the right side of her face. Upon arrival to the ED, the patient exhibited right-sided weakness and slurred speech.

A recent history revealed the patient had experienced a migraine headache in the frontal-temporal region the previous night that resolved with acetaminophen (Tylenol). The patient awakened the next morning in her normal state of health. Additional history reported by her parents included a recent outbreak of shingles to her left eye and nasal region. The patient was treated with a seven-day course of valacyclovir (Valtrex) with resolution. Further history included recurrent opthalmic lesions since the age of seven that required anti-viral treatment at least two times per year. The virus was always presumed to be herpes. No additional medical or surgical problems noted in her history.

The patient had no known allergies and no use of chronic medications. The patient's paternal grandfather died of a stroke at age 48. The maternal grandmother died of a stroke at age 53. The family was unaware of any diagnoses of FMD or carotid/vertebral artery dissections within their immediate

family. The patient's mother has type II diabetes mellitus. The family did not recall any history of vasculitis or coagulopathic disorders. No history of tobacco, alcohol, or illicit drug use existed. Additionally, the patient did not use contraceptives.

PHYSICAL

On initial physical examination, the blood pressure was documented as 140/84, heart rate 102, respirations 16, and temperature 98.2 F. No audible carotid bruit was heard. However, a grade 2/6 systolic murmur was prominent at the left costal margin.

Cranial nerves II through XII were intact bilaterally. The motor exam noted 5/5 strengths on her left side; however, on her right side, she was noted to have the following strengths: 4/5 in deltoids, biceps, wrist extension, triceps, hip flexor, hip abduction, hip adduction, and quadriceps. Her extensor hallucis longus and her gastrocnemius strength was 4/5 on the right. The deep tendon reflexes were 3/5 in the Achilles, quadriceps biceps, brachial radialis, and triceps tendons bilaterally. The patient was noted to have intact sensation to light touch and sharp/dull discrimination in all extremities. No ataxia was present, and gait was not assessed. Laboratory results are contained in Table 3.

Figure 5

Table 3: Laboratory

DIC PANEL	RESULTS		INFECTIONS	RESULTS
Protime	12.7	(11.5-14.5 sec.)	HIV	Negative
INR	1.01	(0.87-1.29)	Quantitative RPR	Negative
PTT	30.1	(22.5-36 sec.)	Varicella Zoster	Positive
Fibrinogen				
HEMATOLOGY	**RESULTS**		**AUTOIMMUNE**	**RESULTS**
WBC	9.2	(4.8-10.8) [x 10^3]	Lupus anti-coagulant	Negative
RBC	4.8	(4.2-5.4) [x10^6]	Rheumatoid Factor	Negative
Hgb	13.3	(12-16) [g/dl]	Anti-nuclear Ab	Negative
Hct	40.8	(36-48) [%]	Anticardiolipin Ab	Negative
Platelets	368			
CHEMISTRY	**RESULTS**		**LIPID PANEL**	**RESULTS**
Na	137	(135-145) [mEq/L]	Total Cholesterol	127 (120-200) [mg/dl]
K	4.2	(3.5-5.1) [mEq/L]	HDL	67 (>=35) [mg/dl]
Hgb A_{1c}	5.2	(<7) [%]	LDL	79 (0-129) [mg/dl]
Creatinine	1.5	(0.5-1.4) [mg/dl]	Triglycerides	92 (0-200) [mg/dl]
BUN	24	(7-22) [mg/dl]		

IMAGING

An initial brain computed tomography (CT) with no contrast revealed a hypodensity at the level of the operculum, and no evidence of an acute bleed. An electroencephalogram (EEG) revealed an asymmetric slowing during sleep, indicating a deep lesion of the left hemisphere, in keeping with the patient's known history. A brain and neck magnetic resonance imaging (MRI) with and without contrast revealed a left basal ganglia stroke, a narrowing of the left ICA at the bifurcation, and decreased flow in the posterior left MCA region. A bilateral carotid, vertebral, and cerebral arteriogram demonstrated evidence of dissection involving the supra-ophthalmic and supraclinoid segments, and bifurcation of the left ICA with evident involvement of the left A-1 and M-1 segments, the latter extending into the left MCA bifurcation. The left internal carotid bifurcation was narrowed approximately 50% and showed evidence of beading that was likely representative of FMD.

