Fibromuscular Dysplasia of Cervical and Intracranial Arteries

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Summary

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Search Strategy

We searched PubMed using the term “fibromuscular dysplasia” in the MeSH database or with the terms “fibromuscular dysplasia”, “fibromuscular hyperplasia” in text word, between PubMed inception and XX, 2016. We also identified scientific papers by reviewing reference lists of relevant articles and through searches of the authors’ personal files. We considered articles published in any languages. Abstracts published only at meetings were excluded. We selected only original articles describing at least one aspect of clinical characteristics, radiological features, or outcomes of cervical or intracranial FMD. Isolated case reports could be included if they described interesting or rare manifestations. When studies included overlapping samples, only the largest and most recent were included unless other articles assessed new or different parameters.

Introduction

As an idiopathic, segmental, noninflammatory, nonatherosclerotic vascular disease of small- to medium-sized arteries, fibromuscular dysplasia (FMD) most commonly affects the renal and carotid arteries but has been described in almost every arterial bed in the body.[1, 2] The principal clinical manifestation of systemic FMD, secondary hypertension, results from involvement of the renal arteries and is sometimes treated with angioplasty or stenting.[2] Conversely, cervical and intracranial (Ce/IC) FMD seems often found incidentally with non-invasive vascular imaging. The broad availability and use of these modalities has led to increased recognition of Ce/IC FMD in recent years.[3] Although generally considered a benign entity when discovered incidentally, the diagnosis of Ce/IC FMD in association with devastating cerebrovascular disease, including ischaemic and haemorrhagic stroke, cervical artery dissection (CeAD), and intracranial aneurysms, or other neurological syndromes raises questions about the true risks of this condition.[3-5]

The origins and pathogenesis of FMD remain uncertain. Similar to other non-atherosclerotic, non-inflammatory cerebrovascular arteriopathies, FMD involves a functional transformation in smooth muscle cells of the arterial medial, ultimately associated with multifocal medial fibroplasia, attenuation of elastic fibres, and abnormal collagen synthesis.[6] One pathophysiological hypothesis involves endothelial dysfunction, which may explain arterial wall remodelling at particular sites induced by varying hemodynamic conditions. Although FMD classically affects specific vascular beds, evidence supports the conception of FMD as a systemic disease.[1]

Thus, we need additional epidemiological and pathophysiologic research. In the meantime, proper recognition and knowledge of Ce/IC FMD remains essential for neurologists and vascular specialists caring for patients with stroke and neurological disease. In this review, we provide a comprehensive overview of the epidemiology, clinical features, diagnosis, management, and prognosis of Ce/IC FMD, along with a proposal for future research priorities.

Epidemiology

Classification

Harrison and McCormack initially described a histological classification for FMD based on arterial wall involvement: medial, intimal and adventitial types, with medial forms accounting for up to 90% of cases.[1] The advent of percutaneous procedures dramatically decreased the proportion of FMD cases with tissue available for histological characterization. In 2012 and 2014, a European consensus statement reclassified FMD angiographically into multifocal ("string of beads"), unifocal (<1cm stenosis), and tubular (≥1 cm stenosis).[2, 7] In 2014, the American Heart Association (AHA) released a scientific statement on FMD and provided a similar classification scheme.[1] Under this classification, both multifocal and unifocal FMD can exist in different vascular territories of the same individual. Angiographic classification is now preferred over the traditional histological types to provide more standardization in defining FMD for future research (**Table 1**). Medial FMD typically correlates with the multifocal subtype whereas both intimal and adventitial types correlate with unifocal subtype.

While formal assessment demonstrates strong correlation between pathological and angiographic features in renal FMD, data on Ce/IC arteries is limited to isolated case reports or small series.[4] Moreover, despite these modern efforts, angiographic classification cannot be

easily applied for Ce/IC FMD for several reasons. First, atherosclerosis, arteritis, external compression, or carotid hypoplasia may mimic FMD and make establishment of the isolated focal pattern very difficult. Second, acute or chronic structural lesions secondary to dissection can make the diagnosis and classification of Ce/IC FMD very difficult. Third, unique forms of FMD exist that do not fit the classical criteria.[8, 9]

Prevalence

Though Connett and Lansche reported the first histologically proven case of FMD of the carotid artery in 1965,[10] the true prevalence of Ce/IC FMD and incidence of cerebrovascular diseases in association with Ce/IC FMD still remain unknown today. In historical series of consecutive angiograms performed in departments of radiology, the prevalence of carotid and vertebral FMD ranged from 0.3% to 3.2%.[4] However, selection bias for patient populations with clinical indication for cerebral angiography, such as stroke, likely confound these studies, and they likely do not accurately reflect the true prevalence of Ce/IC FMD in the general population. Only four of 20,244 autopsies performed at the Mayo Clinic over a period of 25 years, detected FMD of the internal carotid artery (ICA) (0.02%).[11] In contrast, other studies found renal FMD in about 4% of angiograms of potential renal donors.[12] In fact, autopsy may have a low sensitivity to detect minor forms of FMD.[1] Historically, most clinicians have considered renal FMD more common than Ce FMD, however, data from the United States (US) FMD Registry suggests a more equal prevalence, with renal arteries affected in 79.7% and extracranial carotid arteries affected in 74.3% of cases with imaging of those specific vascular beds.[3] Among patients with Ce FMD, 95% are carotid (most often bilaterally) and 60-85% are vertebral (usually coexisting with carotid FMD).[4]

