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Original Paper

Safety Assessment of Endovascular Treatment of Cerebral Aneurysms in Patients with Fibromuscular Dysplasia

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Keywords
Cerebral aneurysm · Fibromuscular dysplasia · Dissection · Subarachnoid hemorrhage · Flow diversion

Abstract
Background: The prevalence of cerebral aneurysms is increased in fibromuscular dysplasia (FMD). The presence of FMD may serve as discouragement to elective endovascular aneurysm treatment. Outcomes of endovascular intervention for aneurysms through vessels affected by FMD have not been reported. ***Methods:*** A prospectively maintained database of patients undergoing intracranial embolization was reviewed for patients with FMD who underwent endovascular aneurysm treatment. ***Results:*** A total of 1,025 patients were screened and 31 (3.0%) had cerebrovascular FMD. These patients underwent a total of 43 embolization procedures; 27 of these procedures were performed through an affected vessel. All but 1 patient were female and the average age was 62 years. "String-of-pearls"-type FMD was the most common subtype (90%). The internal carotid arteries were more commonly affected (65%) than the vertebral arteries (48%). All patients underwent treatment of cerebral aneurysms, most of which (87%) were incidentally discovered; 6 patients (19%) also had incidental vessel dissection. The average aneurysm size was 7.1 mm. The morphology was saccular in 93% of the cases, and 86% were in the anterior circulation. The most commonly performed treatment was flow diversion (67%), in the majority of cases by pipeline embolization. Other procedures performed were coiling (19%), stent-coiling (12%), and intrasaccular flow disruption (2%). All but 1 procedure (98%) were successful. There were no major complications; 1 patient experi-

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enced a transient ischemic attack. Follow-up angiography was performed in 88% of the cases, without evidence for disease progression after treatment. The average time to last angiographic follow-up was 17 months (±13). ***Conclusions:*** Elective embolization of intracranial aneurysms can be performed safely through vessels affected by FMD.

Introduction

Fibromuscular dysplasia (FMD) is an arteriopathy affecting multiple vascular beds throughout the body and commonly the mid-cervical carotid and vertebral arteries. The medial type, the most common histopathology, is characterized on angiography by alternating fibrous constrictions and aneurysmal dilations, commonly referred to as "string of beads" [1]. Of relevance to neurosurgeons and neurointerventionalists, the prevalence of cervical dissection and intracranial aneurysms is increased in patients with FMD [2–4]. As more such lesions are incidentally discovered, the presence of FMD can serve as discouragement to elective treatment of cerebral aneurysms [5]. There are no reports of outcomes of endovascular interventions through vessels affected by FMD.

For this study, we reviewed a prospectively maintained database of patients undergoing intracranial embolization to identify patients with FMD who underwent treatment, and assessed disease severity, procedural outcomes, and progression after treatment.

Methods

The study included a retrospective cohort of patients utilizing an institutional review board-approved, prospectively collected database of patients undergoing endovascular embolization procedures at a tertiary medical center. Four- or six-vessel diagnostic cerebral angiogram reports by experienced neuroradiologists were reviewed to identify patients with FMD, and the diagnosis was subsequently confirmed by review of digital subtraction angiography images. Demographic information, clinical history data, and outcomes were collected from medical records. Anatomic and technical details were collected from intraprocedural events, angiograms, and operative reports. The angiographic appearance of FMD was classified according to the system originally described by Osborn and Anderson [1]. Embolization procedures were performed as previously described [6–8] through femoral access with a triaxial catheter system including a guide sheath, distal intracranial catheter, and microcatheter. Patients recovered in the neurocritical care unit and were typically discharged home on postembolization day 1. Data are presented as means and range for continuous variables and as frequency for categorical variables.