Forty-eight hours after admission, a repeat brain CT without contrast revealed a new infarct in the left anterior cerebral artery (ACA) distribution. The left MCA infarct was unchanged, and there was no evidence of hemorrhagic conversion. The development of a second infarct in a different distribution strongly suggested a dissection upstream of the common carotid at the aortic arch, at the ICA origin from the carotid bifurcation. A transesophageal echocardiogram (TEE) revealed no patent foramen ovale (PFO), no atrial septal wall defect (ASD), no valvular abnormalities, no vegetations, and an ejection fraction of sixty to sixty-five percent. A lumbar puncture revealed no unusual chemistries or culture.

TREATMENT

Treatment included the patient being started on weight based heparin. Transition to warfarin (Coumadin) occurred when a therapeutic INR value of 2-3 was attained. The partial seizures were addressed with the addition of phenytoin (Dilantin) 300 mg orally daily. Both medications would be re-evaluated in three months at a follow-up visit with the neurologist.

DETERMINING DIFFERENTIAL DIAGNOSES

A thorough history of the patient and first-degree relatives provides invaluable information when attempting to rule out conditions that may be associated with or look similar to FMD. The clinician acts as an investigator, taking note of even the smallest of details. For example, if the patient complained of a "thunder-clap" headache one may suspect a subarachnoid hemorrhage (SAH)" [$_{12}$]. Despite age or risk factors, unilateral weakness and aphasia require an immediate head CT without contrast to rule out either an ischemic or a hemorrhagic stroke [$_{12}$]. A diagnosis of an ischemic event in a 15 year-old Caucasian female with no history of recent trauma must cue the provider to think of FMD as a differential diagnosis [$_{9}$]. A review of current data will assist in determining appropriate differentials:

1. A 15 year-old Caucasian female with no prior

neurologic complications.

2. Recent complaint of a migraine headache and history of herpetic lesions.
3. No history of hypertension, elevated cholesterol, smoking, or diabetes.
4. Maternal and paternal grandparents died at an early age from stroke.
5. Left MCA/ACA infarct, left ICA narrowing, dissection at the bifurcation of the left ICA, and evidence of beading similar to FMD

Atherosclerosis can be considered a reasonable differential in the presence of an ischemic stroke. This condition is known to cause narrowing of the medium-to-large vessels in the brain, heart, or extremities. A blood clot may cause a thrombotic event completely occluding blood flow. Usually developing early in life, atherosclerotic symptoms typically do not occur until the fifth or sixth decade of life [13]. In comparison, this patient was young, with no atherosclerotic risk factors. Laboratory data confirmed the patient having a normal lipid panel and hemoglobin A_{1c}. Vascular imaging did not observe calcifications or plaque. Atherosclerosis was ruled out.

Vasculitis must be considered in the differential diagnosis. Typically, angiographic findings reveal segmental narrowing and dilatation of vessels similar to FMD. Vasculitis may be considered non-infectious or infectious. Vasculitis may also be confused with a diagnosis of atherosclerosis or FMD. Differentiation from atherosclerosis is that vasculitis tends to affect younger patients with few to no atherosclerotic risk factors. Both vasculitis and atherosclerosis have an inflammatory component that FMD does not share. FMD is a non-inflammatory process, and patients do not usually exhibit anemia or thrombocytopenia upon laboratory work-up. However, when FMD presents in multiple vessels as in intimal fibroplasias, the angiographic findings are similar to necrotizing vasculitis [1245]. Herpes zoster opthalamicus (HZO) can cause a necrotizing vasculitis that affects the proximal segments of anterior and middle cerebral arteries on the same side of the HZO and a contra-lateral hemiparesis [14]. By comparison, this patient did not present with an active herpetic infection, and no evidence was present of an inflammatory response. Other conditions, such as giant cell arteritis and Takayasu's arteritis, can be differentiated from FMD based on the choice of imaging. In this case, the best imaging technique to differentiate between vasculitis and FMD was an intravascular ultrasound [2]. The case-study patient exhibited what the radiologist identified as classical features of FMD. The job of the clinician is to further rule out any metabolic or infectious process. Vasculitis was ruled out.