Genetic associations

We still lack compelling and well-powered genetic studies in FMD. The incomplete characterization of FMD status of all family members within pedigrees and the high frequency of asymptomatic phenotype preclude accurate calculation of heritability estimates. The US FMD registry showed that 7% of cases report a first or second-degree family history of FMD.[3] A few case reports have described the co-occurrence of FMD in identical twins and other relatives.[13] An old family-based study found FMD in multiple family members from 12 of 20 families, suggesting that FMD may have an autosomal dominant genetic mode of inheritance with incomplete penetrance.[14] A retrospective analysis of 104 patients with renal FMD found familial FMD in 11% of cases using screening angiography.[15] A study of 6 large families found an asymptomatic, abnormal high-resolution echo-tracking phenotype in the carotid arteries of first-degree relatives of renal FMD patients in an autosomal dominant pattern, which supports a shared genetic determination of systemic FMD.[16]

Several candidate gene studies of FMD have been negative or demonstrated only in isolated case reports,[6] and genome-wide association studies are lacking **(Supplemental table 2)**. FMD shares some clinical features with Mendelian vascular connective tissue disorders, such as Marfan's, Ehlers-Danlos, and Loeys-Dietz syndromes.[17] However, systematic screening of a large panel of known genes mutated in these syndromes failed to yield associations with FMD.[17, 18] Whole exome sequencing analysis in 16 FMD patients from 7 families, found no gene variants shared among all affected sib-pairs of at least 3 families, their arbitrary threshold to declare a gene as a putative candidate for FMD.[19] They also excluded causative mutations from common

single-gene connective tissue diseases. Additional larger sequencing studies in families and a more sophisticated pathway-based filtration of genetic variation might yield further results.

Association with systemic arterial disease

Renal artery FMD was reported in 64.5% of patients with cervical FMD, and an almost identical prevalence of cervical FMD (64.8%) was found in patients with renal artery FMD.[3] However, well-designed studies of co-prevalence of Ce/IC and renal FMD are lacking.[4] The heterogenous populations, variable detection methods, and lack of clarity as to screening methods make these studies difficult to compare.

While FMD of the coronary arteries is rarely reported,[20] an association between FMD and spontaneous coronary artery dissection (SCAD) was recently identified.[21] SCAD typically presents as an acute coronary syndrome, including non-ST segment or ST-segment elevation myocardial infarction.[22] In SCAD patients, a high prevalence of extra-coronary FMD lesions is reported (range: 52 to 86%).[21-24] In one of the largest series, 52% of SCAD patients had cervical FMD and 14% had cerebral aneurysms.[22] In the US FMD Registry, only1.8% of patients had myocardial infarction as an initial clinical presentation leading to the diagnosis of FMD, and only 6.5% of patients had any known history of coronary artery disease.[3] These data do not rule out the existence of more frequent but silent coronary lesions in patients with extra-coronary FMD,[25] and may suggest screening for associated coronary artery disease in patients with Ce/IC FMD although we lack data on cost-effectiveness of doing so. There is no data on prevalence of FMD in other arterial beds (e.g. brachial, celiac, hepatic, iliac) in patients with Ce/IC FMD.

Segmental arterial mediolysis (SAM) is a rare non-inflammatory, non-atherosclerotic arteriopathy manifesting with multifocal medial degeneration, arterial dissections, and

aneurysmal formation.[26] Clinically, SAM typically presents in the 5th decade with abdominal pain, and devastating intra-abdominal haemorrhage or visceral organ infarctions secondary to involvement of the small and medium sized splanchnic arteries.[26] SAM may also involve the cervical and intracranial circulation presenting with cerebral ischemia or subarachnoid haemorrhage.[27, 28] Due to the multifocality and vasospastic appearance, SAM may be initially misdiagnosed as systemic vasculitis.[29] Despite a distinct natural history, SAM is radiologically and histopathologically indistinguishable from FMD with prominent medial degeneration and intimal proliferation. As opposed to more common occurrences of arterial dissection typified by intimal tearing, vessel wall dissection in SAM occurs between the media and adventitia due to degenerative "vacuolization" of the outer medial layer.[27] It has been proposed that SAM might be a precursor to FMD, precipitated by a mediolytic "injurious phase" and followed by a "reparative" phase with granulation tissue proliferation and intimal fibroplasia.[26]

Other associated clinical factors

As in the renal artery territory, women have much higher prevalence of Ce/IC FMD than men.[4] However, the role of hormonal factors in FMD remains uncertain. Case-control studies have found no association between FMD and gravidity or exogenous hormone exposure.[1, 30] To date, no studies have investigated endogenous hormone levels in association with Ce/IC FMD or related cerebrovascular disease.

Several case-control studies have shown an increase in the proportion of smokers (current or ever) among those with renal FMD compared to control populations.[31, 32] No similar data exist for Ce/IC FMD. In patients with multifocal renal FMD, smoking appears associated with a younger age at diagnosis of hypertension,[33] and possibly with a more severe phenotype.[30, 34]

Given these associations, hormonal factors like smoking may modify the effect of FMD on the arterial system similar to the associations with aneurysmal growth and rupture.[6, 35]

Variations in renal positioning and mobility contribute to the hypothesis that repeated stretching of the renal artery may cause microtraumas predisposing to FMD.[36] A similar hypothesis may apply to cervical FMD. Traction is maximum in the mid to distal cervical segment of the carotid and distal segments of the vertebral arteries. Extension and lateral rotation of the head and neck enhance stretching and shear forces of the cervical arteries, and may be a link to the association between FMD and CeAD.[37] However, these hypotheses remain speculative, and any mechanical component to the etiology of Ce/IC FMD still needs verification.

