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Research

Cerebrovascular fibromuscular dysplasia

The MGH cohort and literature review

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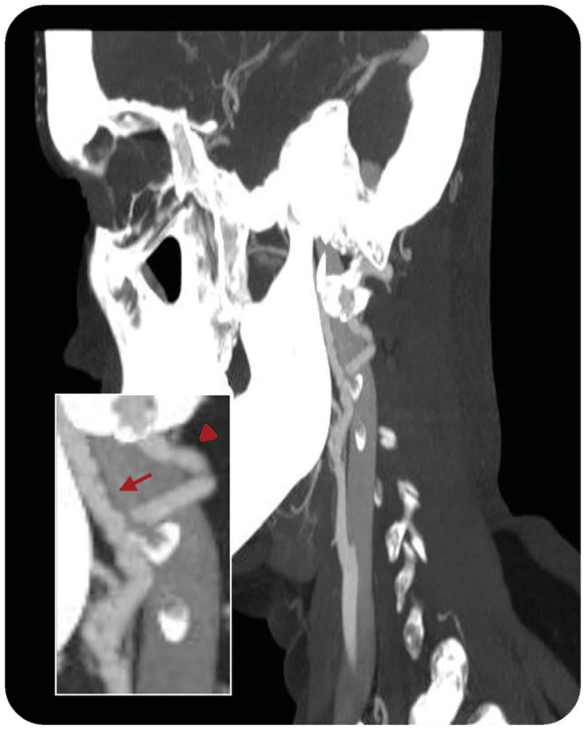
Abstract

Background: Fibromuscular dysplasia (FMD) is a rare noninflammatory, nonatherosclerotic arteriopathy of medium-sized arteries affecting up to 7% of the population. The disease can affect any artery but commonly affects renal, extracranial carotid, and vertebral arteries. The epidemiology and natural course of cerebrovascular FMD is unknown and requires further investigation. **Methods:** We present demographic and outcomes data on a case series of 81 patients with cerebrovascular FMD from Massachusetts General Hospital presenting between 2011 and 2015 followed by a review of the peer-reviewed literature. **Results:** Patients were a median age of 53 years (±12 SD) and the majority were women. Approximately 50% had a history of tobacco use and more than two-thirds had hypertension. Most patients were on monoplatelet therapy with aspirin; during follow-up, 7 of 67 had progressive disease or additional symptoms. One of 67 patients had a cerebrovascular event: TIA. There were 5 of 67 who had noncerebrovascular events or disease progression and 1 death of unclear cause. **Conclusions:** Cerebrovascular FMD may present with myriad symptoms. Our data support that patients with FMD with symptomatic disease have a low rate of recurrent symptoms or disease progression and can be managed conservatively with stroke risk modification, antiplatelet agents, surveillance imaging, and counseling. ***Neurol Clin Pract* 2017;7:225–236**



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Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp**.

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Fibromuscular dysplasia (FMD) is a noninflammatory, nonatherosclerotic arteriopathy of medium-sized arteries affecting up to 7% of the population. The disease is idiopathic but can result in major abnormalities including carotid and vertebral artery stenosis, arterial dissection, and aneurysm formation.[1–4] The most common radiographic appearance is alternating areas of arterial constriction and dilation forming a string of pearls, beaded, or accordion appearance on angiography. FMD can affect multiple and varied vascular beds and can present with similarly varied signs and symptoms including renovascular hypertension, disabling or severe headache, stroke, and TIA.[1] While FMD affecting the renal arteries has been well-described, data on the epidemiology and pathobiology of cerebrovascular FMD are accumulating. First described by Palubinskas and Ripley[5] in 1964, cerebrovascular FMD typically affects the extracranial internal carotid or vertebral arteries with radiographic and histologic features that mirror those observed in renal arteries. However, the epidemiology of cerebrovascular FMD and long-term outcomes and prognosis in patients with symptomatic disease remain under investigation. Therefore, the objective of this article is to review the clinical diagnosis and management and present follow-up data on patients with cerebrovascular FMD. This is particularly timely given the paucity of knowledge with respect to the natural history of FMD and the absence of clinical trials evaluating treatment options. We present clinical and outcome data from a cohort of 81 patients seen in the Massachusetts General Hospital (MGH) FMD integrated care program.