Ehlers-Danlos syndrome type IV (EDS) has been associated with FMD and can be considered as a differential diagnosis. This vascular syndrome produces prominent venous markings and translucent, fragile skin. EDS is a heritable syndrome. A positive family history often reveals a cluster of diagnoses which can be attributed to EDS. Specifically, this syndrome correlates well with a patient who has been diagnosed with medial fibroplasia in the presence of multiple aneurysms or vascular dissections [125]. EDS also correlates to the patient with recurrent dissections despite treatment. Angiographic findings and the presence of the COL3A1 gene assist in the diagnosis of this syndrome [125]. The patient did present with a medial fibroplasia form of FMD and dissection. However, in the absence of the classic findings of EDS, including multiple aneurysms and dissections, additional work-up was deemed unnecessary. Ehlers-Danlos syndrome type IV was ruled out.

IMAGING STUDIES

FMD can be determined only by angiographic findings or a pathological specimen. Emergent brain and vascular imaging and, specifically, catheter-based angiography remain the gold standard for the determination of cerebrovascular FMD [2410]. A head CT without contrast is the first scan required to differentiate between an ischemic and a hemorrhagic stroke [111214]. In the absence of a hemorrhagic event, the clinician must consider that an ischemic event has occurred. Magnetic resonance imaging (MRI) of the brain and contrast-enhanced magnetic resonance angiography (CE MRA) of the neck and brain sufficiently detail the "string of beads" pattern seen in most diagnoses of FMD [2]. A CT angiogram (CTA) of the neck and brain provides an alternative for those individuals who cannot tolerate a MRI. CTA is particularly useful in the identification of stenosis, dissections, and aneurysms that may be associated with FMD [11]. Duplex ultrasonography (DU) is unable to detect FMD in the vertebral and intracranial carotid arteries [10]. However, in patients with carotid dissections, abnormal flow patterns have been identified in more than 90% of patients [10]. DU, used in combination with angiography or magnetic resonance, is almost always confirmatory of dissections and may prove advantageous in the diagnosis of FMD [210].

CURRENT MEDICAL TREATMENT

At this time, no curative treatment exists for the diagnosis of FMD. Treatment is determined by the presenting problem. A carotid artery dissection with no cerebral hemorrhagic event will require intravenous weight-based heparin to be initiated. Once achieving a target international normalized ratio (INR) of 2-3, the patient will be changed to oral warfarin (Coumadin) for a time frame of three to six months [10]. The affected vessel has the highest potential to recanalize during the first three months while on anticoagulation therapy. Therefore, an MRA in three months will re-evaluate the state of the vessel and the need for further treatment. If luminal irregularities persist, the patient will continue antiplatelet therapy. An additional follow-up and MRA study in three months that reveals continued luminal irregularities will likely require the initiation of an anti-platelet agent such as clopidogrel (Plavix) [10]. However, the duration the patient should remain on anti-platelet therapy remains unclear. Current research indicates that, if the patient remains asymptomatic after six months, he or she will likely not experience a repeat event, therefore negating any further medical treatment.

CURRENT SURGICAL TREATMENT

Surgical management for cerebrovascular FMD should be reserved for those patients who remain symptomatic despite medical therapy, and have severely stenotic lesions with evidence of cerebral hypoperfusion [10]. Patients who present with a SAH and have angiographic evidence of aneurysms may require emergent surgical intervention. These aneurysms may require coiling or clipping to prevent further bleeding [12].

Currently, percutaneous transluminal angioplasty (PTA) is the first therapeutic option in the symptomatic FMD patient [3]. PTA is considered to be a safer option than traditional surgical procedures such as an endarectomy [2]. Stenting may be considered when patients have recurring symptoms and have failed traditional anticoagulation therapy or balloon angioplasty [24141516]. Clinicians should be aware that very little comparative interventional data exist to support one procedure over another in the patient with cerebrovascular FMD. Although carotid stenting is an alternative, little is known of the long-term results and the possible complications [10]. Stenting should not be considered as a primary therapy [3].

CONCLUSION

This case study demonstrates the catastrophic events that occur in a symptomatic patient with FMD. Following current guidelines and research can aid in the prevention and minimization of the complications of FMD. Although cerebrovascular FMD remains a relatively obscure diagnosis, clinicians must become aware of not only the short-term implications but also the long-term outcomes. Increasing funding for researchers is a necessary step for those dedicated to finding answers to this complex disease.

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