Clinical features

Signs and Symptoms

Frequently, perhaps most frequently, Ce/IC FMD is *asymptomatic* and diagnosed incidentally during angiography for other purposes.

An isolated *carotid bruit* may be the sole manifestation of cervical FMD. Twenty-two percent of cases of the U.S. FMD Registry presented with isolated bruit[3] but bruit seems less common in older studies where neurologists recruited Ce/IC FMD cases (**Supplemental table 1**).

Pulsatile tinnitus, described by patients as a "swishing" or a "swooshing" sound in the ear, is a very common presenting manifestation of extracranial cervical FMD, observed in up to 30% of cases.[3] Non-pulsatile tinnitus is more rarely observed.

Headaches may be the most common presenting symptom underlying Ce/IC FMD, reported In U.S. FMD Registry, 52% of all cases and 72% of cases with Ce/IC FMD.[3] About one half of these headaches were described as "migrainous" but without clear diagnostic criteria for migraine applied. Similarly, previous case series of Ce/IC FMD have reported recurrent headaches with migrainous features at a high rates, often leading to the FMD diagnosis.[38] Moreover, comparative data from the U.S. FMD Registry suggest that headache co-segregates with other neurovascular symptoms and cerebrovascular manifestations.[38] Although the prevalence of headaches and migraine seems very high in patients with Ce/IC FMD, the underlying pathophysiology remains elusive. Possible mechanisms include alterations in arterial flow (*e.g.* labile hypertension, hyper/hypoperfusion, turbulence), neurovascular dysregulation or dysautonomia, structural injury (*i.e.* dissection, microtrauma), or heightened pain sensitivity.[38] Provocatively, a Chinese study of temporal artery biopsies in patients with intractable migraine found that a large number exhibited changes consistent with FMD.[39] Thus, further study into the pathogenesis of FMD may further inform our understanding of migraine, and vice versa.

Ce/IC FMD may also be associated with nonspecific symptoms including *confusion*, *blurry vision*, and *dizziness*, the latter described mostly as *light-headedness* or *presyncope* as opposed to true vertigo (in the authors' experience). These nonspecific symptoms may represent manifestations of fluctuating blood pressure, persistent migraine aura, dysautonomia from neurovascular disruption in the vessel wall, or possibly elements of somatization.

Cerebrovascular diseases

The putative mechanism of ischemic cerebrovascular disease in patients with Ce/IC FMD could include artery-to-artery thromboembolism, dissection with resultant stenosis or occlusion,

or hemodynamic compromise. Prior case reports have suggested the possibility *in situ* thrombus formation in both extra- and intracranial FMD,[10, 40] particularly in patients with "web-like" internal carotid artery intimal FMD (discussed below).[8, 41] However, in most cases the potential for a causal role of Ce/IC FMD for downstream ischaemic events remains speculative. Multifocal areas of FMD may be mild and incidental to other intrinsic arterial disease. A sizable proportion of patients with Ce/IC FMD have concomitant vascular risk factors, including poorly-controlled hypertension from renal FMD or large artery atherosclerosis.[5]

When not discovered incidentally, Ce/IC FMD is often diagnosed in association with other non-atherosclerotic, cerebro-cervical vasculopathies, notably *cervical artery dissection* (CeAD) and *intracranial aneurysms* (IA).[42] Multiple cohorts demonstrate that individuals with CeAD may have a prevalence of FMD as high as 15 to 20%,[6, 43] and a stronger association between FMD and cases of multiple artery dissection suggests underlying systemic arteriopathy.[44] Concomitantly, the prevalence of carotid and vertebral artery dissection in the US FMD Registry was reported in 15% and 3% of cases, respectively.[3]

The high prevalence of *intracranial aneurysms* (IA) in patients with Ce/IC FMD noted in previous angiography-based case studies likely reflects an overestimation due to selection bias.[4] A meta-analysis of over 500 patients with cervical artery FMD from prior case series found an unruptured IA prevalence of 7.3±2.2%, higher than that expected in the general population.[45] By comparison, the International Study of Unruptured Aneurysms reported "fibromuscular disease" in only 1% of patients.[46] The most recent data from the US FMD Registry, Ce/IC IAs reported in roughly 7% of cases with FMD; although the study did not specify differentiation between intracranial saccular aneurysms and extracranial pseudoaneurysms (related to dissection).[3] Unfortunately, we lack well-designed epidemiological studies investigating any link between

intracranial aneurysm and FMD. A recent case-control study found a strong association between IA and cervical FMD.[47]

Apart from IA, *intracranial FMD* seems rare, but probably more frequent in children.[48-51] Most often, intracranial FMD corresponds to an intracranial extension of extracranial FMD.[4] However, a few cases report isolated intracranial FMD with a typical 'string of beads' appearance on angiography, with or without histological verification, involving the basilar artery,[52, 53] the distal carotid artery, and the middle cerebral artery.[40] Autopsy reports of fatal intracranial artery dissection, or subarachnoid haemorrhage due to middle cerebral artery or basilar artery rupture have occasionally shown histologically proven FMD.[4, 54] Some patients have multiple aneurysms distributed along a single arterial segment and extensive dilatation of the intracranial internal carotid artery with multiple tortuosities (**Figure 1**).[55, 56] This latter angiographic pattern does not correspond to any classical type of FMD mentioned above and intimal FMD was found in the only histologically proven case.[56] In some young patients, intracranial FMD has also been associated with moyamoya syndrome,[4, 57] and carotid-cavernous fistula.[58] In contrast to FMD of extracranial arteries that typically involves the media in most cases, intracranial FMD commonly demonstrates the intimal form. This pathological correlate further supports a possible genotype-phenotype variation by anatomical location in the cerebrovasculature.

