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Fibromuscular dysplasia: its various phenotypes in everyday practice in 2021

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ABSTRACT

Fibromuscular dysplasia (FMD) is a non-atherosclerotic vascular disease that may involve medium-sized muscular arteries throughout the body. The pathogenesis of FMD remains poorly understood, but a combination of genetic and environmental factors may be involved. The majority of FMD patients are women, but men may have a more progressive disease, especially when smoking. Besides the classical phenotype of string of beads or focal stenosis, arterial aneurysms, dissections, and tortuosity are frequent manifestations of the disease. However, the differential diagnosis of FMD is extensive and includes imaging artefacts as well as other arterial diseases. Diagnosis is based on CT-, MR-, or conventional catheter-based angiography during work-up of clinical manifestations, but clinically silent lesions may be found incidentally. Arterial hypertension and neurological symptoms are the most frequent clinical presentations, as renal and cerebrovascular arteries are the most commonly involved. However, involvement of most arteries throughout the body has been reported, resulting in a variety of clinical symptoms. The management of FMD depends on the vascular phenotype as well on the clinical picture. Ongoing FMD-related research will elaborate in depth the current progress in improved understandings of the disease's clinical manifestations, epidemiology, natural history and pathogenesis. This review is focused on the clinical management of adult FMD in daily practice.

Key words: carotid artery dissection, fibromuscular dysplasia, renal artery stenosis, spontaneous coronary artery dissection, visceral FMD

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INTRODUCTION

Fibromuscular dysplasia (FMD) is an idiopathic, segmental, non-atherosclerotic and non-inflammatory disease of medium-sized muscular arteries, leading to stenosis [1–3]. Two types of angiographic appearance exist (Figure 1A–C): (1) multifocal (MF) FMD, alternating areas of stenosis and dilation (the so-called 'string of beads'), which usually occurs in the mid and distal portions of the artery; or (2) focal (F) FMD, which may occur in any part of the artery [1, 4, 5]. Aneurysms, dissections, and arterial tortuosity are also frequent manifestations of the disease, but these lesions can only be attributed to FMD in the presence of a typical string-of-beads or focal stenosis, as these lesions have been described in other vascular diseases as well [3, 6–8]. Renal and cerebrovascular arteries are most frequently involved,

but all other medium-sized arteries may be affected [3, 9–14]. Involvement of >1 vascular bed, i.e., multivessel FMD, is seen in a substantial proportion of patients, ranging from 30% to 57% [3, 9–13, 15].

The prevalence of FMD in the general population is unknown because this disease is often clinically silent. FMD may be diagnosed during work-up of clinical symptoms and/or signs, but can also be discovered incidentally during imaging tests performed for other reasons [3, 16]. The clinical manifestations of FMD depend on the vascular beds involved and the vascular phenotype. FMD may be asymptomatic, as well as be at the origin of severe or even life-threatening complications [13]. The diagnosis of FMD also requires exclusion of other vascular diseases, such as atherosclerosis, monogenic (e.g., Ehlers Danlos type 4) and

inflammatory arterial diseases (e.g., large vessel vasculitis), as well as imaging abnormalities/artefacts (e.g. arterial spasm, standing waves) [3].

Diagnosis is made by imaging, i.e., duplex ultrasound, computed tomography (CT) or magnetic resonance (MR) angiography, while catheter-based arteriography remains the gold standard [3].

Management of FMD depends on the clinical presentation and the arterial lesion(s). Medical therapy with or without revascularization (endovascular or surgical) may be needed. However, clinical trials evaluating the efficacy of medical therapy with or without intervention are lacking.

As FMD is a chronic arterial disease, long-term follow-up is recommended. The frequency of follow-up will largely depend on the clinical presentation, but at least annual follow-up is advised by the international consensus [3]. Follow-up includes a clinical and physical examination, reviewing adherence to medical therapy, blood chemistries (e.g., renal function, electrolytes, lipids, and glucose), and urinalysis for albuminuria. Imaging follow-up, should be customized to each patient based upon the nature, extent and severity of arterial lesions and severity or recurrence of symptoms. Patients who have undergone revascularization procedures may require more frequent imaging surveillance [3]. Pregnant women with FMD also require more intensive follow-up, especially those with renal FMD because of an increased risk of gestational hypertension, preterm birth and, to a lesser extent preeclampsia, and those with known aneurysms, because of increased rupture risk [3, 17, 18].

Recent prospective registries and ongoing research have substantially improved our knowledge and understanding of the disease's clinical manifestations, epidemiology, natural history, and genetics [9–12, 19]. FMD is no longer considered a rare cause of renovascular hypertension in young women, but rather appears as a systemic arterial disease, which may occur in both sexes at any age and with a wide range of manifestations. Yet, while up to 90% of patients with FMD are women, men have a more aggressive course with a higher frequency of aneurysms and dissections [9, 11, 20]. The pathogenesis remains poorly understood, although a combination of genetic (particularly the *PHACTR1* variant), mechanical, hormonal, and environmental factors, such as smoking, may play a role [21–23].