METHODS

The Fireman Vascular Center is a major clinical referral center for the Northeast and New England regions of the United States. Demographic, treatment-related, and outcome data were collected on 81 patients with cerebrovascular FMD who presented to our center as part of this cohort study.

Standard protocol approvals, registrations, and patient consents

Data presented are from Massachusetts General Hospital. Eighteen of the 81 patients (approximately 20%) were separately also enrolled in the US registry and therefore made up a small fraction (4%) of the 447 patients enrolled in the US registry. The remainder of patients included in this study did not participate in the US registry. Patients were enrolled in our FMD registry between 2011 and 2015. Prior to enrollment we received approval from our institutional ethical and standards review board and obtained written and informed consent from participants.

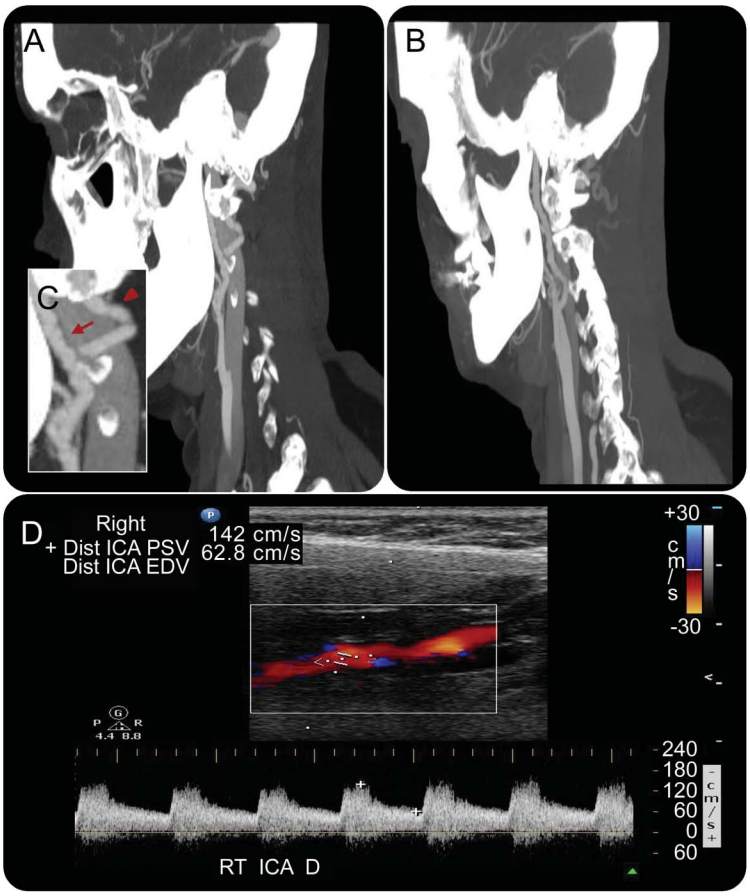
The diagnosis of cerebrovascular FMD was based on radiographic appearance of an arteriopathy consistent with a diagnosis of FMD involving the carotid or vertebral arteries on duplex ultrasonography, CT or magnetic resonance angiography, or invasive arteriography (figure). Other vascular territories were often involved, including renal and mesenteric arteries. Information regarding recurrence of symptoms, stroke-like events, or TIAs was obtained from retrospective chart review of follow-up visits. TIA was defined as a transient focal neurologic deficit without radiographic evidence of stroke. Stroke was defined as a focal neurologic deficit involving a particular vascular distribution with radiographic findings on CT or magnetic resonance brain imaging consistent with a diagnosis of stroke. Descriptive demographic data are presented as percentages, mean, or median ± SD.

RESULTS

Clinical characteristics of the MGH FMD cohort and treatment

Eighty-one patients between ages 19 and 83 years with a diagnosis of FMD were evaluated between 2011 and 2015. All patients in the study had carotid artery FMD. Seventy-one of 81 patients had additional abnormalities in the vertebral artery consistent with FMD.

Figure Example of cerebrovascular fibromuscular dysplasia (FMD)



(A–C) CT angiogram demonstrates FMD affecting the mid to distal internal carotid artery (ICA) bilaterally. The accordion or string of beads appearance is noted in the ICA by an arrow. There are additional changes in the vertebral artery suggestive of FMD as well (arrowhead). (D) Carotid artery ultrasound of the right ICA demonstrates increased peak systolic and diastolic velocities with vessel irregularity.

