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REVIEW

Cerebrovascular Fibromuscular Dysplasia – A Practical Review

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Abstract: Fibromuscular dysplasia (FMD) is a rare idiopathic, segmental, noninflammatory and nonatherosclerotic arteriopathy of medium-sized arteries. It is classically considered to be a disease of young and middle adulthood, with females more commonly affected than males. FMD is a systemic disease. Although historically considered to be rare, cerebrovascular FMD (C-FMD) has now been recognized to be as common as the renovascular counterpart. Extracranial carotid and vertebral arteries are the most commonly involved vascular territories in C-FMD with the clinical presentation determined by vessels affected. Common symptoms include headaches and pulsatile tinnitus, with transient ischemic attacks, ischemic stroke and subarachnoid or intracerebral hemorrhage constituting the more severe clinical manifestations. Cervical artery dissection involving carotids more often than vertebral arteries and intracranial aneurysms account for the cerebrovascular pathologies detected in C-FMD. Our understanding regarding C-FMD has been augmented in the recent past on account of dedicated C-FMD data from North American, European and other international FMD cohorts. In this review article, we provide an updated and comprehensive overview on epidemiology, clinical presentation, etiology, diagnosis and management of C-FMD.

Keywords: fibromuscular dysplasia, stroke in young, dissection, tinnitus

Introduction

Fibromuscular dysplasia (FMD) is a rare idiopathic, segmental, noninflammatory, and nonatherosclerotic disease that causes abnormal cellular proliferation and architectural distortion in the walls of medium- and small-sized arteries.[1–7] FMD is primarily a stenotic disease, with the spectrum being expanded to include aneurysms, dissection as well as abnormal tortuosity of the vessels.[1,2] The lesions could be either "focal" causing a single stenotic lesion, or "multi-focal" manifesting as alternating areas of stenosis and dilatation contributing to a classic "string of beads" or "accordion" phenotype.[1,5] Being a rare disease, the majority of the data regarding FMD are derived from multiple international registries such as the United States Registry for FMD, French-Belgian ARCADIA registry (Assessment of Renal and Cervical Artery Dysplasia) and the European International FMD registry and initiative (FEIRI).[1,2,7,8] The first international consensus statement on the diagnosis and management of FMD was published in 2019 by the working group "Hypertension and the Kidney" of the European Society of Hypertension (ESH) and the Society for Vascular Medicine (SVM), thereby ensuring a uniformity in the diagnosis, evaluation and management of this hitherto rare disease.[1] Even though FMD can develop in any age group, it is classically considered to be a disease of young and middle adulthood, with mean age of presentation ranging between 43 and 53 years across the different registries.[1–7] Females have consistently shown a predilection for development of FMD (82–95% across the registries), with males likelier to have a more severe but focal disease and higher prevalence of aneurysms and dissection.[1–6] FMD can involve any medium or small sized artery of the body, with renal blood vessels being the most common site of involvement followed by cerebrovascular circulation.[1,2,6] A majority of the subjects with FMD had multi-focal involvement (71.9–76%) with prevalence of multi-vessel subtype ranging between 31.2% and 55.1%.[1,2,6] In order to be labelled as multi-vessel FMD,

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there should be a stenotic lesion (either focal or multi-focal) in at least one vascular bed, with stenosis, aneurysms, dissection or tortuosity in other vascular territories.[1]

As FMD is a systemic disease, it has kaleidoscopic manifestations with an incidental diagnosis of vascular imaging abnormalities not being uncommon. Hypertension was the common presenting manifestation in up to 72% of subjects in FEIRI registry, with cerebrovascular presentation noted in up to 11.6%.[2] Although historically considered to be rare, cerebrovascular FMD (C-FMD) has now been recognized to be as common as the renovascular counterpart with the aid of systematic screening of vascular beds from cranium to pelvis in any index case of FMD, as per recommendations from the International consensus statement.[1] C-FMD may manifest with benign symptoms such as headaches, pulsatile tinnitus with the other less common symptoms being neck pain, carotidynia, blurry vision as well as dizziness.[2–6,9,10] However, the more dangerous manifestations of C-FMD include cerebrovascular events that encompasses transient ischemic attack, ischemic stroke, subarachnoid hemorrhage or unruptured intracranial aneurysms as well as intracerebral hemorrhage.[2–6] Cervical artery dissection (CeAD) involving carotids more often than vertebral arteries was documented in 6–27% of FMD cohorts in the various registries, thereby constituting the most common vasculopathy causing dissection in the young to middle adulthood.[2–6] Our understanding regarding C-FMD has been augmented in the recent past on account of dedicated C-FMD data from North American, European and other international FMD cohorts.[4–6]