RENAL FMD

The typical clinical presentation of renal FMD is a young to middle-aged Caucasian woman with arterial hypertension [9–12, 15]. While the prevalence of FMD in the general population is unknown, studies from living kidney donor candidates indicate a prevalence of renal FMD of about 3.3% [24]. The prevalence of renal FMD among patients with hypertension enrolled in the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial was 5.8% [25, 26]. Among subjects with FMD in the US,

European and ARCADIA registries, the renal arteries were involved in 66%–91% of patients [9–12, 15, 19]. The majority of these patients have a multifocal type of FMD (up to 95%) and multivessel involvement (up to 57%) [9–12, 19] (Figure 1). Patients with focal and multifocal lesions differ in age at diagnosis of FMD (30 years vs 49 years), in age at diagnosis of hypertension (26 vs 40 years), in sex distribution (female to male ratio, 2:1 vs 5:1), in initial blood pressure (157/97 mm Hg vs 146/88 mm Hg), in current smoking (50% vs 26%), in prevalence of unilateral renal artery lesions (79% vs 38%), in presence of kidney asymmetry (33% vs 10%), in renal revascularization procedures (90% vs 35%), and in hypertension cure rates in patients who underwent revascularization (54% vs 26%) [5, 9]. Besides multifocal and focal stenotic lesions, renal FMD may present as aneurysms and/or dissections (Figure 1D). Recently it was shown in 72 patients with renal infarction related to renal artery dissection (RAD) that FMD was the third main cause of spontaneous RAD. New onset RAD occurred in 25% of these patients with FMD, while de novo extra-renal dissection was present in only 6.3% after a follow-up of 51 months [27]. Renal artery dissection may be asymptomatic or present with distal thromboembolic events (e.g., renal infarct). Renal infarction, often related to underlying dissection, may be an initial manifestation of renal FMD [28, 29].

Diagnosis

In case of suspicion of renal FMD, the international consensus recommends performing a computed tomographic angiography (CTA) as the first step to confirm the diagnosis. A contrast-enhanced magnetic resonance angiography (MRA) is an alternative if CTA is contraindicated. CTA however has a better spatial resolution and visualizes small calcifications better, thereby providing a more accurate discrimination of FMD from atherosclerotic renal artery stenosis. Duplex ultrasound as the first diagnostic test for renal FMD should only be considered in specialized centers with extensive experience in duplex ultrasound for evaluation of FMD [3].

Although catheter-based angiography is the gold standard for imaging the location and morphology of FMD, it is indicated only when its findings are expected to affect patient management, or when a high clinical suspicion persists despite negative findings on CTA or MRA. In patients with MF renal artery FMD, imaging alone does not allow determining the severity and hemodynamic significance of renal artery stenosis as renal blood flow and plasma renin are often normal [30]. Therefore, translesional pressure gradient measurement is recommended by the international consensus in order to assess the hemodynamic significance of stenosis, as well as post-angioplasty to ensure the pressure gradient has been obliterated. In experienced centers, the procedure may be combined with intravascular ultrasound or optical coherence tomography [3].