Results

Cerebral angiogram reports were screened for a total of 1,025 patients who underwent embolization procedures, and 31 patients (3.0%) were identified and subsequently confirmed as having cerebrovascular FMD. These patients underwent a total of 43 embolization procedures. Among the patients having more than one procedure, 6 had multiple distinct aneurysms treated, 2 patients underwent staged stent-coiling procedures, 2 underwent flow diversion for residual aneurysm neck filling after coiling during the acute stage of subarachnoid hemorrhage (SAH), and 2 underwent a second flow diversion procedure for persistent aneurysm filling. A total of 19 patients had treatment through an affected vessel, and 27 procedures were performed through an affected vessel. All but 1 patient were female, a majority were white (77%), and the average age was 62 years. "String-of-pearls"-type FMD

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Table 1. Demographics and FMD characteristics

	n	%
FMD patients	31	3.0
FMD cases	43	
Mean age ± SD (range), years	61.7±11.4 (46–89)	
Female gender	30	96.8
Race		
White	24	77.4
Black	6	19.4
Hispanic	1	3.2
FMD type		
String of beads	28	90.3
Tubular stenosis	1	3.2
Atypical	2	6.5
Vessels affected		
1	1	3.2
2	15	48.4
3	9	29.0
4	6	19.4
Associated pathology		
Cerebral aneurysm	31	100.0
Dissection	6	19.4
Presentation		
Subarachnoid hemorrhage	4	12.9
Stroke	0	0.0
Incidental	27	87.1

FMD, fibromuscular displasia.

was the most common subtype (90%), while tubular stenosis (3%) and atypical FMD (7%) were found in a minority of patients. All but 1 patient had more than one vessel affected. All patients underwent treatment of cerebral aneurysms, most of which (87%) were incidentally discovered; 6 patients (19%) also had incidental vessel dissection (Table 1).

The internal carotid arteries were more commonly affected (65%) than the vertebral arteries (48%), with overlapping involvement of the anterior and posterior circulation in 17% of the cases. The cervical segment was involved in most patients with internal carotid artery (ICA) involvement. The petrous segment was involved in less than 10% of the patients, and cavernous or intracranial ICA FMD was not seen. The most commonly affected segment of the vertebral artery was V3 (44%), followed by V2 (24%). The V4 segment was involved in a minority of patients (10%), and intracranial involvement was not seen. In each case, the average length of the vessel affected was between 2.5 and 3.2 cm (Table 2).

The average size of a treated aneurysm was 7.1 ± 3.6 mm. The morphology was saccular in 40/42 cases (93%). Aneurysms were located in the anterior circulation in 37 cases (86%), and along the ICA in 33 cases and the anterior cerebral artery in 4 cases. The most common anterior circulation aneurysm locations were true ophthalmic (n = 9), paraophthalmic (n = 9), in the posterior communicating artery (n = 4), in the supraclinoid ICA (n = 4), and in the anterior communicating artery (n = 3). Aneurysms were located in the posterior circulation in 6 cases (86%), 4 of which were basilar apical aneurysms.

The most commonly performed treatment was flow diversion, which was performed in 29 cases (67%), in the majority of cases by pipeline embolization. Other procedures performed were coiling (19%), stent-coiling (12%), and intrasaccular flow disruption (2%). The average fluoroscopy time was 40 min and the radiation dose was 2,095 mGy. All but 1 procedure (98%) were successful. Verapamil was administered for vasospasm in 3 cases (7%), balloon

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Table 2. Vessel involvement

	Right		Left	
	n	%	*n*	%
Any ICA involvement	21	67.7	19	61.3
Cervical	21	67.7	18	58.1
Petrous	2	6.5	3	9.7
Cavernous/intracranial	0	0.0	0	0.0
Average ICA length involved ± SD (range), cm	3.0±1.8 (1.3–7.5)		3.2±2.0 (1.0–9.5)	
Any vertebral involvement	15	48.4	15	48.4
V2	9	29.0	6	19.4
V3	13	41.9	14	45.2
V4	4	12.9	2	6.5
Intracranial	0	0.0	0	0.0
Average vertebral length ± SD (range), cm	2.8±1.6 (1.3–6.5)		2.5±1.2 (0.7–4.5)	

ICA, internal carotid artery.