Eight of 81 patients had bilateral carotid FMD. The median age at the time of enrollment was 53 years (±12 SD). Consistent with the previously reported female predominance, 78 of 81 patients in our cohort were women. A history of tobacco use was reported in 49.2% of patients. A history of hypertension was reported in 68%. Approximately 50% of patients described a history of headache while one-third described a history of dizziness or tinnitus. Seven percent of patients had a history of stroke and 16% had TIA. In 35% of patients, FMD was associated with arterial dissection and in 20% there was an associated aneurysm. Dissections were discovered in the bilateral internal carotid and vertebral, celiac, superior mesenteric, and abdominal aortic arteries. Aneurysms were found in the renal, internal carotid, vertebral, intracranial right middle cerebral, anterior cerebral, and basilar arteries. A small percentage of patients (4%) had a history of subarachnoid hemorrhage (table 1). Most patients were on at least 1 antihypertensive agent and 1 antiplatelet agent. A total of 64.5% of patients were on aspirin alone, 3.8% on clopidogrel alone, and 10% on dual antiplatelet therapy with both aspirin and clopidogrel. One third of patients were not taking antihypertensive agents and more than 80% were on no more than 2 antihypertensive medications. The initial average systolic blood pressure was 124 ± 18 mm Hg (SD) and average diastolic blood pressure was 74 ± 10 mm Hg (SD). A total of 30.9% (21/68) were on some form of statin (table 2).

Table 1 Clinical and demographic data

Characteristics	Values, mean ± SD (range) or % (n)
Median age, y	53 ± 12 (19–83)
Female	96.0 (78/81)
Oral contraceptive pill use	19.0 (4/21)
Smoking	49.2 (32/65)
Pack-years smoking	12 ± 2.4 (1–30)
Signs/symptoms prior to diagnosis	
Hypertension	68.0 (51/75)
Stroke	7.3 (5/68)
Hemispheric TIA	16.1 (10/62)
Amaurosis fugax	8.2 (4/49)
Horner syndrome	9.3 (4/43)
Aneurysm	20.0 (11/55)
Subarachnoid bleed	4.1 (2/49)
Dissection	35.3 (18/51)
Headache	52.3 (34/65)
Dizziness	35.7 (15/42)
Tinnitus	30.2 (13/43)
Cervical bruit	43.2 (16/37)

Follow-up and outcomes

Between 2011 and 2015, patients returned for 0 to 6 follow-up visits depending on when they were enrolled in the registry. Sixty-seven of 81 patients were seen in an outpatient clinic after the initial consultation. The median follow-up period was 2.4 years (25th–75th interquartile range of 1.24–3.23 years). Seven of the 67 had additional symptoms or objective findings including cerebrovascular and noncerebrovascular disease or disease progression. One patient had a new intracranial aneurysm. The aneurysm was detected on repeat CT angiogram 2 years after the initial diagnosis of FMD. It was a small 2 mm right cavernous carotid artery aneurysm arising from the medial wall. Another had a TIA with no history of stroke or TIA. This patient had other vascular risks including hypertension and diabetes. In this case, there was no significant carotid or vertebral artery stenosis or radiographic progression of disease. There was one death of unclear etiology. Other findings during the follow-up period include brachial artery FMD requiring interposition and reverse saphenous vein graft, mild progression of renal artery stenosis on duplex ultrasonography, renal infarction, and an incidental new diagnosis of renal clear cell carcinoma. The majority of patients had stable disease with no additional clinical symptoms or signs. Eighty-two percent of patients at last follow-up were on aspirin alone; 4% were on dual antiplatelet therapy with aspirin and clopidogrel. The remainder were on no antithrombotics. Thirty-two percent of patients were on some form of statin.