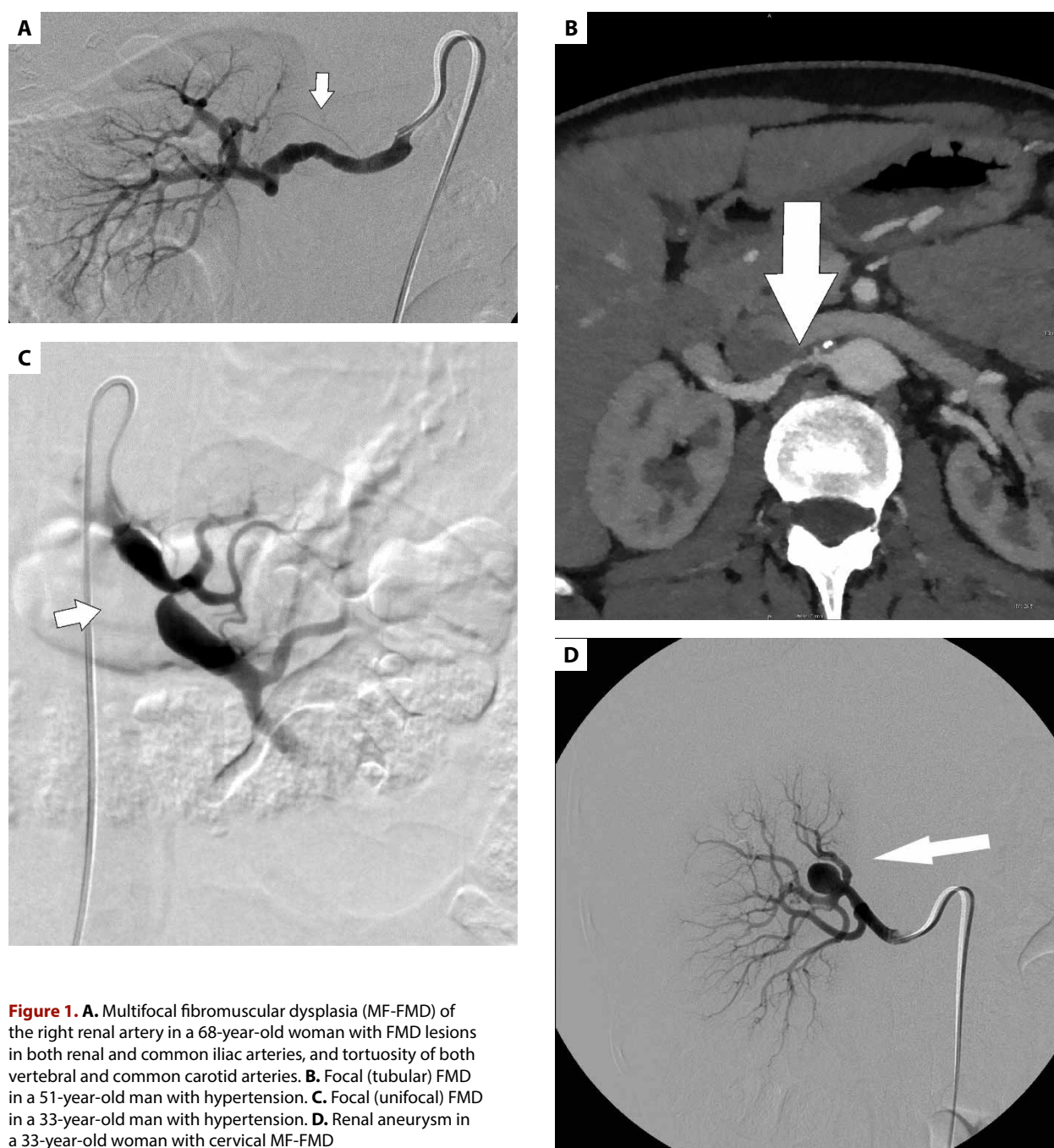


Figure 1. **A.** Multifocal fibromuscular dysplasia (MF-FMD) of the right renal artery in a 68-year-old woman with FMD lesions in both renal and common iliac arteries, and tortuosity of both vertebral and common carotid arteries. **B.** Focal (tubular) FMD in a 51-year-old man with hypertension. **C.** Focal (unifocal) FMD in a 33-year-old man with hypertension. **D.** Renal aneurysm in a 33-year-old woman with cervical MF-FMD

Treatment

Hemodynamically significant renal FMD (translesional pressure gradient $\geq 10\%$) should be treated with angioplasty without stenting, as stent kinking and fracture have been reported in the setting of renal FMD [3, 31–33]. Revascularization with stenting is reserved for the treatment of procedural complications, such as a dissection or arterial rupture. Repeat angioplasty can be attempted following primary failure of angioplasty or recurrent stenosis; however, multiple procedures are not recommended to avoid jeopardizing future surgery [3]. Surgery is recommended following failure of angioplasty and remains the primary approach in patients with complex FMD lesions of the

arterial bifurcation or branches, and stenosis associated with complex aneurysms [34]. Endovascular treatment with covered stent or coil embolization, or surgery are also needed if a renal artery dissection is progressive or causes renal hypoperfusion or a secondary aneurysm develops. Intervention for renal artery aneurysms (RAA) in the general population is performed for all symptomatic aneurysms and if the size exceeds 2 cm. However, RAAs tend to have a benign natural history with extremely low rupture rates and slow growth rates in the general population [35]. Specific data for RAA in FMD are lacking. In pregnant women or women of childbearing age an aneurysm of any diameter is considered to be an absolute indication for elective repair,

considering the risk of rupture with associated high fetal and maternal mortality [36]. Potential procedures to treat aneurysms include coiling, covered stents, or surgery (i.e., resection and/or bypass). Procedures should be avoided if an occluded aneurysm is detected, or if treatment may sacrifice vital organ parenchyma [37–40].

Outcomes following revascularization for renal FMD have been variable [5, 41, 42]. This may partly result from the difficulty to estimate the hemodynamic significance of a stenotic lesion with the different noninvasive and invasive imaging methods [43–45]. In a meta-analysis by Trinquart et al. [41], the rate of cure of hypertension (defined as blood pressure <140/90 mm Hg without medication) ranged between 14% and 85% after angioplasty across 11 clinical studies. The probability of being cured was associated with younger patient age at the time of treatment and shorter duration of hypertension. A repeat procedure was performed in 18% of the patients. In addition, the presence of a higher serum creatinine (1.45 mg/dl vs 0.82 mg/dl) and a high-normal renal resistive index (0.74 vs 0.59) may jeopardize cure after angioplasty [46]. Savard et al. [5] reported that F-FMD was associated with a higher hypertension cure rate after angioplasty than MF-FMD.

Recurrence of stenosis after percutaneous transluminal renal angioplasty (PTRA) may occur in a short time, especially in F-FMD. Therefore, the International Consensus recommends follow-up with renal duplex ultrasonography (DUS) every 6 months for 2 years to detect restenosis [3]. Patients with MF-FMD might require a less frequent follow-up, however lifelong follow-up is advised as restenosis can occur much later. In a recent cross-sectional study of 26 patients with FMD (15 F-FMD, 11 MF-FMD), Oribe et al. [47] showed that these two angiographic types of FMD have indeed a different clinical course. In addition, patients with MF-FMD and with a younger age of onset may not only present with restenosis but also with *de novo* stenosis at different segments of the renal arteries, justifying long-term follow-up (>10 years).

The treatment of hypertension in patients with renal FMD, regardless of whether or not revascularization is performed, follows the international guidelines for the management of high blood pressure [48, 49]. All antihypertensive medications can be prescribed in renovascular hypertension, although angiotensin converting enzyme inhibitors or angiotensin receptor blockers are preferable in this setting.

Despite the absence of placebo-controlled studies of antiplatelet therapy for FMD the use of antiplatelet agents (low dose aspirin, 75–100 mg daily) is recommended by the international consensus for both symptomatic and asymptomatic patients with FMD in view of the theoretical risk of thrombotic and thromboembolic events [3]. Indeed, turbulent flow due to multifocal FMD, marked arterial tortuosity, and other FMD-related lesions may cause platelet aggregation [3]. However, the benefits and potential risks

of long-term low dose aspirin treatment should be weighed on an individual basis.

After PTRA, short-term (e.g., 4–8 weeks) dual antiplatelet therapy and long-term low dose aspirin are justified. If a renal artery dissection — with or without renal infarction — occurs, short-term anticoagulation or dual antiplatelet therapy (e.g., 3–6 months) followed by long-term antiplatelet therapy is recommended [3]. During follow-up visits post revascularization antihypertensive and antiplatelet therapy has to be reassessed.