Diagnosis

Cervical FMD affects the middle and distal portions of the internal carotid and vertebral arteries at the level of the C1 and C2 vertebrae, arterial areas typically spared by atherosclerosis. There is a lack of studies that assessed accuracy of the different tools used in practice.

Duplex ultrasound is an excellent non-invasive tool to detect and follow patients with FMD involving extracranial carotid and vertebral arteries (**Figure 2**). It is unusual to visualize the "string of beads" appearance on ultrasound, although Color Power Angio facilitates visualization of the beading when present.[59] The most common ultrasound findings are a combination of increased velocity of blood flow, tortuosity, and turbulence in the mid to distal vessel.[1] The severity of stenosis in multifocal FMD cannot be determined by ultrasound or any other cross-sectional imaging technique, as criteria used for atherosclerosis are not valid for FMD.[1] In focal stenosis, a discrete area of increased velocity and turbulence is visualized. Other findings such as irregular vascular wall thickening, extreme tortuosity, dissection, intramural hematoma, and aneurysm occur frequently in patients with Ce/IC FMD, but are not specific for the diagnosis.[42, 60] The string of beads corresponds to multifocal stenosis, which represents multiple areas of focal hyper-echoic thickening of the arterial wall alternating with thin dilated areas.[61] The S curve, corresponding to a redundancy of the mid-distal internal carotid artery in the shape of an "S", was recently found more frequent in Ce FMD patients than in controls.[60] However, it is important to recognize that the S curve is not specific for Ce/IC FMD, as other conditions may also be associated with extreme arterial tortuosity.

Cervical FMD should be easily differentiated from atherosclerosis on ultrasound, since atherosclerosis occurs in the proximal internal carotid artery and is often associated with plaque. Other arterities, such as Takayasu's and giant cell arteritis, are distinguished from FMD by long smooth areas of stenosis with circumferential hypoechoic wall thickening. Additionally, these entities most commonly occur in the common carotid arteries and other branches arising from the aortic arch, as opposed to FMD typically being absent from the common carotids.

Commentaire [ET1]: (JWO image? if ET agrees, to verify for copyrights because already published in Circulation 2014, a small part of the arrow for seagull is lacking)

Computerized tomography (CT)-angiography of the head and neck with a voxel spatial resolution of about 0.75 mm, is a very useful non-invasive tool to assess Ce/IC FMD (**Figure 3**).[62] The preferred technique includes contrast bolus injection with bolus-tracking acquisition that allows for detection of luminal defects and arterial wall dysplasia. Post-processing is a helpful tool in the diagnosis of Ce/IC FMD, including volume rendering, maximum intensity projection, and multi planar reconstruction. Although CT-angiography is very accurate for the diagnostic "string-of-beads " or "pearl necklace" appearance of Ce/IC FMD, it may be insufficient for mild, isolated or narrow forms.[2, 61, 62]

Magnetic resonance (MR)-angiography is a very promising exam to detect or confirm FMD (**Figure 3**).[2, 62] At 1.5 Tesla, the spatial resolution is close to 1 mm. Choice of acquisition techniques and protocols such as "time-of-flight", contrast enhanced time-of-flight, or 3D Contrast Enhanced Fast Spin Echo are left to the discretion of imaging centers as none of these sequences are clearly superior over the others for the diagnosis of Ce/IC FMD. However, dynamic contrast enhancement is recommended to reduce artifact due to turbulence and flow modification. Similar to CTA, post-processing of MR-angiography may also assist in the diagnosis.

With a spatial resolution of 0.2 mm, digital subtraction angiography remains the gold standard for diagnosis of Ce/IC FMD (**Figure 3**).[2, 61, 62] Compared to CT and MR-angiography, digital subtraction angiography is more sensitive for the detection of Ce/IC FMD, particularly for mild, isolated or narrow forms, and carotid diaphragms.[63] However, digital subtraction angiography does carry a risk of iatrogenic dissection, although it is unknown whether FMD increases that risk. Other figures are available in supplemental material.