DISCUSSION

We present data from 81 patients with FMD treated at MGH and their demographic and outcome data. The age at diagnosis, sex distribution, and concurrent symptoms are similar to data presented from the US registry. While we are a large referral center for patients with stroke and

Table 2 Medication treatment

Treatments	Values, mean ± SD or % (n)
Antihypertensives	
Angiotensin-converting enzyme inhibitor	19.2 (14/73)
Angiotensin receptor blocker	19.7 (14/71)
β-Blocker	33.8 (24/71)
Diuretic	25.3 (18/71)
Ca channel blocker	19.7 (14/71)
α2 agonist	0.0 (0/71)
Combination antihypertensive therapy	
0	33.3 (23/69)
1	36.2 (25/69)
2	18.8 (13/69)
≥3	11.6 (8/69)
Systolic blood pressure, mm Hg	123 ± 18
Diastolic blood pressure, mm Hg	74 ± 10
Antithrombotics	
Acetylsalicylic acid only	64.5 (51/79)
Clopidogrel only	3.8 (3/79)
Acetylsalicylic acid and clopidogrel	10.1 (8/79)
Coumadin only	1.3 (1/79)
Coumadin and acetylsalicylic acid	2.5 (2/79)

vascular disease, this cohort represents a fraction of patients with FMD who have symptomatic disease. The natural history of FMD in asymptomatic patients remains unclear. Those with symptomatic disease likely represent a group of patients at higher risk of developing recurrent events or progressive disease, which introduces bias in this population. Likewise, there is an inherent bias in the tertiary referral center population, which may reflect more symptomatic patients or different rates of follow-up and repeat diagnostic testing. While the study population might be biased, we find the progression of disease in this potentially higher-risk group of particular interest.

Epidemiology of FMD

Several studies support the observation that renal FMD affects up to 7% of the general population. Among potential kidney donors, renal FMD was found in 4%–7% of cases.[6,7] In one study of 819 consecutive routine autopsies, approximately 1% were found to have FMD.[6] The prevalence of carotid or vertebral FMD seems smaller, with studies publishing anywhere from 0.3% to 3% of cases found on catheter angiography.[8] In a large case series of 20,244 autopsies performed at Mayo Clinic, cerebrovascular FMD was found in only 4 patients.[9] Based on these estimates, cerebrovascular FMD appears to be a rare arteriopathy. While there are few studies that can estimate the prevalence of FMD in the general population, we suspect a lower prevalence than in cases undergoing autopsy or preparing for kidney donation. These population-based differences in risk may explain the differences in prevalence observed in prior studies. Our sample and indeed the cohorts previously published likewise may not represent the spectrum of clinical symptoms or patient characteristics in

Headache is a common first complaint, reported in 50%–78% of patients, therefore FMD should be considered in patients with new-onset headache late in life.

patients with FMD in the general population as patients who are asymptomatic are unlikely to be included in such registries.

FMD tends to affect more women than men. In the previously published largest reported case series of FMD (n = 447), 91% were women.[10] In most other case series, the majority of cases were women. In other published case series, the ratio of men to women was approximately 1:3, as in the Cardiovascular Outcomes in Renal Atherosclerotic Lesions angiographic core laboratory database of 997 patients.[6] FMD can affect all age groups but typically affects middle-aged individuals with a median age at diagnosis of 50 years.[1,10] In our case series, the age at presentation and female predilection was similar to data from the US FMD registry. Similar to the US FMD registry, we also found a high percentage of patients with a previous diagnosis of hypertension.[10] Anecdotally, FMD is often thought of in patients on >2 antihypertensive agents or with refractory hypertension. However, most patients in our series were on no or only one antihypertensive agent, with blood pressures that seemed well-controlled. Therefore, uncontrolled or refractory hypertension may not be a reliable sign associated with a diagnosis of FMD.

Although FMD has been described in almost every arterial bed,[3,11] there are limited data on the association between cerebrovascular FMD and ischemic or hemorrhagic stroke. A recent American Heart Association (AHA) Scientific Statement about FMD[1] and a European consensus article[2] highlight the need for increased awareness and more data on outcomes and management. There have been few reports on outcomes in patients with cerebrovascular FMD during follow-up after their initial diagnosis. We followed patients in our cohort for 4 years after their initial presentation. Fourteen patients (17%) of our cohort were not seen in follow-up. The cause for loss to follow-up is unclear but we acknowledge that their loss to follow-up may bias the outcome of this cohort as it is unknown if they had adverse events or no events. Nonetheless, it seems that even in this cohort of patients with symptomatic FMD, most patients did not have progressive disease or recurrent symptoms during a 4-year follow-up period. These data suggest that patients with FMD may have a low rate of recurrent/new symptoms or progressive disease. Similar to prior studies, most patients were typically treated with single antiplatelet agents for primary and secondary stroke risk reduction. The low rate of disease progression or recurrent symptoms observed in our population may be attributable to a number of factors including behavioral/lifestyle modifications, frequent follow-up, antiplatelet use, and blood pressure control.