The treatment of hyperlipidemia follows the current European Society of Cardiology/ European Atherosclerosis Society (ESC/EAS) guidelines, as there are no data to support the use of statins in patients with FMD without hypercholesterolemia [50].

Smoking cessation should be strongly encouraged for all patients with FMD. Besides the known health-related benefits in the general population, patients with FMD who smoke reportedly have a more progressive and severe disease than non-smokers [22, 23]. However, this association was not confirmed in the ARCADIA-POL study [51].

CEREBROVASCULAR FMD

Systematic imaging of all arterial beds beyond the initial site of diagnosis has revealed lower to similar frequency of involvement of cervical (24.6%–80.4%) compared to renal (66.1%–90.7%) artery disease [3, 9–12, 15, 16, 19].

Headache (especially migraine), pulsatile tinnitus, dizziness, or light-headedness are non-specific symptoms that may be the consequence of cerebrovascular FMD. However, patients can be asymptomatic or may present with focal neurological deficits, such as transient ischemic attack or stroke [3, 4, 9, 52–56]. In case of cervical artery dissection (ceAD), these focal neurological symptoms may be accompanied by neck, face, or head pain [6].

FMD-related cerebrovascular lesions include carotid and vertebral artery stenosis, arterial dissection, and aneurysm formation (Figure 2). Multifocal FMD is the most common phenotype and typically affects the mid-distal portion of the internal carotid or 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. Intracranial FMD is rare and typically co-occurring with extracranial FMD. An unruptured aneurysm (Figure 2C) is often the primary manifestation of intracranial FMD [53, 54]. These aneurysms are more often found in a high-risk location (posterior circulation) and are of larger size than non-FMD related aneurysms [57]. The prevalence of intracranial aneurysms is also significantly higher than in the general population [6, 57]. Therefore, and because of the risk of rupture, brain screening with CTA or MRA is recommended for all patients with confirmed FMD in any location [3]. The risk of rupture depends on aneurysm-re-