Classification and Diagnostic Criteria

Despite being identified as early as 1938, advancements in the field of FMD have been hampered by a lack of well-accepted definitions, classifications, and diagnostic criteria. The first international consensus statement on FMD[1] encompassing the recommendations from the European[11] and the American Heart Association[12] provided the solution for the nuances, providing a universally accepted classification based on imaging findings, thereby making the previously prevalent histological classification of FMD obsolete.[1] The former classified FMD into either focal or multi-focal types on the basis of angiographic imaging.[1,5] Focal FMD constitutes either a single concentric (less than 1 cm in length)[7] or tubular (1 cm or more) narrowing which can affect any segment of the vessel. On the contrary, the multi-focal sub type encompasses alternating areas of stenosis and dilatation producing the typical "string of beads appearance" typically affecting the mid and distal portions of the affected vessels.[1,5] Multi-focal FMD constitutes the most common type (90%) followed by the focal variant constituting the remaining 10%.[11,12] Despite being primarily a stenotic disease, the imaging spectrum in FMD has been expanded to include aneurysms, tortuosity and dissection.[1] Extreme tortuosity involving the mid to distal portions of the internal carotid artery resulting in an "S" shaped curve has been identified more commonly in those with FMD (up to 32% on carotid duplex studies),[13] even though it is not pathognomonic. However, to maintain standardization, the current international consensus statement clearly mentions that the presence of isolated aneurysms, dissection, or tortuosity is insufficient to diagnose FMD, which requires the concomitant presence of at least one focal or multi-focal arterial stenotic lesion. The statement also defines the presence of the latter in at least one vascular bed; the presence of aneurysms, dissection or tortuosity in another vascular bed is considered multi-vessel FMD involving all the vascular territories.[1] Systematic screening of the other vascular beds in any index case of FMD has led to the documentation of a high prevalence of multi-vessel FMD as highlighted by the prevalence of the same in the multiple international FMD registries – 57% in the European International Fibromuscular Dysplasia Registry and Initiative (FEIRI),[2] 66% in the French-Belgian ARCADIA registry (Assessment of Renal and Cervical Artery Dysplasia)[8] and 55% in the latest update of the United States FMD registry.[1,7] In addition to this, the data from FEIRI have also revealed that those FMD patients with focal disease were, on average, younger by ten years and more frequently males but with lesser prevalence of bilateral and multi-vessel disease as compared to multi-focal FMD phenotypes.[2] Both the FEIRI[2] and ARCADIA[8] registries indicated that those with multi-vessel FMD were likelier to have the multi-focal phenotype as well as a cerebrovascular presentation.

Epidemiology

The prevalence of C-FMD in the general population is unknown on account of the rarity of the condition as well as the fact that it can remain clinically silent and undiagnosed until being picked up incidentally on imaging studies performed for another reason.[1–6] Renovascular FMD was detected in 3–4% of healthy renal donor candidates[1] as against the prevalence of C-FMD in 0.02% of consecutive autopsies done at the Mayo clinic over 25 years.[14] Even though

historically considered to be rarer, C-FMD has now been increasingly identified to be equally prevalent as renovascular FMD due to the widespread and uniform practice of screening of blood vessels from cranium to pelvis in every case of FMD as recommended by the international consensus statement.[1] C-FMD has female predilection with 91–96% of study subjects being women.[4,6] It is classically a disease of the fifth and sixth decade of life, with mean age of diagnosis in the MGH cohort and North Central London vascular cohort being 53 (range 19–83) and 63 (range 21–96) years, respectively.[4,6] Family history of FMD ranges between 2.4% in ARCADIA[8] to 3.0% in FEIRI[2] and 5.4% in the US FMD registry.[7] C-FMD typically involves the extracranial portion of the carotid and vertebral arteries, with intracranial FMD being rare and predominantly seen as an extension of the extracranial abnormalities or in subtypes of pediatric C-FMD.[1–6] The lesions classically involve the mid and distal portion of the cervical internal carotid artery and V3 or V4 segments of the vertebral arteries which are typically spared by atherosclerosis.[5] Extracranial internal carotid arteries were affected in 85–100% of pure C-FMD cohorts with bilateral involvement identified in up to 61%.[4,6] Vertebral artery involvement was demonstrated in up to 87% of C-FMD subjects,[4,6] with the majority being in conjunction with carotid artery abnormalities. The salient variables of the FMD registries have been summarized in Table 1.

The spectrum of C-FMD includes the classical phenotype of stenosis in addition to aneurysms, dissection, and tortuosity. FMD is considered to be the most common vasculopathy contributing to cervical artery dissection (CeAD), with an overall prevalence of 21% of all C-FMD subjects (16% affecting the carotid and 5% involving the vertebral arteries).[15] In a study of 81 C-FMD subjects in MGH, the prevalence of dissection was 35.3%[4] compared to 16% among 86 subjects in the North Central London vascular cohort.[6] Data from the international FMD registries also revealed wide fluctuations in the prevalence of arterial dissection as depicted in the range of 5.6%, 28.1% and 15.1% seen in FEIRI, US FMD registry[1,7] and ARCADIA registry, respectively.[8] The independent risk factors for cervical artery dissection in the ARCADIA registry included age more than 50 years, male gender, history of migraine or hypertension as well as multi-vessel FMD.[3,8] Similar observations were also made in FEIRI, with multivariate analysis revealing older age [OR 1.02 (1.01–1.05), p = 0.03], male sex [OR 4.35 (2.33–7.69), p = 0.005], stroke or cerebrovascular presentation [OR 2.19 (1.01–4.52), p = 0.04] and multi-vessel FMD [OR 3.15 (1.74–5.87), p = 0.001] as strong predictors for arterial dissection.[2] In addition, multiple arterial dissections were more common in the FMD cohort, reaching up to 37%.[4,5]

The most common intracranial vascular abnormality in C-FMD is a cerebral aneurysm.[1] They are more likely to remain unruptured and incidentally detected on vascular imaging and commonly be of a saccular type.[3] The prevalence of intracranial aneurysms is higher in the FMD cohort than in the general population (7% vs less than 5%).[16] In the earliest reports of the US FMD registry published in 2012, 12.9% of women with FMD had at least one intracerebral

Table 1 Summary of the Salient Epidemiological Characteristics of the ARCADIA, US Fibromuscular Dysplasia (US FMD) Registry and the European/International Fibromuscular Dysplasia Registry and Initiative (FEIRI)

Variable	ARCADIA	US FMD Registry	European/International FMD Registry
Study population (n)	469	1885	1022
Females (%)	84	95	82
Age at diagnosis of FMD (Median in years)	53	53	46
Multifocal FMD (%)	92	95	72
Multivessel FMD (%)	48	55.1	57.4
Vascular territory involved			
Renal (%)	79	66	91
Cerebrovascular (%)	50	80	63
Dissections (%)	16	28	6
Aneurysms (%)	26	23	22

aneurysm, with multiple aneurysms in 4%.[7] About 29% of them had a size of 5 mm or more, with a majority of them located in the posterior circulation, both being high risk features indicating the potential for rupture.[1,3,7] C-FMD specific cohorts from MGH and North Central London revealed prevalence of intracranial aneurysms between 9% and 20%.[4,6] It is uncertain as of now whether FMD per se increases the risk of rupture of intracranial aneurysms over and above that seen in the general population, which is less than 1% per year. Moreover, the predictors for the presence of aneurysms in multivariate analysis in patients with FMD enrolled in the European and International FMD registry (FEIRI) were of the multi-focal phenotype (OR 1.91 (1.26–2.98), $p = 0.003$) and multi-vessel involvement (OR 3.99 (2.89–5.57), $p < 0.001$).[2]