Table 3. Procedural details and outcomes

	n	%
Procedure type		
Flow diversion	29	67.4
Coiling	8	18.6
Stent-coiling	5	11.6
Intrasaccular flow disruption	1	2.3
Mean fluoroscopy time ± SD (range), min	40.3±19 (17–88)	
Mean radiation dose ± SD (range), mGy	2,095±936 (824–5,113)	
Success	42	97.7
Spasm/verapamil	3	7.0
Balloon angioplasty	5	11.6
Rupture/perforation	0	0.0
Thrombosis	1	2.3
Complications		
Transient ischemic attack	1	2.3
Stroke	0	0.0
Intracranial hemorrhage	0	0.0
Subarachnoid hemorrhage	0	0.0
Dissection	0	0.0
Groin hematoma	1	2.3
Death	0	0.0

angioplasty was required in 5 cases (12%), and stent thrombosis, which resolved with abciximab administration, was seen in 1 case (2%). There were no major complications such as stroke, SAH, intracranial hemorrhage, and death. No iatrogenic dissections occurred. Minor complications included 1 patient with a transient ischemic attack without any imaging correlate, and 1 patient with groin hematoma that did not require transfusion (Table 3). Follow-up angiography was performed in 88% of the cases, without evidence for FMD disease progression after treatment. Complete aneurysm occlusion with no contrast opacification

was observed in 22/28 patients (79%) who underwent flow diversion with pipeline embolization. The average time to last angiographic follow-up was 17 months (±13).

Discussion

In this retrospective study of more than 1,000 patients undergoing intracranial embolization procedures, predominantly for aneurysm, the prevalence of FMD was 3.0%. The patients with FMD underwent a total of 43 embolization procedures, 27 of which were performed on 19 patients through a vessel affected by FMD. Clinically, there were no major complications. Angiographically, follow-up imaging was performed on 88% of the patients, with no evidence of disease progression. Our results demonstrate the safety of elective endovascular treatment of intracranial aneurysms in patients with FMD.

Patients with FMD have increased rates of arterial dissection and cerebral aneurysms. Historically, FMD was commonly diagnosed in patients undergoing cerebral angiography for SAH, leading to inflated estimates of the aneurysm prevalence in FMD on the order of 20–50% [9, 10]. In a meta-analysis, Cloft et al. [2] removed patients with SAH from FMD series and found the prevalence of asymptomatic unruptured intracranial aneurysms to be 7.3%. The reported prevalence of unruptured intracranial aneurysm in the US registry for FMD was 4.6%, although only 64% of the patients had any intracranial vascular imaging and there were patients not included in this number who reported a history of SAH without a known aneurysm. By including the extracranial carotid and vertebral artery, the prevalence of aneurysms rose to 12.3% and the prevalence of dissection along the carotid or vertebral artery was 21.7% [3]. A more recent report from the US FMD registry found that 12.9% of women with FMD who had vascular imaging had an intracranial aneurysm [4]. Even after adjusting for the preponderance of women among people with FMD and people with aneurysm, the prevalence of aneurysms among FMD patients exceeds the population average, which is between 0.4 and 6.0%, higher in prospective angiographic studies and lower in retrospective autopsy studies [11]. Given the increased prevalence of aneurysms among patients with FMD, multiplicity is not a surprising finding, and indeed 6 patients in this series underwent separate treatments of distinct aneurysms.

Cerebral aneurysms in patients with FMD are a potentially unique pathology whose natural history warrants study to determine risks and benefits of elective treatment. True saccular aneurysms lack a tunica media and internal elastic membrane, whereas vessels affected by FMD – including the circle of Willis, though it is rarely apparent on angiography – show disordered fibroplasia within the tunica media [12]. These processes could compound or neutralize the rupture risk of intracranial aneurysms; yet their natural history in patients with FMD has not been independently characterized. Cloft et al. [2] sought to calculate the prevalence of aneurysms in FMD by removing patients with SAH from the equation. This assumes FMD aneurysms do not pose a different risk of rupture, an assumption the authors acknowledged and thought reasonable in the absence of evidence to the contrary. Study leaders from the US FMD registry more openly acknowledged the need to use existing guidelines regarding when to treat unruptured aneurysms in the absence of specific data on aneurysms in patients with FMD [3]. At least one study has suggested that once an aneurysm ruptures in a patient with FMD, there may be higher rates of vasospasm that lead to worsened outcomes [13].