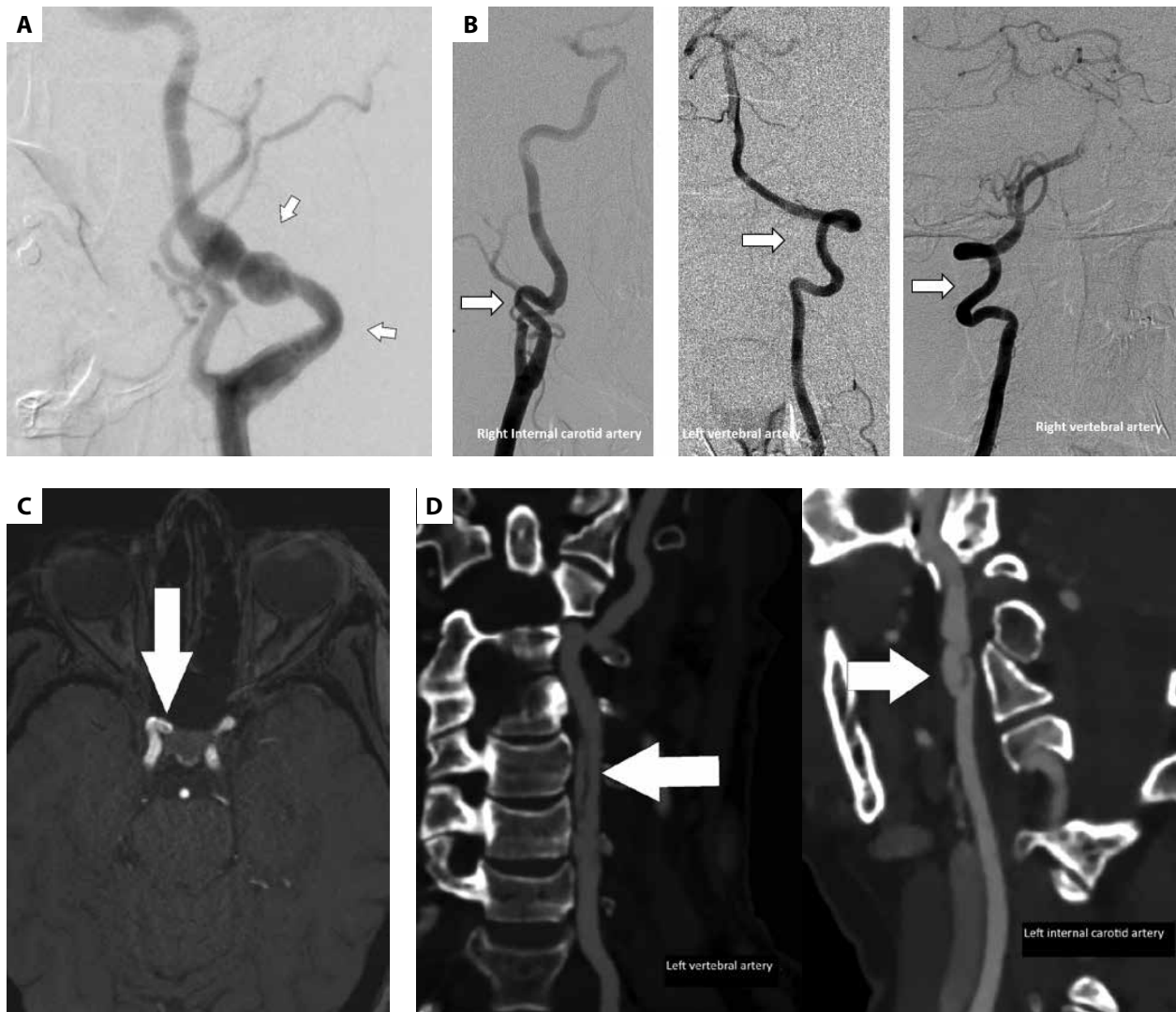


Figure 2. **A.** Multifocal fibromuscular dysplasia (MF-FMD) of both carotid arteries with aneurysmal dilatation in a 48-year-old woman with bilateral MF-FMD of the renal and common iliac arteries. **B.** Tortuosity of carotid and vertebral arteries in a 68-year-old woman with MF-FMD of both renal and common iliac arteries. **C.** Small saccular aneurysm of the right cavernosal internal carotid artery in a 46-year-old woman with bilateral MF-FMD of the renal arteries. **D.** Dissection of the left internal carotid artery and left vertebral artery post partum in a 33-year-old woman

lated factors (size and growth, irregular shape, and location of aneurysms), and patient modifiable and nonmodifiable characteristics (arterial hypertension, smoking, alcohol use, patient age ≥ 70 years], geographical region, i.e., Japan, Finland, prior history of rupture, female sex, multiple intracranial aneurysms, family history of ≥ 2 relatives with unruptured intracranial aneurysms or subarachnoid hemorrhage) [58]. Whether the risk of rupture of intracranial aneurysms is higher in patients with FMD than in the general population ($< 1\%$ per year) remains uncertain [53, 57].

Cervical (carotid or vertebral) artery dissection is a frequent event of FMD (Figure 2D). The prevalence varies between 9% and 39.5%, and is highest among patients with a neurological presentation leading to diagnosis of FMD [6, 10, 11, 16, 53, 59, 60]. In the US FMD registry, the prevalence of carotid artery dissection is 3 to 4 times higher than vertebral artery dissection [6, 10]. Multiple ceADs are frequent in patients with FMD and the prevalence is esti-

mated to be up to 37% [6, 10]. In patients with ceAD, the overall prevalence of cervical FMD ranges between 8% to 20%, and the diagnosis of FMD is more frequently reported in patients with multiple and recurrent ceAD [11, 61–63].

Several factors, including younger age, migraine (especially migraine without aura), mechanical trigger events, and infections have been reported to be associated with ceAD [64]. In the ARCADIA (Assessment of Renal and Cervical Artery Dysplasia) registry, male sex, age < 50 years, history of migraine, and involvement of ≥ 3 vascular beds are also reported as independent risk factors for ceAD in FMD, while fewer patients had a history of hypertension [60].

Recent data from the IPSYS (Italian Project on Stroke at Young Age) ceAD study showed a different risk factor profile between ceAD patients with and without cervical FMD (ceFMD). A history of migraine, the presence of intracranial aneurysms, and the occurrence of minor traumas before the event were associated with ceFMD [65]. However, no

differences in clinical characteristics between patients with ceAD and FMD and those without FMD were observed in the ARCADIA-POL registry [59].

Recurrence rate of ceAD is rather low. Of 147 known ceFMD patients, of whom 52 had an aneurysm and another 52 a dissection, only 3 patients (5.8%) experienced a new dissection and none of the patients developed a new aneurysm after a mean follow-up of 35.3 months [66]. The prevalence of recurrent ceAD was also low (3.3% after a median follow-up of 34 months) in the IPSYS ceAD study. Having FMD and migraine were independent predictors of ceAD recurrence [65].

Diagnosis

CTA or contrast-enhanced MRA has replaced catheter-based angiography as the initial imaging modality. The latter remains the diagnostic gold standard, but its use is reserved for complicated cases that require intervention (repair of an aneurysm or pseudoaneurysm related to dissection, or severe stenotic lesions causing focal neurological symptoms). In experienced centers, vascular DUS can be used in the evaluation of carotid FMD; however, distal carotid lesions may escape DUS. Furthermore, it is inadequate to assess vertebral and intracranial arteries. Carotid DUS may be useful for follow-up of carotid artery FMD [1, 3, 4].

Treatment

Asymptomatic carotid or vertebral string of beads, even severe are not an indication of revascularization [3].

The treatment of migraine in patients with FMD follows the same approach as in patients without FMD and may include lifestyle modification to avoid triggering factors, preventive therapies, and medications to halt migraines. However, vasoconstrictive agents should be avoided, especially in patients with a history of ceAD [67].

The approach to pulsatile tinnitus in patients with FMD may include sound or cognitive behavioral therapy besides reassurance. Consultation with an otolaryngologist is advised to evaluate hearing and to assess for other causes of tinnitus beyond FMD [3, 68]. Preventive aneurysm exclusion can be performed by surgical clipping or endovascular coiling with or without additional insertion of regular or flow-diverting stents. The choice of the treatment modality depends on anatomical factors and the assessment of the neurointerventionalist, and, in the absence of specific evidence, does not differ from that of patients without FMD. In patients with low rupture risk aneurysms, or high risk of preventive repair-related complications, or if patients prefer conservative therapy, observation with follow-up imaging to detect growth or change in morphology is advised. To plan follow-up imaging intervals, the ELAPSS score may help estimate the 3- and 5-year risk of aneurysm growth, which is an established surrogate for rupture. The frequency for follow-up imaging can then be planned accordingly [68, 69].