Despite the lack of widespread longitudinal data, FMD is considered a benign vasculopathy with no or rare extension of FMD lesions on serial follow-up imaging studies.[3,15] In a longitudinal follow-up study with a mean follow-up duration of 35 months (range of 5–153 months), none of 146 patients with multi-focal FMD had developed new lesions on serial cervical imaging in previously unaffected arteries with no evidence of progression of the affected vascular segments.[14] In the above-mentioned study, no aneurysms were detected during the follow-up duration, while CeAD was documented in three subjects who had established multi-focal FMD in the parent vessel segment at baseline.[15] Nevertheless, the current international consensus statement advises performing at least one assessment for intracranial aneurysms with either CT angiography or MR angiography, with the timing of follow-up imaging to be customized according to the individual patient's pattern and severity of the underlying disease.[1]

Clinical Presentation

Although C-FMD has the propensity to remain clinically asymptomatic and incidentally diagnosed when subjected to imaging studies performed for other indications, there is ample information regarding the clinical manifestations that are considered cardinal and the possible symptoms/signs of C-FMD. One of the most common as well as cardinal symptom of C-FMD is chronic headache (especially of migrainous type which is new in onset in the fifth or sixth decade of life) seen in up to 70% of C-FMD cohorts.[1,3–5] The possible pathophysiological mechanisms of headaches in C-FMD include alteration in the cerebral blood flow contributing to hyper or hypoperfusion, altered pain sensitivity, autonomic dysregulation as well as structural damage secondary to cervical artery dissection and microtrauma.[1,3,5] In addition, headaches were more likely to occur in those FMD subjects with a history of cervical or intracranial arterial dissection or intracranial aneurysms.[3] The second cardinal symptom of C-FMD is pulsatile tinnitus, which is defined as a swooshing or whooshing sound which is synchronous with the heartbeat, reported by 16.9% in FEIRI registry[2] as against 37.2% of the study subjects in the US FMD registry.[7] C-FMD sufferers with pulsatile tinnitus were likelier to be women (OR 3.00, $p = 0.002$), younger in age at the time of FMD diagnosis (OR 1.12 for every 10 year reduction in age, $p = 0.011$), have associated headaches (OR 1.82, $p < 0.001$), neck pain (OR 1.64, $p < 0.001$), dizziness (OR 2.01, $p < 0.001$), with cervical bruit noted on physical examination (OR 2.73, $p < 0.001$).[7] Pulsatile tinnitus was more commonly associated with pathological involvement of the extracranial carotid artery affected by dissection, stenosis, extreme tortuosity as well as carotid webs, in turn contributing to vascular turbulence generating the swooshing or whooshing sound, even though the exact pathophysiological mechanism is unclear.[7] The clinical correlate of vascular turbulence is a demonstration of cervical bruit on neck auscultation, which constitutes the most common and cardinal physical sign in C-FMD. The latter is best heard by auscultation with the bell of the diaphragm at the level of angle of the mandible and can be seen in up to 40% of C-FMD subjects.[4,5]

The remaining spectrum of cardinal manifestations of C-FMD includes the more ominous cerebrovascular presentation which includes transient ischemic attack (TIA) (8–53%), ischemic stroke (8–35%), cervical artery dissection involving carotids more often than vertebral arteries (6–27%), subarachnoid hemorrhage (SAH) or unruptured intracranial aneurysms (3–49%) as well as intracerebral hemorrhage (ICH) (6–13%).[2–6] The mechanism of TIA and Ischemic stroke in C-FMD appears to be diverse, which could be secondary to cerebral hypoperfusion or artery to artery embolism as a consequence of cervical artery dissection or vascular stenosis, embolism from an area of vascular dilatation or extreme tortuosity or due to the microangiopathy affecting the perforator vessels secondary to long standing hypertension.[1,2,5] ICH, which is the less common component in the cerebrovascular spectrum of C-FMD, results from hypertensive cerebrovascular small vessel disease, intracranial extension of cervical artery dissection or rupture of intracranial aneurysms.[3] On the other hand, SAH primarily occurs due to rupture of intracranial aneurysms and rarely

due to intracranial extension of the cervical vertebral artery dissection.[3] Cervical artery dissection results in unilateral head and neck pain (carotidynia) which may be associated with evidence of ipsilateral Horner's syndrome (partial ptosis, miosis, anhydrosis and loss of ciliospinal reflex) due to the disruption of the sympathetic plexus located on the carotid vascular sheath secondary to the aftereffect of dissection.[16] Other less common and non-cardinal symptoms of C-FMD include non-migraine headaches (such as tension-type), non-pulsatile tinnitus, and dizziness/lightheadedness. Table 2 depicts a summary of the clinical manifestations of FMD.

Arterial webs or diaphragms are believed to share histological characteristics with FMD, characterized by non-inflammatory, non-atheromatous intimal fibroplasia, which has led several investigators to label them as "atypical FMD"[3,5,17] especially in the black African and Afro-Caribbean female population, even though the exact etio-pathogenesis of the latter remains to be poorly understood. The arterial web is defined as a thin endoluminal diaphragm located predominantly in the extracranial carotid artery[14] (typically in the posterolateral wall of the carotid bulb) or vertebral artery (V3 segment or ostium), frequently identified as a linear defect on the angiogram that does not change with modification of the patient's position. They are postulated to be the etiology of ipsilateral ischemic stroke and TIA in otherwise cryptogenic strokes as demonstrated in a population-based case-control study,[17] with the potential mechanism being embolism generated from vascular stasis at or distal to the aneurysmal bulb or due to focal dissection.[3,5] However, another notable feature of the carotid web is that they lack the typical lesion morphology of focal or multi-focal FMD and do not harbor aneurysms, dissection or classic atherosclerotic vascular lesions or risk factors.