Clinical presentation of cerebrovascular FMD

Typical FMD presentation Patients with cerebrovascular FMD are most likely asymptomatic at disease identification. Overall, presenting signs and symptoms are nonspecific, including headache, dizziness, tinnitus, and bruits. A minority of patients will present with more consequential cerebrovascular disease including stroke, TIA, subarachnoid hemorrhage, or arterial dissection.

Headache is a common first complaint, reported in 50%–78% of patients,[10,12] therefore FMD should be considered in patients with new-onset headache late in life. The headache often has migrainous features and may require chronic medication use.[10] Another common symptom is pulsatile tinnitus, which is seen in a quarter of patients with FMD. Often described as a whooshing sound in the ears, it can serve as a clue for diagnosis and should

not be dismissed when reported by a patient. An equal number of patients report nonpulsatile tinnitus. Neck pain is reported in 18%–22% of cases and is usually unilateral.[10,12] In one review, 50% of patients with FMD complained of depression and anxiety.[12]

Cerebrovascular disease and stroke in the young As a group, cerebral arteriopathies are the most common cause of stroke in the young, accounting for 20%–35% of strokes in young adults.[13–15] The connection between FMD and stroke in young adults is mostly mediated by cervical artery dissection. In the US FMD registry, 18.3% had arterial dissection, with the carotid arteries involved in 13% and vertebral arteries in 3.6% of cases.[10] Notably, the frequency of multiple artery dissections was also higher in the FMD population. A recent report found a higher prevalence of FMD in patients with multiple rather than with single cervical artery dissection (15% vs 3%).[16] Interestingly, when analyzing registries of arterial dissections, the frequency of FMD as an etiology varies greatly; one large multicenter series with almost 1,000 patients reports this prevalence as 5.6%,[16] while other smaller series (100 patients and fewer) report 16.5%–21%.[17] One single-center case series followed 103 consecutive patients admitted for cervical artery dissection, with mean follow-up of 4 years. In this series, of 5 patients with recurrent dissections, FMD was found in 4.[17] Based on these data, FMD should be considered in young patients with spontaneous or multiple dissections or early-onset hypertension and if there are comorbid illnesses such as unexplained headache, intermittent dizziness, or tinnitus.

Radiographic and histologic types

FMD typically affects the middle and distal segments of the internal carotid and vertebral arteries at the level of the C1 and C2 vertebrae, a location often spared by atherosclerosis. The majority of cervical FMD cases involve the internal carotid artery, often bilaterally, while vertebral artery involvement is less common and often coexists with carotid FMD.[2,8] Recent AHA consensus criteria have condensed the angiographic subtypes into 2 categories: multifocal (beaded) and focal. Multifocal disease is the more common variety and generally represents the histologic subtypes that involve the medial arterial layer. Focal disease represents only 1%–2% of angiographic FMD and involves the intimal layer. There has been a recent case report and population-based study from French Martinique, describing atypical, carotid bulb FMD, as a relatively common cause of ischemic anterior circulation stroke in young patients in that nation.[18,19] The medial fibroplasia form of FMD is the most common histologic subtype, with discontinuous areas of fibroproliferative collagenous tissue that interrupts the smooth muscle.[2] Medial and perimedial hyperplasia forms of medial dysplasia also exist.[20]

Intracranial FMD is rare, often presenting with intracranial aneurysms and typically co-occurring with extracranial FMD.[21–23] There have been case reports of patients with extracranial FMD who developed multiple intracranial fusiform dilations and aneurysms, including one pathologically proven case from Germany where aneurysms developed along a single arterial segment.[24,25] It is not known whether patients with intracranial FMD harbor unique risk factors such as α-1 antitrypsin deficiency,[26] though associations in young patients have been found between FMD and moyamoya disease[27,28] and the reversible cerebral vasoconstriction syndrome (RCVS).[29,30] It is important to note that the diagnosis of FMD is typically based solely on angiographic appearance, making it difficult to exclude underlying systemic conditions such as α-1 antitrypsin deficiency or angiographic mimics like moyamoya disease, RCVS, primary angiitis of the CNS, atherosclerosis, radiation arteriopathy, infectious vasculitides, Takayasu disease, and other medium-vessel arteriopathies. However, most experts recommend that any confirmed finding of FMD requires imaging of the intracerebral arterial circulation to exclude potentially lethal aneurysms.