There would seem to be a heightened risk of iatrogenic injury associated with endovascular treatment through fragile and tortuous FMD vessels, but reports are limited. Fuse et al. [5] shared the case of a 30-year-old male with SAH from a ruptured posterior inferior cerebellar artery aneurysm who underwent vessel sacrifice and multiple transcatheter vaso-

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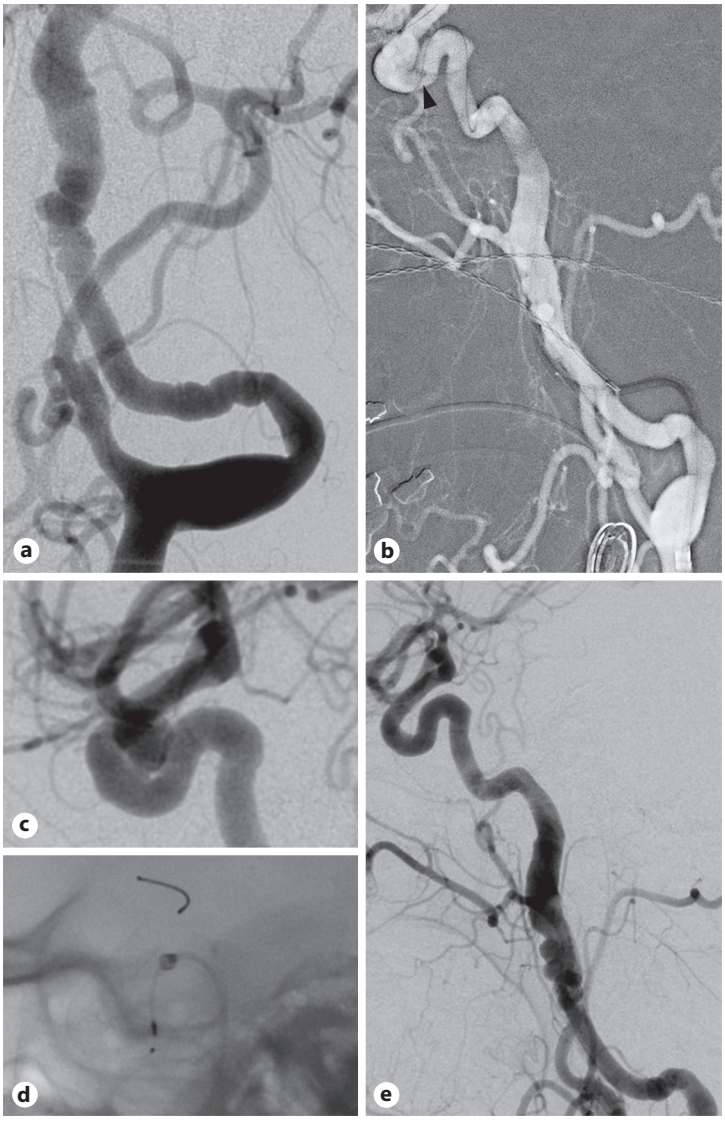

Fig. 1. Digital subtraction angiograms. **a** Anterior-posterior view of the proximal internal carotid artery hairpin loop and string-of-beads fibromuscular dysplasia (FMD) affecting the cervical internal carotid artery (ICA). **b** Mid-embolization lateral roadmap with a guide sheath proximal to the FMD within the distal common carotid and a distal access catheter (black arrowhead) within the mid-horizontal segment of a type IV cavernous ICA. **c** Pre-embolization lateral angiogram showing an 8-mm supraclinoid ICA aneurysm. **d** Pipeline embolization deployment across the neck of the aneurysm. **e** Six-month follow-up lateral angiogram showing complete aneurysm occlusion without evidence of FMD progression.

spasm treatments, and who then developed a 3-cm iatrogenic dissecting aneurysm of the external carotid artery. The authors concluded that particular care is needed when performing endovascular interventions in the presence of FMD. An unacknowledged reluctance to treat through FMD may be evidenced in the relative minority of intracranial aneurysms in the US FMD registry to undergo elective treatment (36%) and the abiding reliance on surgical clipping (43%) [3], both of which counter national trends toward elective endovascular treatment of unruptured aneurysms [14]. That registry reports elective treatment of 16 intracranial aneurysms in patients with FMD, but it does not break down open versus elective treatment, procedural outcomes, and whether the aneurysm was located on a vessel with angiographically apparent FMD [3]. Similarly, a Belgian series of 123 patients with FMD likewise reports coiling of 7 incidentally discovered cerebral aneurysms without reporting outcomes [15]. Our series presents the first reported outcomes of treating dependent aneurysms through FMD-affected vessels. We performed 43 embolization procedures on patients with FMD, 27 through a vessel showing angiographic signs of disease without major complications or signs of progression on follow-up imaging.