Imaging

Currently available evidence does not recommend one imaging modality over any other in diagnostic evaluation of C-FMD, even though digital subtraction catheter-based angiography (DSA) is widely considered as the gold standard imaging tool.[1,3,5] On account of theoretically increased risk of iatrogenic dissection in FMD subjects, the utility of DSA is now increasingly limited to a subset of patients with severe as well as complicated vascular findings warranting endovascular interventions such as the repair of aneurysms or pseudoaneurysms secondary to dissection or in those with symptomatic stenotic vascular lesions who failed guideline directed best medical management.[1,3,5] Hence, the most common imaging investigation utilized worldwide for the initial diagnostic evaluation of C-FMD is either CT angiogram or contrast enhanced MR angiogram of the cerebrovascular circulation.[1,3,5] C-FMD tends to involve cervical portion of the carotid (middle or distal portion of internal carotid arteries) and vertebral arteries (V3, V4 segments), with intracranial involvement resulting either from extension of the cervical pathology or in certain subsets such as children.[5] Unruptured intracranial aneurysm is the primary manifestation of intracranial FMD, and the current consensus statement recommends at least one time assessment for the presence of intracranial aneurysm with CT angiogram or MR angiogram of cerebral vessels irrespective of the initial site of vessel involvement in FMD.[1] In specialized high volume

Table 2 Differential Distribution of Clinical Symptomatology of FMD Cohorts

Clinical Symptom	Prevalence
Headache (Migrainous and Nonmigrainous)	8.4–70%
Pulsatile tinnitus	16.9–37.2%
Cervical bruit on exam	Up to 40%
Transient Ischemic Attack	8–53%
Ischemic stroke	8–35%
Carotid and Vertebral arterial Dissection	6–27%
Sub arachnoid hemorrhage	3–49%
Intracerebral hemorrhage	6–13%

centers, carotid duplex ultrasonography is also employed as the initial imaging investigation, even though there are no validated diagnostic criteria for the same.[1] The duplex findings that support the diagnosis of C-FMD include elevated velocities, turbulence and tortuosity involving the mid-distal segments of cervical ICA which are typically spared in atherosclerosis. Carotid duplex study may also be utilized for surveillance and follow-up monitoring in patients with cervical artery dissection or stenosis, with a potential limitation of the latter imaging tool being lack of appropriate window in a subset of individuals (Figures 1–4). Another potential utility of ultra-high-frequency ultrasound (UHF-US) is in the detection of subclinical vascular imaging abnormalities in FMD, such as the "triple signal" pattern in common carotid artery.[3] Carotid duplex studies of normal common carotid artery reveal either one or two echogenic interfaces, whereas in those FMD subjects with subclinical carotid involvement there might be an additional echogenic interface contributing to the classic "triple signal" pattern. The latter sign is considered to represent increased vessel wall stiffness of the common carotid artery, although it is not specific to FMD. The multicenter FUCHSIA trial [very high frequency ultrasonography for arterial phenotyping in patients with cervico-cerebral artery dissection (CCeAD), hypertension, spontaneous coronary artery dissection (SCAD) and fibromuscular dysplasia (FMD)] launched in 2017 also provided insights into the presence of thickening and disarray of carotid and radial blood vessel walls in the FMD cohort as compared to healthy controls.[18]

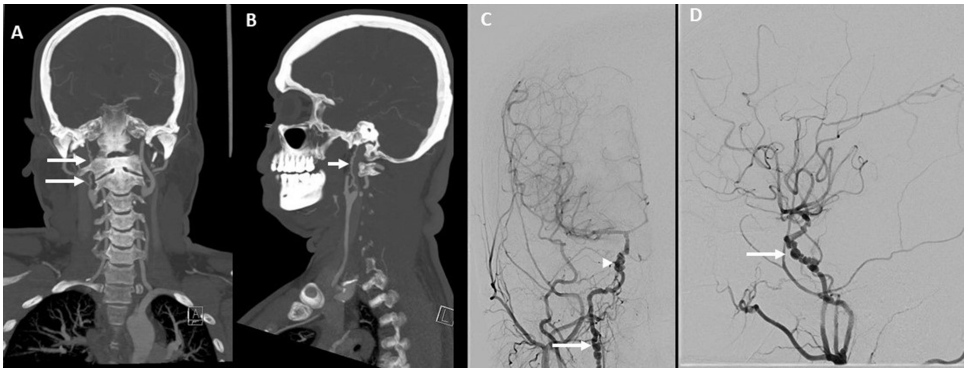

Figure 1 Vascular imaging in a young male patient with a history of right sided amaurosis fugax and right frontal ischemic stroke. Coronal (**A**) and sagittal (**B**) views of CT angiogram demonstrate moderate to severe stenosis of the entire right internal carotid artery cervical segment soon after its origin with significant irregularity and beading (white arrows). Anteroposterior (**C**) and lateral-oblique (**D**) views on digital subtraction angiogram of right internal carotid artery showed alternate stenosis and dilatation of the extracranial segment (white arrow (**C**)) and intracranial cavernous-supraclinoid segments (arrowhead (**C**); white arrow (**D**)), suggestive of "beading" typical of FMD.