Etiology

The etiology of FMD is unknown. Prior studies suggest sex/hormonal, environmental, and genetic considerations. The higher prevalence of FMD in women suggests an endogenous

We advocate for CT or MRI of the entire aorta and its branches in all patients with suspected FMD.

hormonal component, though no definitive link has been shown. A pilot study in renovascular FMD[31] found expression of progesterone receptors in vascular smooth muscle cells of 6 patients with FMD and no expression of this receptor on those without FMD. There has also been the suggestion that cigarette smoking may be related to increased risk of FMD.[1,10] In the US FMD registry, 37.2% were smokers. This is higher than in the general population but may approach the rate of smoking in stroke populations. In the 1988 Lausanne stroke registry of 1,000 patients with 0.4% diagnosed with FMD, as many as 64% of patients with atherosclerosis and 39% with embolic disease were smokers.[32] In the Trial of Org 10172 in Acute Stroke Treatment registry published in 2001, the rate of smoking was lower. Thirteen percent of the stroke population were smokers with a range of 8%–25% depending on stroke subtype.[33] The rate of smoking was higher (44%) in the Helsinki stroke registry of younger patients aged 15–49 years.[15] There is a well-known association between smoking and stroke risk. We found an even greater percentage of smokers in our FMD cohort than that found in the prior FMD registry, suggesting that similar to stroke, there may be an association between smoking and either FMD disease pathobiology or progression.[34]

Genetic considerations

FMD is a complex heritable condition.[35] However, the genetics of FMD require further investigation. It has been reported in patients with α-1-antitrypsin deficiency, most commonly caused by mutations in *SERPINA1*.[36] Individual case reports have described FMD in first-degree relatives, suggesting heritability. In general, estimates of heritability have been hampered by the necessity of invasive or advanced imaging. In an older study of the families of 20 patients with FMD,[35] 12 families, or 60% of this cohort, had between 1 and 11 relatives with clinical symptoms suggesting FMD. Accumulated data support autosomal dominant inheritance with incomplete penetrance or more likely complex trait inheritance. Multiple research groups are actively investigating the genetic variation responsible for FMD and more information about specific genes will no doubt be available in the next several years.

FMD predisposes to cervical dissection. Cervical dissections have been reported in several familial conditions, most prominently vascular Ehlers-Danlos syndrome (OMIM 130050) caused by mutations in *COL3A1* and Loeys-Dietz syndrome (OMIM 609192) caused by mutations in *TGFBR1*, *TGFBR2*, *SMAD3*, or *TGFB2*. Cervical dissections have also been reported in Marfan syndrome (OMIM 154700) and in *ACTA2* gene mutations (OMIM 611788). However, in one study including patients who had additional features prompting genetic analysis (aortic dissection, aortic aneurysm, external features of connective tissue disease, or family history of premature death), no variants were discovered in the *FBN1*, *COL3A1*, *TGFBR1*, *TGFBR2*, *SMAD3*, *ACTA2*, *PLOD1*, *TGFB2*, or *COL5A1* genes.[37,38] Across both studies, no definitively causal variants were discovered. These data illustrate that there may be futility in current genetic testing for FMD and the need for larger population-based genetics studies.

Management, surveillance, and disease prevention

No randomized controlled trials compare treatment options in FMD. In patients with ischemic strokes, antithrombotic medications—either antiplatelet therapy or anticoagulants—are often administered. Emerging data suggest that addressing modifiable vascular risk factors such as

Table 3 Activities to avoid for patients with fibromuscular dysplasia with cervical artery dissections