Other manifestations

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Arterial diaphragms

Arterial diaphragm corresponds to a thin translucent endoluminal web (**Figure 4**) that does not change or disappear after modification of the patient's head position.[63] Since the first description in 1967,[64] more than 50 cases with ischemic stroke associated to arterial diaphragms have been reported and a recent population-based case-control study in French West Indies demonstrated a strong association between ischemic stroke and carotid bulb diaphragm.[65] In almost all cases treated by surgery, intimal fibrosis or hyperplasia without atheromatous or inflammatory lesions was found on histology.[4, 8, 41] Thus, this entity, also referred to as "arterial webs" in the literature,[66, 67] has been classified as "atypical FMD" by several authors, although whether this entity represents a FMD subtype or an distinct disease remains unknown.[8]

Compared to classical FMD, carotid artery diaphragms are located at the carotid bulb or the proximal ICA, and VA diaphragms are observed at the V3 segment or at the ostium.[8, 63] Carotid diaphragms are usually bilateral and not associated with typical FMD lesions elsewhere.[8] These lesions are typically found ispilateral to ischaemic stroke or TIA in young (~45 years) patients. Strikingly almost all described cases occurred in patients of African- or Afro-Caribbean origin. The sex-distribution is slightly skewed towards women (60%). A mega-bulb may be observed in some patients.[41] The diagnosis of diaphragm is challenging. Duplex ultrasounds are not sensitive enough in the absence of significant stenosis,[68] and MR-angiography resolution may be insufficient.[9] First cases were diagnosed on conventional angiography, but the generalized used of new generation CTA seems to have increased detection of arterial diaphragms. The septum can be evident on axial sections.[8, 67]

Potential mechanisms leading to ischaemic stroke include thrombus formation at the site

of the diaphragm, especially because of stasis upstream to the web, and focal dissection.[41, 67] In small series of patients with carotid bulb diaphragm, the rate of recurrent ischaemic events seems particularly high without treatment or on antiplatelet therapy alone,[8, 67] up to 20% at 1 year in the largest study.[8] Therapeutic options have included surgery,[8, 41, 67] anticoagulants,[41] and stenting.[63, 69] No recurrence was reported after surgery (follow-up of 22 months in the largest study) or stenting (follow-up ranging from 3 months to 12 years).

Ce/IC FMD in Children

Both stroke and FMD in children are different than in adults. Arteriopathies cause a majority of both occurrence and recurrence of childhood arterial ischemic stroke, but the mechanisms remain poorly understood.[70, 71] The development of better systems to classify and diagnose childhood cerebral arteriopathies,[72] will provide more than anecdotal case reports to include FMD in the classification.

A recent study combined a large series of new cases with the existing literature of children with stroke and possible FMD.[51] Analysis of 81 cases facilitated comparisons of pathologically-proven versus clinically-suspected pediatric FMD. In pathologically proven FMD, intimal fibroplasia predominated (89%) and none had the more typical medial fibroplasia seen in adults. Ischemic strokes (63%) were most common than hemorrhagic strokes and were often multifocal (40%). Many children presented early including 33% who presented in the first year of life. Angiography demonstrated focal, stenotic arteriopathy in most children (78%) rather than the typical "string–of-beads" seen in adults. Systemic arteriopathy occurred frequently with 63% having renal arteriopathy and 72% having involvement in all of the major arterial beds. Thirty-five percent had a diagnosis of moyamoya. Only 25% of these children received anti-

inflammatory and/or antithrombotic therapies. Outcomes at a mean of 43 months were poor in 63% with high stroke recurrence rates (36%). In contrast, those with only clinically-suspected FMD based on arterial imaging were older, normotensive, had string-of-beads angiography and good outcome, suggesting a different disease.

Several differential diagnoses need to be known in children. The most common variety of childhood cerebral arteriopathy, often referred to as focal cerebral arteriopathy (FCA),[71] presents an acute, monophasic disease of the distal internal and proximal middle cerebral arteries in healthy school-aged children. FCA features distinctive angiography with alternating areas of stricture and dilatation, "banding", or a "string-of-beads" appearance, drawing comparisons to FMD. However, FCA lacks other features of FMD such as renal or systemic arteriopathy, and evidence suggests FCA mechanisms may include inflammatory vasculitis or intracranial dissection.[73, 74] Many case reports of childhood stroke labelled as "FMD" based on intracranial angiography may therefore represent FCA. Quantified arterial tortuosity in a large case-control study of children with ischemic stroke found that abnormal tortuosity not only associated with arterial dissection (as hypothesized) but also with FCA, supporting a role of abnormal inherent vascular biology in childhood ischemic stroke.[75]

Similar consideration should be given for moyamoya disease, another etiology of childhood stroke that shares commonalities with FMD including co-occurrence of hypertension, possible renal and systemic arteriopathy, and intimal fibroplasia pathology.[76] However, moyamoya syndrome is associated with many genetic conditions (*e.g.* trisomy 21, neurofibromatosis-1) and a large proportion of familial cases are now attributable to specific gene mutations, RNF-213 being most common.[77] These combine with a growing number of genetic arteriopathies that, like pediatric FMD described above, include infantile presentations of

stroke combined with systemic arteriopathy such as ACTA-2 mutations.[78] That FMD associated with childhood stroke so often presents early in life with multisystem disease strongly suggests one or more genetic explanations.

The definitive diagnosis of FMD in a child with stroke required to advance classification and management strategies currently rests on vascular pathology. Evidence-based pathological FMD classification is well established and the systems developed by Harrison and McCormick and Stanley appear valid and applicable to childhood stroke.[4] The applicability of biopsies obtained from other sites (e.g. nephrectomy) or accessible arteries (e.g. superficial temporal artery) to intracranial disease is unclear. Thus, imaging biomarkers specific to Ce/IC FMD arteriopathy in children are highly desirable and correlations have been drawn between angiographic features and pathological classifications in adults.

Management

In the absence of randomized trial in Ce/IC FMD, current medical and interventional strategies rely on observational data.