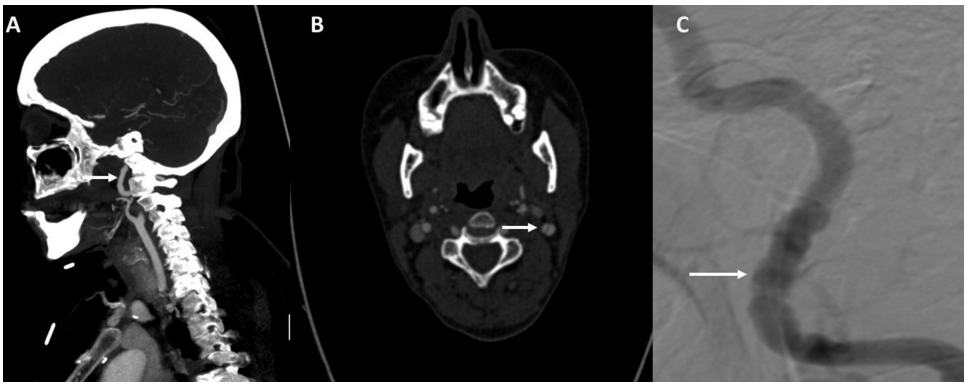

Figure 2 Vascular imaging in a young female patient presenting with acute aphasia and right hemiparesis. Sagittal view (**A**) on CT angiogram demonstrates mild irregularity with beading in the distal cervical segment of the left internal carotid artery (white arrow) and a dissection in the proximal internal carotid artery soon after the bifurcation seen on axial views (**B**), white arrow)). Magnified lateral view (**C**) on digital subtraction angiogram of right internal carotid artery confirms mild "beading" in the distal cervical segment of the carotid.

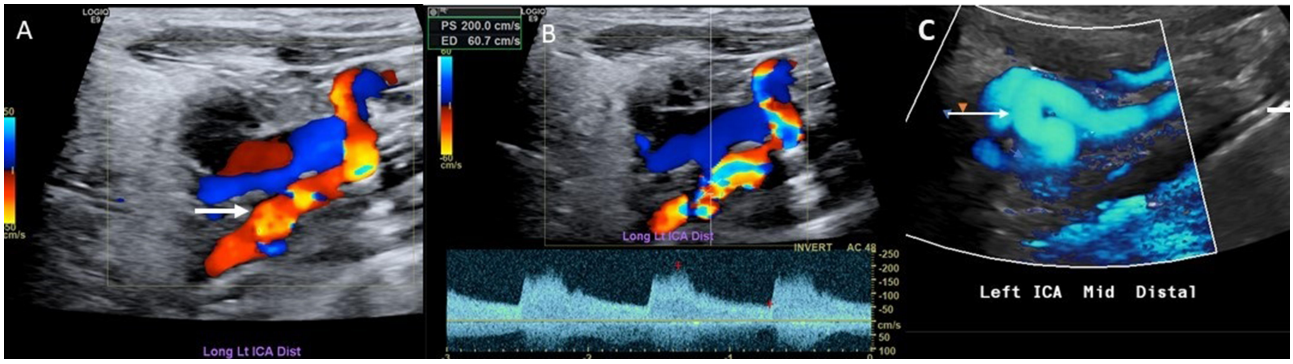

Figure 3 Colour Doppler imaging (**A**) of the distal internal carotid artery exhibiting the typical pattern of tortuosity and marked turbulence. Colour Doppler imaging (**B**) showing turbulence and spectral analysis demonstrating high peak velocity (200 cm/s). Colour power angiography (**C**) demonstrates severe tortuosity of the distal carotid artery with redundancy.

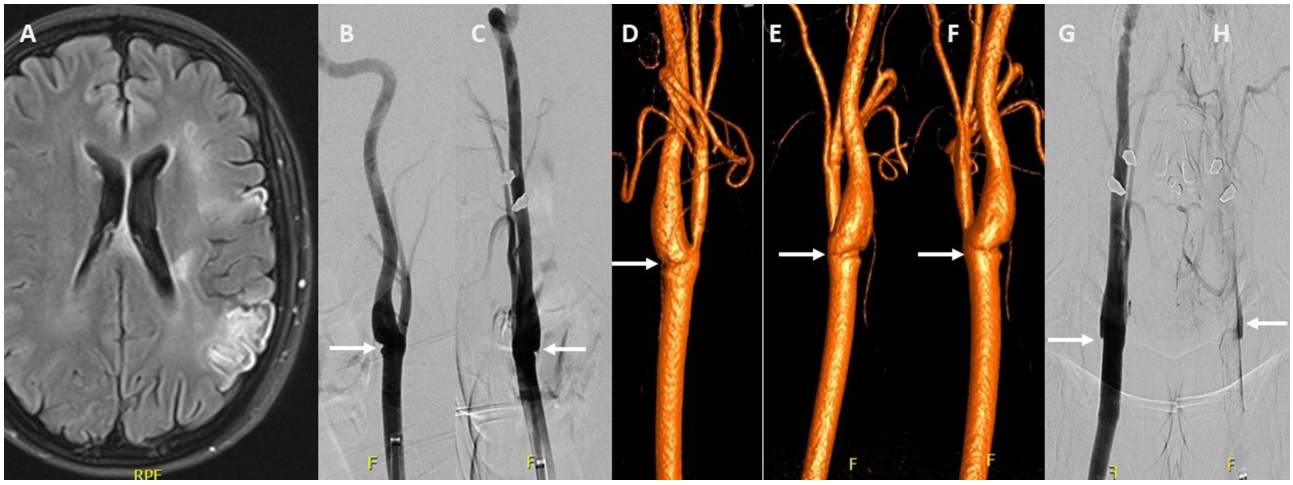

Figure 4 Imaging in a young female with recurrent, left hemispheric strokes despite medical management including antiplatelet therapy. Axial FLAIR MRI brain image (**A**) shows multiple areas of cortical and subcortical hyperintensity in the left anterior hemisphere. Anteroposterior (**B**) and lateral (**C**) views on digital subtraction angiogram of the left carotid bifurcation show a shelf-like ledge along the posterior wall of the proximal internal carotid artery, with minimal intraluminal projection (arrows) without causing significant stenosis. 3-Dimensional rotational angiogram reconstructions (**D**–**F**) shows the carotid web circumferentially involving the posterior wall. The patient was treated with carotid artery stenting (**G**, arrow) and delayed angiogram (**H**, arrow) shows stasis adjacent to the stent, suggesting the nidus of thrombus formation leading to recurrent stroke in medically managed patients.