Avoid or use caution with activities that increase the risk of sudden, rapid, or severe neck motion or raise intrathoracic or abdominal pressure
Chiropractic neck manipulation
Yoga and pilates poses with hyperextension/flexion of the neck
Strenuous weight lifting with breath holding
Prolonged neck flexion or hyperextension (i.e., ceiling painting, mechanic work, hairdressing)
Extreme sports with risk of neck injury
Roller coasters
Ziplining
High-intensity aerobics
Straining, excessive coughing

hypertension, diabetes mellitus, and hyperlipidemia lowers the threshold for stroke from any cause.[39,40] Hence, aggressive treatment of these risk factors is warranted in patients with FMD. Various surgical and endovascular techniques have been attempted, including percutaneous transluminal angioplasty and stent deployment, graduated intraluminal dilation with or without surgical resection and anastomosis, and endarterectomy.[41] There are no definitive data to suggest that surgical measures are better than conservative medical management. Surgical intervention is not recommended for asymptomatic FMD. In those with hemispheric strokes, antiplatelet agents are usually considered first unless there is flow limiting severe carotid stenosis, in which case endovascular intervention can be considered.[42] Our approach to surveillance of patients with FMD is to monitor with yearly carotid duplex ultrasound examinations unless new symptoms arise. We advocate for CT or MRI of the entire aorta and its branches in all patients with suspected FMD. Patients with FMD with cervical artery dissections often ask what activities to avoid. Patients with FMD with dissection must be keenly aware of these limitations, given their likelihood of recurrent dissection.[43–45] Our suggested list of these activities is shown in table 3 and reflect the advice we generally give patients in our clinical practice.

CONCLUSION

Cerebrovascular FMD may present with myriad symptoms; however, our data support that patients with FMD with symptomatic disease have a low rate of recurrent symptoms or disease progression. The majority of patients with FMD are asymptomatic or have vague symptoms, which may result in a delay in diagnosis. One potential construct for diagnosing FMD includes suspicion in patients with ischemic stroke from cervical artery dissection or multiple spontaneous cervical artery dissections, especially occurring in women (age 50) with early hypertension, late-onset headache (with migrainous components) with tinnitus, or cervical bruits. CT or MRI of the entire aorta and its branches is reasonable in patients with suspected FMD. Patients with FMD with large vessel involvement, ascending thoracic aortic aneurysm, or external features of connective tissue disease may benefit from cardiovascular genetic evaluation to rule out the presence of a mendelian vascular condition. However, routine genetic testing is not recommended. Patients with FMD should be advised about optimal management of hypertension and hyperlipidemia, and must be repeatedly encouraged to stop smoking. It is reasonable to have patients on aspirin therapy though there are no randomized trials comparing outcomes for patients with FMD given antiplatelet therapy vs placebo. We routinely remind patients of the warning symptoms of arterial dissection, TIA, or stroke.

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Received July 8, 2016. Accepted in final form November 28, 2016.

AUTHOR CONTRIBUTIONS

Andrea M. Harriott: data analysis, interpretation, literature review, manuscript revision and preparation. Eli Zimmerman: data analysis, interpretation, literature review, manuscript preparation. Aneesh B. Singhal: data collection, interpretation, manuscript revision and preparation. Michael R Jaff: data collection, interpretation, manuscript revision and preparation. Mark E. Lindsay: data collection, interpretation, manuscript revision and preparation. Guy A. Rordorf: data collection, interpretation, manuscript revision and preparation.

STUDY FUNDING

No targeted funding reported.

DISCLOSURES

A.M. Harriott serves as Junior Editor for *Cephalalgia*. E. Zimmerman reports no disclosures. A. Singhal serves on scientific advisory boards for Biogen and the NIH; serves as Assistant Editor for *Medical Gas Research*; receives publishing royalties from UpToDate, Inc.; serves as a consultant for Biogen Idec and as an Event Adjudicator for Thrombolysis in Myocardial Infarction Trial Group; receives research support from Boehringer Ingelheim, NIH/National Institute of Neurological Disorders and Stroke, American Academy of Neurology, UpToDate, and Medlink Inc.; has served as a medicolegal expert witness for individual cases concerning stroke; and his spouse is an employee of Biogen and holds employee stock and stock options in Biogen. M.R. Jaff serves on scientific advisory boards for BiO2/Novella and Philips/Volcano; has received funding for travel and/or speaker honoraria from Philips/Volcano and VIVA Physicians; serves as a consultant for Abbott Vascular, Boston Scientific, Cordis, Cardinal Health, and Medtronic Vascular; and holds equity investments in PQ Bypass and Vascular Therapies. M.E. Lindsay receives research support from NIH/NHLBI. G.A. Rordorf reports no disclosures. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp**.