Medical

As opposed to renal artery FMD where much of the treatment revolves around managing hypertension, the indications to treat Ce/IC FMD are much less clear. In the absence of other cerebrovascular complications, isolated Ce/IC FMD has a fairly benign natural history. However, observational data and general consensus suggest placing patients on an antiplatelet medication for prophylaxis against ischemic stroke.[1] Daily aspirin is a reasonable choice with little evidence to suggest alternative antiplatelet agents, combination therapy offer any additional benefit for primary or secondary stroke prevention.[79, 80]

In the Cervical Artery Dissection in Stroke Study (CADISS), among 250 patients with CeAD randomized between antiplatelet and anticoagulation therapy within 7 days of symptom onset, there was no difference in the rate of stroke between groups, supporting preventive medical management in favor of antiplatelet therapy.[81] The trial confirmed an overall favorable prognosis in CeAD, particularly in patients presenting with only local signs or symptoms and after the initial 10 days from randomization when no further stroke events occurred. However, some equipoise remains about optimal medical management in hyperacute CeAD presentations (< 7 days) when the risk of stroke is ostensibly highest.[82]

As in other cerebrovascular disease, a multidisciplinary approach strengthens management decisions in Ce/IC FMD. Consultation with a vascular neurologist helps to verify the etiology and localization of symptoms referable to the affected arterial territory.[2]

Migraine is a common and potentially disabling association in patients with Ce/IC FMD. Similar to other medical management in Ce/IC FMD, limited published literature exists to help guide pharmacotherapy in this population. Extrapolating from migraine treatment guidelines, preventive options could include beta blockers, topiramate, and tricyclic antidepressants (e.g. amitriptyline).[83] Valproate is also supported with good evidence as a migraine preventive, but is contraindicated in women of child-bearing age. Supplemental options for migraine prevention include magnesium oxide, riboflavin, and herbals such as butterbur. For those with chronic migraine (> 14 headache days per month), Botulinum toxin injection is indicated,[84] although no studies have specifically addressed this in FMD patients.

For abortive migraine treatment in patients with Ce/IC FMD caution must given to the use of sympathomimetic drugs, such as triptans and ergots, particularly in patients with comorbid cardiovascular disease, dissection, or aneurysms. However, with limited published literature to

address this challenge, one can consider triptan therapy for episode migraine in patients with otherwise stable Ce/IC FMD.[38] Other abortive options include prochlorperazine or metoclompramide in combination with diphenhydramine, or non-steroidal anti-inflammatories if used sparingly in patients with co-prevalent renal disease.

Regarding non-pharmacologic treatment options, it is worth emphasizing that chiropractic spinal manipulation should be avoided in patients with Ce/IC FMD due to the theoretical increased risk of CeAD.[85]

Endovascular/Surgical

The multisocietal guideline on the management of patients with extracranial carotid and vertebral artery disease has stated that revascularization is *not recommended* for patients with asymptomatic FMD of a carotid artery, regardless of the severity of stenosis (class III, level C).[86] A variety of surgical procedures (resection-anastomosis, endarterectomy, graduated or balloon intraluminal dilatation) were used in the past to treat patients with cervical FMD, with apparent low rate of complications.[4] However, apart in patients with carotid diaphragm who may require endarterectomy,[8] these techniques seem no longer indicated. In some patients with stenosis related to FMD responsible for severe haemodynamic impairment, recurrent ischaemic event, or more commonly disabling tinnitus, endovascular treatment may be indicated. Percutaneous angioplasty with or without stenting has been proposed in case reports or small series, with good clinical results.[63, 87-89] The long-term results of endovascular treatment are, however, unknown.

In patients with cervical artery dissection, management is similar to that of patients without FMD.[90] Stenting may be considered for carotid or vertebral artery dissection but is usually reserved for situations where patients continue to have cerebrovascular ischemia despite good medical therapy.[91, 92] The technique for stenting is the same, though careful attention

should be made to avoid creating iatrogenic dissection during groin access, guide catheter placement or worsening of the dissection when crossing the lesion. Self-expanding stents are preferred, though if good flow through the stent is not attained, angioplasty may be required. Post-dissection pseudoaneurysms may be observed, although whether FMD increases the risk is unknown. Several studies have shown that these pseudoaneurysms do not carry a risk of ischaemic events in the long-term and therefore rarely require endovascular treatment.[93]

The management of IAs in FMD patients does not differ from that in patients without FMD, although one could feel there is a higher potential risk of rupture in this population.[94, 95] Most aneurysms are amenable to coil embolization, especially with newer devices that are available to assist in treatment of wide necked aneurysms.[96] Surgical clipping is also feasible in many cases, and the decision for best treatment modality will depend on patient and anatomical factors.[97]

Similarly, there are no specific indications for endovascular procedures in case of intracranial dissection,[98] or for direct or indirect cerebral bypass in case of occlusive arterial disease, such as moyamoya syndrome,[99] although these conditions are very rare in FMD and treatment still controversial.