Histology

The classic histopathological findings in FMD include cellular proliferation contributing to arterial fibrosis and architectural distortion of medium- and small-sized arteries.[1,3] The histological subtypes of FMD depend on the site of pathological changes in the vessel wall, such as medial (the most common subtype), followed by intimal and adventitial (periarterial) fibroplasia.[5–8] Multi-focal FMD, which is the most common subtype, has medial fibroplasia on histopathological evaluation, characterized by functional transformation in smooth muscle cells of the arterial media, eventually associated with plurifocal medial fibroplasia, attenuation of elastic fibers, and abnormal collagen synthesis. They, in turn, contribute to interruption of smooth muscle cells with discontinuous fibro-collagenous tissue, resulting in the vascular phenotypes of FMD.[5,19] Focal FMD subtype has intimal fibroplasia as the most common histopathological correlate.[5] Another interesting caveat is the genotype–phenotype association seen with anatomical location in the cerebrovascular vasculature as evidenced by the fact that FMD of extracranial vessels typically involve the media as against the predominant involvement of intima in the intracranial vessels.[5] Historically, FMD classification systems utilized the histological subtypes which have now become obsolete on account of lack of pathological specimens available for

diagnosis and increasing utilization of imaging studies for making the diagnosis of FMD leading on to utilization of international consensus statement,[1] European[11] and the American Heart Association recommendations.[12]

Etiology

The exact cause of FMD remains unknown despite several postulated genetic, mechanical, and hormonal causes. It is possible that a mix of genetic, hormonal, and environmental factors contribute to the development of FMD.[20]

Genetic Factors

Genetic components of FMD include sporadic and familial forms. However, symptoms in family members are only occasionally recorded (<5%).[3,20,21] It is difficult to identify which individuals have inherited FMD from family members and which ones suffered from a sporadic genetic mutation. This is due to the prevalence of FMD occurring in asymptomatic patients (3–6%) and the influence of the environmental factors. Nevertheless, genetic studies have suggested an autosomal dominant inheritance pattern with partial penetrance.[3,22,23]

Evidence supports the existence of numerous genetic variables that are associated with FMD. Genome-wide association analysis has allowed researchers to isolate rs9349379-A, a single nucleotide polymorphism (SNP) in the phosphatase actin regulator 1 (PHACTR1) gene on chromosome 6, as a common risk factor. SNP regulates the expression of PHACTR1 and endothelin-1 (EDI1). EDI1 plays a marked role in arterial tone, leading us to believe that its malfunction may be involved in the development of FMD. The PHACTR1 locus has also been proven to be an important gene in cardiovascular diseases such as coronary artery disease, migraine, spontaneous coronary artery, carotid dissection, and vascular hypertrophy. According to the genetic testing registry of NIH, this gene produces a protein that binds to actin and regulates the reorganization of the actin cytoskeleton. They also play roles in tubule formation and endothelial cell survival.[7,24] Single nucleotide polymorphisms (SNP) increase the risk of FMD almost 1.4 times.[23] An incidental finding in a recent investigation of the genetic risk score of spontaneous coronary artery dissection (SCAD) was an elevated risk of occurrence in patients already affected by FMD. The most common vascular disorder that co-occurs with spontaneous coronary artery disease (SCAD) is FMD because of its shared chromosomal variants in the PHACTR1 gene.[25,26] This further strengthens the theory of a strong genetic component in FMD and other vascular diseases.

As previously mentioned, FMD is a polygenic disease, and several rare exonic coding genetic variations have been linked to FMD.[27] One of which is in the collagen type V alpha 1 chain COL5A1 gene, c.1540G > A p. (Gly514Ser). This resulted in the substitution of glycine with serine at position 514 of the protein. This produces a phenotype present in adult multi-focal FMD and other vascular disorders, such as aneurysms and dissections involving the external iliac and celiac arteries and carotid artery tortuosity.[28]

Ultimately, the genetic components of FMD remain a vast and relatively unexplored topic. Comprehensive genome-wide analyses of genetic variations are needed to identify both rare and common genetic variations and mutations that contribute to the sporadic and familial causes of FMD. These investigations are currently being conducted to fill the unanswered gaps in the genetic etiology of FMD.[3]

Environmental Factors

It has been proposed that tobacco use may be a pathogenic factor contributing to FMD. Case-control studies have shown a connection between renal FMD and both current and past smoking habits. Current smokers attained an earlier diagnosis of FMD and hypertension than non-smoking patients.[29,30] According to the US registry for FMD, patients who had smoked before had a much greater rate of aneurysms than those who had never smoked, and there was a tendency for smokers to have more catastrophic vascular events.[31] These findings do not, however, support the notion that smoking is a necessary condition for FMD development but only one of the possible risk factors. FMD is also thought to be linked to endogenous or exogenous female hormone exposure; however, the precise nature of this association is not yet known. Although the disease affects women more frequently than men, there have been very few studies[32] that have established a definitive link between the two. According to a report from the US Registry for FMD, there are significant sex-related disparities in the clinical symptoms. For example, cerebrovascular symptoms are more prevalent in FMD-affected

women, whereas arterial dissection, aneurysm, and renal artery symptom rates are greater in men with FMD.[3,31] There are theories proposing that progesterone may play a role in the etiopathogenesis of FMD due to an imbalance between the oestrogen and progesterone receptors in arteries affected by FMD. This is supported by a case-control histology study in which the histological samples of patients with renal artery FMD were characterized by increased progesterone receptor expression in the nuclei of smooth muscle cells, which was absent in the samples of the control patients.[1,33] Mechanical stress to the renal arterial walls and excess mobility of the kidneys are also thought to be etiological factors of FMD. Although studies have shown a weak relationship between the two, the results have not been statistically significant enough to draw definitive conclusions.[29]