In the absence of data from randomized trials specific to FMD, management of ceAD among patients with FMD is similar to that of patients without FMD [3, 63]. In the acute phase and depending on the clinical presentation, intravenous thrombolysis and/or mechanical thrombectomy is applied if the patients meet criteria for treatment [64, 70]. Patients who remain symptomatic, developing TIA or stroke despite optimal medical therapy, and patients with symptoms/signs of cerebrovascular hypoperfusion due to carotid stenosis, can also be treated with mechanical thrombectomy followed or preceded by carotid artery stenting [3, 71]. Most patients with ceAD will not require invasive treatment, but antithrombotic treatment — either an anticoagulant or an antiplatelet agent — for at least 3–6 months — is given in order to prevent recurrent ischemic events. Antiplatelet therapy is generally continued lifelong, if not contraindicated [3, 63, 70]. Whether or not lifelong antiplatelet therapy is needed in completed healed ceAD is not known, as there are no supporting data. However, the radiographic morphology (e.g., residual stenosis, dissection-related aneurysm) and the low risk of recurrence, may guide a pragmatic decision made on a case-by-case basis. Pseudoaneurysms resulting from a dissection are at low risk for ischemic events or rupture and rarely require endovascular treatment [72]. As minor traumas are often associated with ceAD, some physical activities or manipulations (roller coaster ride, heavy weight lifting, chiropractic neck manipulation) are best avoided in patients with cerebrovascular FMD [3, 54, 63, 64].

An endoluminal ‘carotid web’ or ‘carotid bulb diaphragm’, visualized as a linear defect on CTA or MRA, has been classified as a focal variant of intimal FMD of the carotid bulb by some authors. It has been described predominantly in black/Afro-Caribbean patients and is associated with a high risk of recurrent ischemic stroke, justifying carotid stenting or endarterectomy [73–75].

VISCERAL FMD

The prevalence of visceral artery (VA) FMD varies between 14%–21% in patients with FMD who underwent systematic imaging studies [9–13, 76]. This relatively high frequency strengthens the need for a systematic evaluation of all vascular beds, including visceral arteries, regardless of initial FMD involvement. The celiac axis, superior mesenteric and splenic arteries are the most frequently involved (Figure 3). Most patients with VA-FMD are asymptomatic, and VA-FMD is often an incidental finding on imaging studies performed for other reasons. Both liver and intestine are indeed relatively resistant to ischemia (double hepatic blood supply) and collateral circulation through the inferior mesenteric artery (Riolan’s arcade), unless at least two of the major arteries are obstructed. Visceral artery FMD can nevertheless present as mesenteric ischemia caused by progressive stenotic lesions of the mesenteric territory, resulting in nausea, postprandial flank or abdominal pain and weight loss; an abdominal bruit can be present at