Prognosis

No population-based data have established the incidence of stroke or transient ischemic attack (TIA) in patients with Ce/IC FMD, although the natural history in the absence of associated vasculopathy appears to be relatively favourable. While a history of stroke or TIA was reported in 19% of patients in the US FMD Registry, this is likely an overestimate of the natural history given the enriched selection of patients referred to the registry sites as well as an over-

representation of ischemic cerebrovascular disease among those undergoing vascular imaging.[3] Among an older cohort of 79 patients with cervical FMD identified by cerebral angiography and followed for an average of 5 years, 3 patients suffered subsequent stroke or TIA not specifically localized to the affected artery or arteries.[100] In a more recent study of 36 patients with carotid and/or vertebral FMD followed for a median of 3.5 years, three patients suffered stroke during follow-up.[5]

Conclusion and future directions

Although Ce/IC FMD has been known for many years, much remains to be done to improve knowledge of the disease. The top research priorities in FMD have been listed in a recent statement from the American Heart Association.[1] We may summarize the priorities specific to Ce/IC FMD as follows:

- Determination of the co-prevalence of Ce/IC and renal FMD ;
- Evaluation of the natural history of Ce/IC FMD, especially the risk of and risk factors for (1) incident and recurrent extra- and intra-cranial dissection ; (2) stroke and TIA ;
- Evaluation of the prevalence and incidence of *de novo* IA and whether FMD is associated with a higher risk of growth and rupture ;
- Determination of the optimal therapy for primary and secondary prevention of cerebrovascular complications in FMD ;
- Characterization and understanding the mechanisms of migraine and/or headaches ;
- Characterization of less specific systemic neurological symptomatology.

The Assessment of Renal and Cervical Artery Dysplasia (ARCADIA, NCT02884141) and PROgression of FIbromuscular LEsions (PROFILE, NCT) French research programme is

currently addressing the co-prevalence of Ce/IC and renal FMD and the risk of clinical or radiological progression in a population of about 500 Ce/IC and/or renal FMD patients. Baseline analyses will be available in 2017.

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Table 1 – Angiographic Classification of Fibromuscular Dysplasia[1, 2]

	Multifocal	**Unifocal**
Angiographic appearance	• Alternating dilatation and constriction of the vessel (string of beads) • Areas of dilatation are larger than the normal calibre of the artery • Occurs in the mid and distal portion of the renal, internal carotid, and vertebral arteries • May occur in any other artery in the body†	• Focal concentric (< 1cm) or tubular stenosis (≥ 1cm)*
Typical histology	• Medial fibroplasia (most common) • Perimedial fibroplasia (rare)‡	• Intimal fibroplasia (most common) • Adventitial (periarterial) fibroplasia (rare) • Medial hyperplasia (rare)
Associated features	Aneurysm, dissection, and vessel tortuosity of medium-sized arteries may be present; multifocal and focal lesions may coexist in the same patient (20%).	

*Lesions are not necessarily confined to the middle or distal portion of the artery (i.e. may occur in any arterial segment).

†There are no cases of aortic fibromuscular dysplasia that are well documented pathologically.

‡This rare form of fibromuscular dysplasia typically occurs in young girls (e.g. 5 to 15 years of age). Although there is a beaded appearance to the renal arteries, the beads are smaller than the normal renal artery and less numerous.

Figure 1 - Cervical FMD associated with intracranial aneurysms

A. Coronal view of a Maximum Intensity Projection (MIP) on a tridimensional TOF sequence MRI of a patient harboring a cervical FMD associated with intracranial aneurysms (doted white arrow). B. Antero-posterior angiogram of a left ICA on the same patient. C. Antero-posterior angiogram of a left ICA in a different patient, showing on the same image the large intracranial aneurysm and cervical FMD (black arrow head).

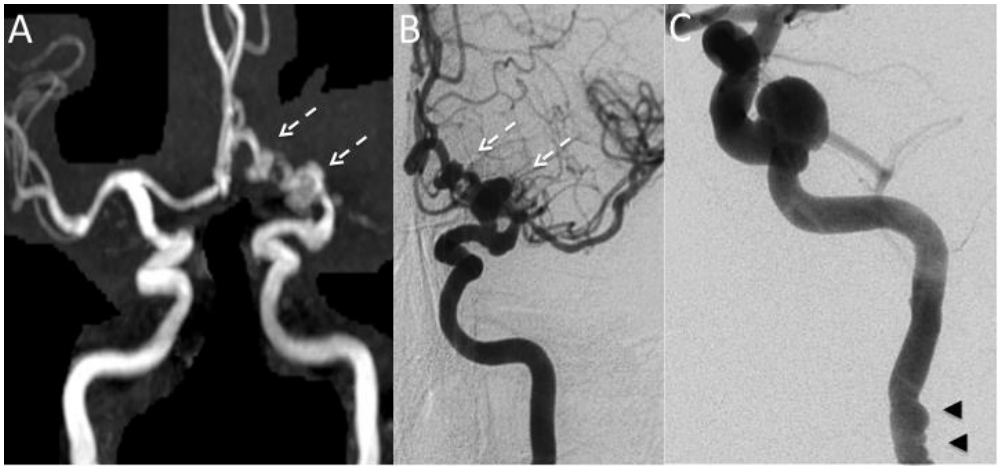

Figure 2 – Typical duplex ultrasound findings of carotid FMD.

A. B-mode imaging showing the beading and tortuosity of the mid and distal internal carotid artery. B. Color Doppler of the distal internal carotid artery exhibiting the typical pattern of tortuosity and marked turbulence. C. Color Doppler showing turbulence and spectral analysis demonstrating high peak velocity (419 cm/s) and end-diastolic velocities (186 cm/s). The "seagull" (arrow) indicates that the stenosis is quite severe. D. Color power angiography demonstrating severe tortuosity and redundancy (S curve) of the internal carotid artery.