Few studies have suggested that FMD is a systemic disease, and unaffected arterial segments can exhibit subclinical changes. These include a triple signal pattern in the common carotid arteries, the presence of a brachial artery with a smaller diameter, and impaired smooth muscle cell activity.[20,34,35] A muscular to elastic gradient suggests that subclinical anomalies are more noticeable in muscular medium-sized arteries often unaffected by atherosclerosis but specifically affected by FMD.[35]

Treatment

Due to the lack of randomized controlled data, the management of cerebrovascular manifestations of FMD is largely guided by observational data from case series and expert opinions. As mentioned previously, the first international consensus statement on the diagnosis and management of FMD, published in 2019, is an important step towards providing a uniform framework for the diagnosis, evaluation, and management of FMD.[1]

Because of the high rate of involvement of other arterial beds, patients with FMD, regardless of the initial site of involvement, should undergo imaging of all vessels from the brain to the pelvis at least once to identify other areas of FMD as well as to screen for occult aneurysms and dissections. This can be achieved by using CTA or contrast enhanced MRA.[1] Other general considerations include the involvement of a multidisciplinary team, especially in cases of multi-vascular territory involvement and follow-up at least annually.

In cerebrovascular diseases related to FMD without stroke, it is reasonable to start antiplatelet therapy in the absence of contraindications to prevent thrombotic and thromboembolic complications.[1,7,36,37] This included patients with FMD without cervical artery dissection or intracranial aneurysm, since pathophysiological studies suggest that areas of vessel dilatation and intra-arterial webs may serve as a nidus for thrombus formation.[38] However, there have been no randomized placebo-controlled trials on the use of antiplatelet agents for FMD. Similarly, there have been no trials to support one agent over another, combination treatment, or dosing studies. Therefore, careful assessment of individual patient characteristics should be performed in each case to balance the benefits of thromboembolic prevention and bleeding complications. Aspirin was the most commonly used agent in the US registry,[36] and it was reasonable to start at a dose of 75–100 mg daily.[1] For patients with asymptomatic carotid FMD without cervical artery dissection, endovascular or surgical management is not advised regardless of the degree of stenosis.[39] Hypertension is common in patients with FMD, either essential or secondary to renal artery involvement, and needs to be controlled in the long term. Current guidelines for the management of hypertension may be used,[40,41] since data regarding the ideal blood pressure target or choice of agents are lacking in FMD. However, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) have been recommended for renovascular hypertension,[41,42] and beta blockers may have a protective effect in patients with spontaneous coronary artery dissection.[43] Short-term blood pressure control and targets need to be individualized, especially in the setting of symptomatic cerebrovascular FMD, such as hypoperfusion related to stenosis from cervical artery dissection or a ruptured intracranial aneurysm. The use of statins is not routinely indicated in patients with FMD,[1] unless it is used for other indications, such as concurrent hyperlipidemia or atherosclerosis. Smoking cessation is strongly recommended for all FMD patients who continue smoking.

There are no dedicated trials on the management of cervical artery dissection in patients with FMD and, therefore, the treatment is essentially the same as that in patients without FMD who develop cervical artery dissection. This includes acute treatments, such as intravenous thrombolysis and endovascular mechanical thrombectomy with or without carotid artery stenting in cases of large-vessel occlusion or critical carotid stenosis.[44] Secondary stroke prevention may include the use of single or combined antiplatelet agents or the short-term use of anticoagulants for 3–6 months.[45] In patients

with persistent cerebrovascular symptoms, despite medical management, endovascular options such as stenting may be used. This is particularly useful in patients with hypoperfusion-related symptoms of severe or critical stenosis, associated with flow limitation and insufficient collateral circulation.[46] Patients with cervical artery dissection and continued thromboembolic events without hypoperfusion-related symptoms responded well to optimized medical management, and the vast majority did not require any endovascular intervention. As summarized above, long-term management strategies include the indefinite use of antiplatelet agents in the absence of contraindications, hypertension management, and smoking cessation. Therefore, patients should be advised regarding physical limitations.[1] Activities such as chiropractic neck manipulations or roller coaster rides are best avoided given their known association with cervical artery dissection in the general population. Activities that induce milder degrees of cervical strain without rapid hyperextension of lateral rotation of the neck should be addressed individually.