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To achieve these outcomes, no matter the aneurysm location or endovascular treatment modality, catheter access is a universally important technical consideration in treating patients with FMD. We routinely use a triaxial system for intracranial embolization, with minimal modification for FMD cases, as in the illustrative case of a quinquagenarian with an 8-mm left-sided supraclinoid ICA aneurysm treated with the pipeline embolization device (Fig. 1). For anterior circulation procedures, a 6-Fr guide sheath such as the AXS Infinity or NeuronMax is advanced to the carotid bifurcation, which is typically spared of FMD features [16]. Distal positioning of the guide sheath is essential to support the navigation of contemporary flexible distal intracranial catheters through the alternating fibrous bands and dilations of FMD as well as the common loops in the cervical ICA. Limiting step-off between coaxial catheters helps reduce the risk of dissection. The diseased segment is navigated under high magnification with a device-specific microcatheter and often a J-tipped 0.014″ microwire. The hydrophilic coating and rounded tips of contemporary distal intracranial catheters such as the Catalyst 5 [17] minimize vessel wall trauma while the catheter is tracked beyond the diseased segment to the cavernous ICA at a minimum. Prophylactic use of an intra-arterial spasmolytic such as verapamil can also be helpful to limit vasospasm in and around FMD segments. When possible, device deployment is performed under demagnified views, allowing constant observation for catheter construct stability in the cervical segment.

The patients included in this study constitute a representative sample of patients with FMD. They were predominantly middle-aged, female, and white [18, 19]. Most patients had more than one vessel affected. Cervical ICA involvement was the most common, although vertebral involvement was more common than in most series, which is estimated at 10–36% [1, 19]. This may be due to the improved resolution achieved by digital subtraction angiography, which was used for all patients in this series, compared to ultrasound, MRA, and CTA, which were used in a majority of cases in other studies [19, 20], on which bony landmarks obscure the assessment of the vertebral artery, especially around the V3 segment. Although multiple angiographic subtypes of FMD can be observed in a single patient, the string-of-beads appearance predominated in more than 90% of the cases in this series, as is typical in the literature [19].

Although the focus of this study is on the safety of a variety of endovascular embolization procedures in the setting of FMD, there is reason to think that FMD patients may differ from the general population in healing and regrowth after aneurysm embolization. The most commonly performed procedure reported in this series was flow diversion with the pipeline embolization device (29 cases). Aneurysm obliteration was achieved in 22/28 patients (79%), with angiographic follow-up at a mean interval of 17 months. This is similar to our observation of complete occlusion in 78% of all patients undergoing anterior circulation pipeline embolization for cerebral aneurysm at 12-month follow-up angiography (forthcoming data).

Limitations of this study include defining FMD angiographically without any corresponding histopathology [19]. It has long been accepted that the most commonly observed angiographic subtype (string of beads) corresponds to the most commonly observed histopathological subtype (medial) [1]. The string-of-beads phenotype is relatively easily distinguished from stationary waves, vasospasm, or atherosclerosis by the presence of dilations larger than the normal parent vessel and by its relative isolation to the cervical region; however, the less common phenotypes – tubular stenosis and atypical FMD – have a less specific radiographic appearance, which may lead to their underdiagnosis in this and other series. Additionally, due to our status as a referral center, angiographic follow-up was not complete but was obtained for only 88% of the patients.

Conclusions

Cerebral aneurysms are common among patients with FMD. Endovascular treatment of aneurysms through vessels affected by FMD is technically challenging, but it can be done safely.

Disclosure Statement

A.L. Coon is a consultant and proctor for Medtronic, Stryker, and MicroVention. G.P. Colby is a consultant for MicroVention and Codman.

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