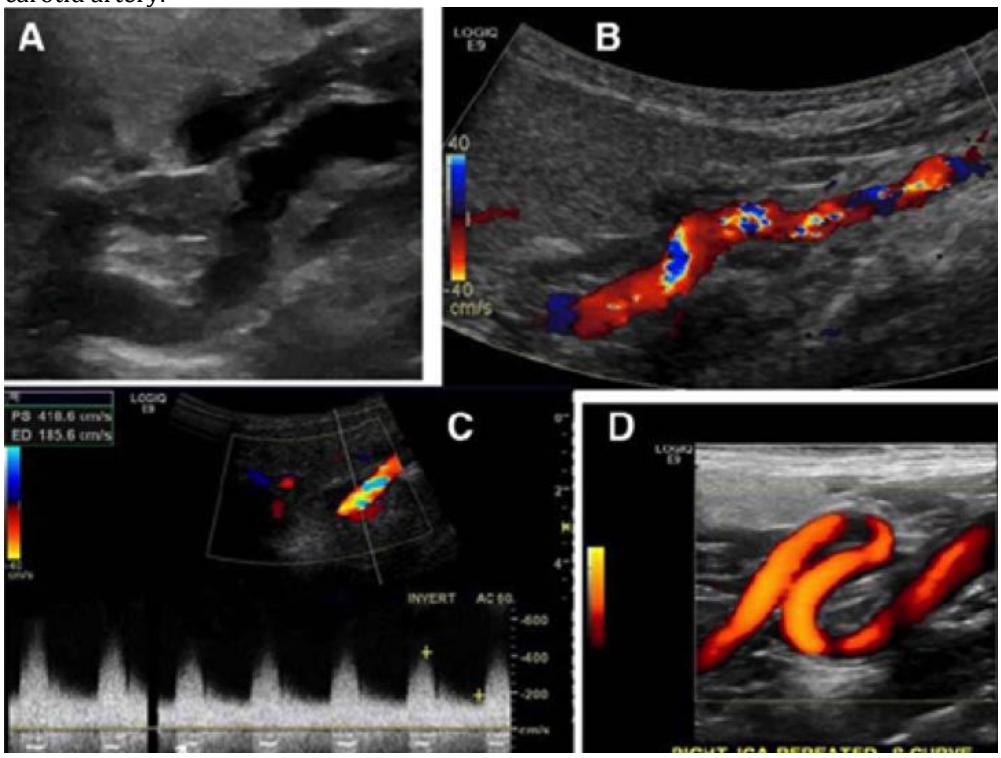

Figure 3 – Multimodal aspect of the same vessel of a typical multifocal cervical FMD.

A. Angio-CT, volume rendering reconstruction of a left cervical ICA with « string of beads » aspect. B. Angio-CT, maximum intensity projection reconstruction of the same artery. C. Oblique projection of conventional angiography. D. 3D T1 contrast enhanced MR-angiography in maximum intensity projection reconstruction.

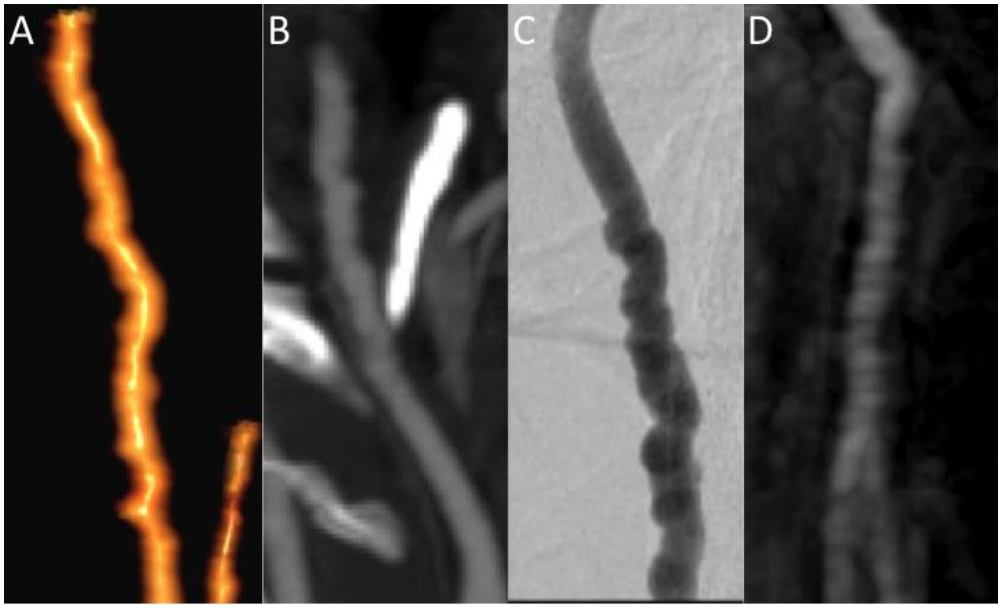

Figure 4 – Diaphragm form of FMD

A. Conventional angiography of an internal carotid artery, showing a thin translucent endoluminal diaphragm (white arrow). B. Regular and thin intraluminal filling defect on an oblique reconstruction of cervical angio-CT (white arrow). C. Axial appearance on the same exam (white dotted arrow). D. Another example of carotid diaphragm on conventional angiography. E. Macroscopic view of carotid bulb diaphragm: focal and non-circumferential thin membrane (white arrow) located on the posterior wall of the carotid bulb.