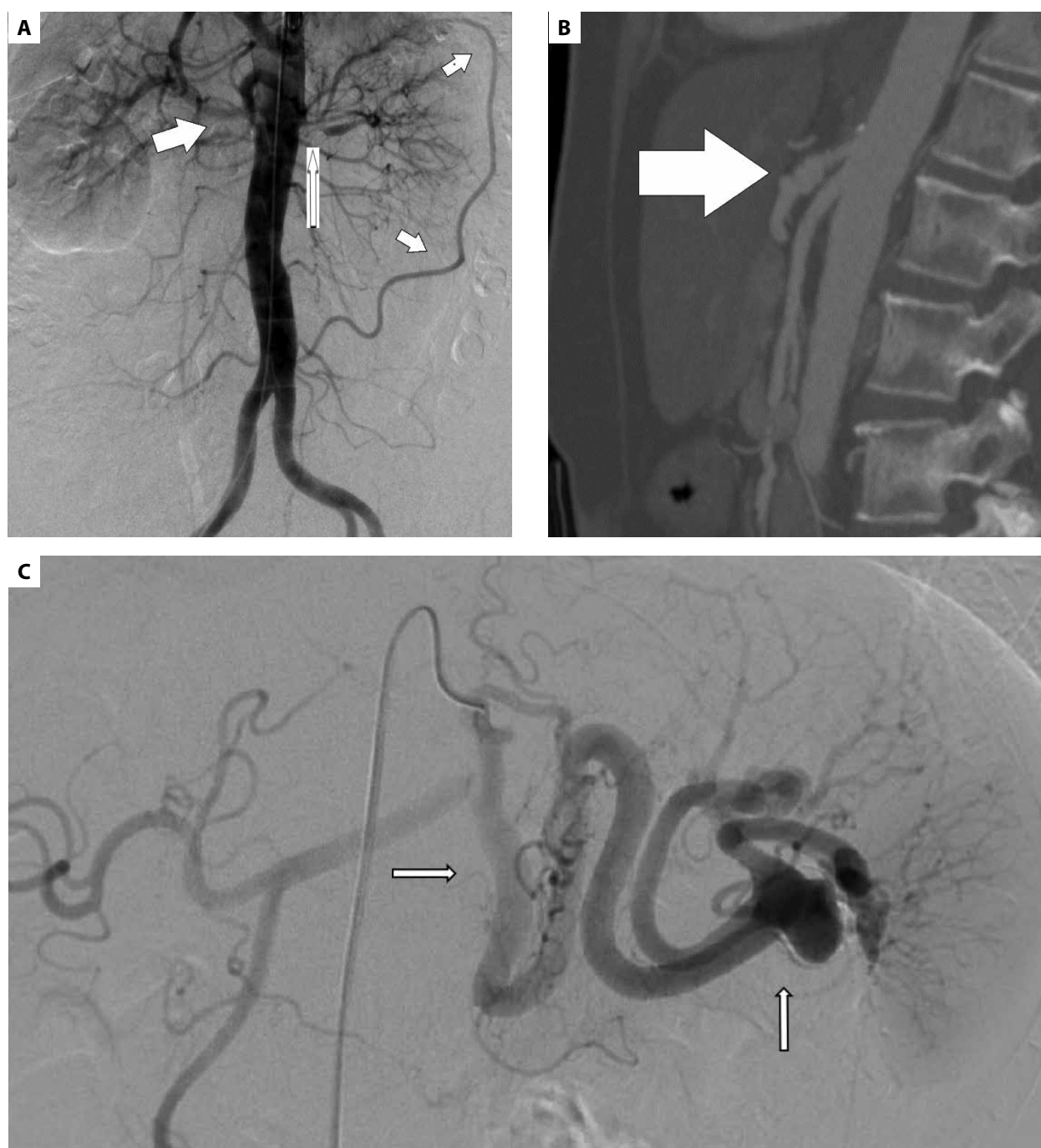


Figure 3. **A.** Focal stenosis of superior mesenteric artery with prominent arcade of Rioloan in a 49-year-old man with focal stenosis of renal artery (long arrow). **B.** Multifocal-fibromuscular dysplasia (MF-FMD) of the coeliac trunk in a 70-year-old woman with SCAD (courtesy of D. Adlam, Leicester, UK). **C.** Tortuosity and aneurysm of the splenic artery in a 62-year-old woman with MF-FMD of the right renal and left common iliac arteries

physical examination. Severe forms have been reported, eventually resulting in hemicolectomy, multi-organ failure, and eventually death. Acute ischemia and/or infarction is usually due to arterial dissection or embolism from an aneurysm causing acute abdominal pain and potentially shock [3, 12, 13]. Patients with VA-FMD are more likely to have aneurysms and dissections compared to patients with FMD without visceral involvement [76].

We recently showed that patients with FMD have smaller visceral arterial diameters when compared with patients

without FMD. This may represent a new phenotype of FMD. The lower BMI seen in these patients compared to matched controls may be explained by chronic mesenteric ischemia resulting from FMD lesions [77].

Diagnosis

CTA and MRA are generally used to confirm diagnosis, while catheter-based angiography remains the gold standard. Screening for VA-FMD should not only be performed in symptomatic patients, but also in patients with renal and/

or cervicocephalic FMD [1–3, 6, 13]. Conversely, patients with VA-FMD should be screened for renal and/or, to a lesser degree, extracranial involvement, as concomitant renal or cervicocephalic involvement was found in, respectively, 41/75 and 3/75 patients with VA-FMD [52]. The combined involvement was also more frequently present in women than in men (80% vs 36%) [78].

Treatment

Treatment — endovascular or surgical — of VA-FMD depends on symptomatology, type/location and extent of the arterial involvement, the presence of aneurysms or dissections, prior vascular events, comorbid conditions and age of the patient. Smoking is discouraged and arterial hypertension and hyperlipidemia are treated according to the guidelines. Pharmacologic treatment with antiplatelet drugs, in mono or dual therapy, and with anticoagulation is comparable to that proposed for renal FMD [13].

ILIAC AND LOWER EXTREMITY FMD

Lower extremity FMD has been reported in common iliac, internal iliac, common femoral, deep and superficial femoral and popliteal arteries, but most commonly the external iliac arteries are involved. The lesions are typically multifocal and bilateral [3, 14, 52, 79] (Figure 4A). According to the recent registries, FMD involving the iliac arteries is present in 7%–62% of patients [9, 11, 12, 14]. Most patients with lower extremity involvement are asymptomatic and may be diagnosed by femoral bruit noted on physical examination or incidentally on imaging studies. Iliac artery FMD can seldom cause limb symptoms, including claudication, foot or toe ischemia, and atypical leg symptoms, by luminal narrowing, microthrombi with distal embolization and

thrombosis due to dissection; aneurysms may also occur, but are seldom complicated by rupture [3, 79, 80].

Diagnosis

Duplex ultrasound, CTA, MRA, or catheter-based angiography can be used for the diagnosis; however, DUS will inadequately visualize the iliac arteries. The FMD findings have to be differentiated from atherosclerotic disease based on nature of the lesion and absence of plaque [52].

Treatment

Angioplasty is the preferred treatment of choice in symptomatic patients and carries a high technical success rate. Surgery is reserved for complicated cases, progressive aneurysm growth following dissection or for treating complications of endovascular treatment. However, most patients are asymptomatic and can be managed conservatively including antiplatelet therapy [14].

UPPER EXTREMITY FMD

Upper extremity FMD has been reported in 3% (7/232) and 15.9% (10/63), respectively, of patients who underwent upper extremity imaging in the ARCADIA-POL and US Registries [10, 12]. It has been documented in the subclavian, axillary, radial, and ulnar arteries, but the brachial artery is most often involved [10, 81] (Figure 4B). Involvement is most commonly of the multifocal type and bilateral. The majority of patients are asymptomatic [81]. If present, symptoms of upper extremity FMD may include Raynaud's phenomenon, paresthesia, hand or arm claudication, and finger or hand ischemia (rest pain, discoloration, ulceration, or gangrene) resulting from thromboembolism or dissection [81]. Brachial FMD can be suspected in asymptomatic