Given the significant prevalence of unruptured intracranial aneurysms in the FMD population, these patients should be screened at least once for intracranial aneurysms using brain CTA or MRA regardless of the initial site of vascular involvement.[1] However, it is unknown whether vascular imaging should be repeated in patients who undergo negative initial screening for cerebral aneurysms, and management is controversial because it is unknown whether FMD poses an increased risk of rupture.[47] The rate of high-risk features of cerebral aneurysms detected in the US registry was 43%, with a size of 5 mm; 19% were located in the posterior circulation.[48] Currently, the management of unruptured cerebral aneurysms in FMD is based on common considerations as in the general population. This includes an assessment of high-risk clinical and aneurysm characteristics to decide whether to proceed with conservative management and careful observation versus intervention for aneurysm occlusion in those patients with FMD. The optimal frequency of follow-up imaging is unknown if a conservative approach is chosen.[1] Aneurysm occlusion can be achieved by using endovascular or open microsurgical options. The field of neurointerventional surgery has witnessed remarkable developments that have enabled safe and effective treatment of most aneurysms. However, each case should be discussed in a multidisciplinary cerebrovascular group to ensure that the most appropriate strategy is employed, specific to the patient and aneurysm profile. The management of hypertension is especially important in intracranial aneurysms and should be strictly controlled because hypertension is a well-established major risk factor for aneurysm development, growth, and rupture.[49] Similarly, patients should also be advised to quit smoking. Subarachnoid hemorrhage related to a ruptured intracranial aneurysm or intracerebral hemorrhage in patients with FMD is managed in the same manner as in those without FMD. Multiple studies have confirmed symptomatic carotid webs to be present in a higher proportion of women, a higher proportion of black patients, and a lower prevalence of traditional vascular risk factors.[50] Carotid webs usually produce luminal narrowing of <50% without hemodynamic flow limitation. Since the pathophysiology is more related to the development of thrombi due to alterations in laminar flow and the creation of stasis above and below the web, medical management with antiplatelet therapy for platelet overactivation or anticoagulant therapy to avert stasis clotting makes theoretical sense. However, available evidence suggests that medical management may be less advantageous for secondary stroke prevention. In a systematic review of 289 symptomatic carotid webs across 15 series,[51] stroke recurrence rate was 26.8% in the medical group during a follow-up period of 2–55 months. Therefore, interventional procedures to reduce thrombotic propensity through anatomic removal (endarterectomy) or reduction (stenting) of the web have been used. In the same systematic review, there was no recurrence of cerebral ischemic events during the follow-up period of 3–60 months. In addition, there were no cases of periprocedural mortality, and the major complication rate was 0.5%. This excellent safety record with carotid webs compared to similar interventional procedures for symptomatic atherosclerotic stenotic disease is likely related to younger patient age, absence of long and irregular atheromatous plaques, absence of unstable plaque with intraplaque hemorrhage, and the non-inflammatory nature of carotid webs. In addition, carotid stenting is technically less complex because pre- and post-stent angioplasty is rarely required.[52]

Symptomatic control of chronic headache and pulsatile tinnitus is also paramount since these are significant influencers of the quality of life in patients with FMD.[53] Chronic migraine is the most common phenotype of headache;[54] however, caution must be exercised since the migraine phenotype of headache may also occur in ischemic stroke and is often associated with cervical artery dissection. The diagnosis of FMD should be considered and imaging should be pursued in patients with cardinal symptoms or signs of cervical artery FMD. No specific data are available for

the management of migraine in patients with FMD,[53,54] and the general treatment principles for episodic and chronic migraines would similarly apply in these patients based on the headache burden.[53] Many prophylactic medications, including newer calcitonin gene-related peptide (CGRP) receptor antagonists and monoclonal antibodies against CGRP and its receptor, are available for prophylactic and abortive treatment of migraine.[54] CGRP is a potent vasodilator with important vasodilating effects that prevent organ ischemia under normal physiological states.[55] CGRP and its receptors are distributed not only in the central and peripheral nervous systems but also in the cardiovascular system, both in blood vessels and in the heart.[56] CGRP may act as a vasodilatory safeguard during cerebral and cardiac ischemia, and blockage of this system could potentially worsen ischemic events.[56,57] Currently, there is insufficient evidence that gepants and CGRP monoclonal antibodies are contraindicated in patients with cardiovascular diseases, including stroke or myocardial infarction.[58] Thus far, their use has not been clearly linked to an increased risk of stroke or MI, but erenumab may be associated with hypertension.[58] While we await long-term data, caution should be exercised, especially when prescribing these medications for small-vessel ischemic disease. The choice of medication should also be balanced with the knowledge that prophylaxis with non-specific oral medications is prone to adverse effects and leads to high rates of non-adherence, ranging from 17% to 20% adherence by 12 months.[59] Triptans are 5HT-1B/1D agonists that are used for abortive treatment of migraine, but their use is contraindicated in patients with vascular risk factors due to vasoconstrictive properties. However, studies have not fully supported this contraindication,[60] and literature is not clear on an absolute contraindication[61] for stroke, myocardial infarction, and uncontrolled hypertension.[58] All the above considerations of migraine management are not specific for patients with FMD, but careful patient selection and informed decision-making should be employed if using triptans or other vasoconstrictive agents in the setting of FMD, especially with a prior history of cervical artery dissection.

Prognosis

Patients with cerebrovascular FMD do not appear to have an increased risk of FMD progression or non-specific lesions. Kadian-Dodov et al[15] reported regarding 146 patients with multifocal FMD who underwent follow-up cervical imaging. Among these, none had developed FMD in a previously unaffected artery and none had FMD progression in previously involved arteries after a mean follow-up of 35 months (range, 5–153 months). No patient had a new aneurysm, and three (2%) patients had a new cervical artery dissection during follow-up (all 3 patients with new cervical artery dissection had already had multifocal FMD lesions on the same cervical artery at baseline). The risk of all strokes or TIA during follow up was less than 0.5% per year in two series of patients with cervical FMD.[62–64]Overall, in the absence of stroke complications, the prognosis of isolated cerebrovascular FMD appears relatively favorable, but data on the risk factors for the progression of FMD are lacking.[7,8]

Conclusion

Cerebrovascular involvement is common in FMD with rates ranging from 50% to 80% in prominent international FMD registries. While often asymptomatic, cerebrovascular FMD can present with numerous symptoms ranging from pulsatile tinnitus and chronic headache to more dangerous presentations such as cervical artery dissection and intracranial aneurysms causing ischemic stroke and subarachnoid hemorrhage, respectively. The publication of the first international consensus statement on the diagnosis and management of FMD in 2019 has aided in ensuring uniformity in the diagnosis, evaluation, and management of FMD. There has been significant improvement in our understanding of clinical and radiological manifestations from cohort studies. However, large areas of insufficient knowledge remain, including the natural history of cerebrovascular FMD, genetics and pathophysiology, risk factors for its progression, and optimal preventive as well as symptomatic treatment strategies. Prioritizing these research questions will help further improve our understanding of cerebrovascular FMD and enhance management of this complex vascular disease.

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