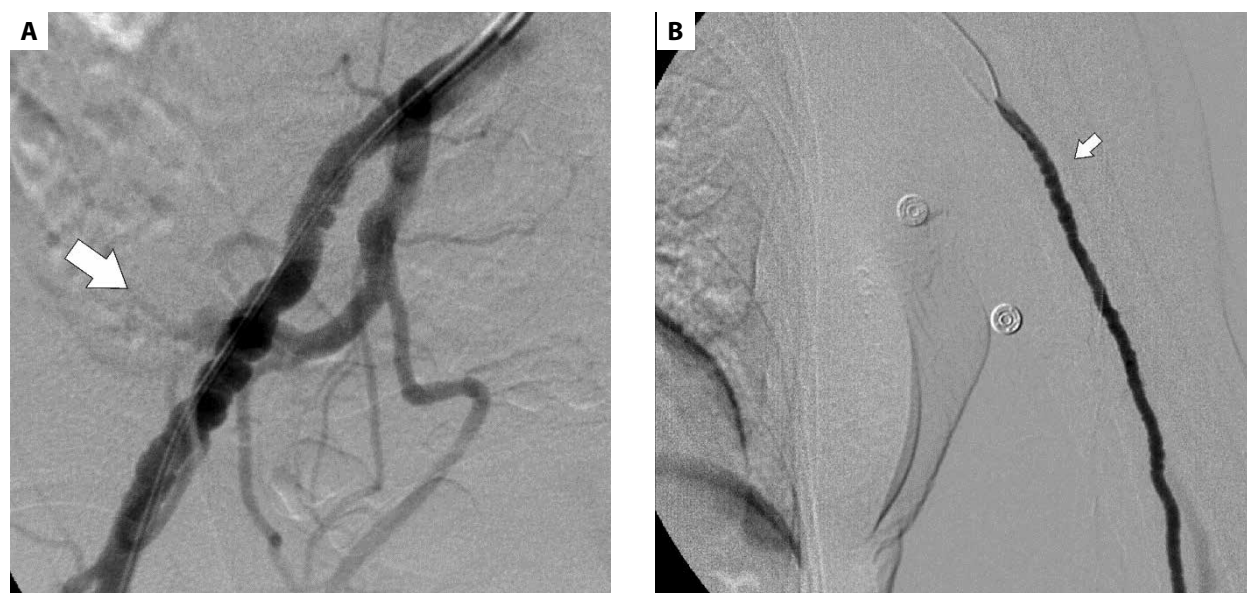


Figure 4. **A.** Multifocal fibromuscular dysplasia (MF-FMD) of the common iliac artery in a 68-year-old woman with FMD lesions in both renal and common iliac arteries, and tortuosity of both vertebral and common carotid arteries. **B.** MF-FMD of the right brachial artery in a 67-year-old woman

subjects, if a brachial bruit and/or discrepant arm blood pressures are identified on physical examination [81].

Diagnosis

Diagnosis can be made by DUS, as atherosclerosis is uncommon in upper extremity arteries, except in patients with severe chronic kidney disease (Mönckeberg's sclerosis). However, many other diseases can cause a Raynaud phenomenon and upper extremity ischemia. Therefore, whenever the underlying cause is uncertain, and especially if digital ischemia is unilateral, imaging with arteriography is recommended to detect potentially treatable (endovascular or surgical) diseased arteries. Usually, CTA or MRA is performed as initial diagnostic tool, while catheter-based angiography is reserved to rare patients who need vascular intervention [3].

Treatment

Depending on the presentation, treatment can be conservative, endovascular with angioplasty, or surgical with thrombolysis, excision/resection of the diseased artery segment with primary anastomosis or grafting with reversed saphenous vein [81–83].

CORONARY FMD AND SCAD

Spontaneous coronary artery dissection (SCAD) is an uncommon cause of acute coronary syndromes, and occurs predominantly in young to middle-aged women [84–87]. Saw et al. [87] published the first case series of SCAD with concomitant FMD. Since then, several other extra-coronary arterial lesions including aneurysms, dissections, focal stenosis, and aortic root dilation have been described in patients with SCAD [88]. While SCAD is rare in patients with FMD, being present in only 2.7% of patients in the US FMD Registry, the prevalence of FMD in SCAD survivors ranges between 41% and 86% of SCAD-survivors, depending on modality and completeness of imaging [6, 84]. The most common affected vascular beds are the cervical, renal, and ilio-femoral arteries [84]. Extracoronary FMD in SCAD patients is mostly of the multifocal phenotype and appears to be benign and non-progressive in the short to medium term, with low reported rates of non-coronary major adverse cardiovascular events in SCAD-survivors [84, 88, 89]. Following discovery of the association between SCAD and extra-coronary MF-FMD, and despite the extreme rarity of typical coronary string of beads, the concept of coronary FMD has been proposed [87, 88, 90–92]. The latter should be considered in presence of marked coronary tortuosity — usually defined as ≥ 3 bends (defined as a $\geq 45^\circ$ change in vessel direction) — however, the intravessel or multivessel symmetry sign, corkscrew appearance, dissection, aneurysm, distal tapering or long, smooth narrowing of the coronary arteries have all been described [92]. To ascribe these lesions to FMD, the presence of at least one focal or multifocal arterial lesion in another vascular bed is required.

Coronary artery tortuosity is also highly prevalent in the SCAD population and is associated with recurrent SCAD, which occurs most often within segments of tortuosity [93]. Nevertheless, arterial tortuosity may have multiple causes, may be found in apparently healthy subjects and is also associated with increasing age, female gender and cardiovascular risk factors [94].

SCAD and FMD share common genetic risk variants including the *PHACTR1* locus [95]. Notably however, the effect size may be different between patients presenting primarily with SCAD or with FMD [84, 95, 96]. Common genetic variants associated with SCAD are also associated with SCAD risk among patients with FMD [86]. Overall, these data may suggest that SCAD and FMD are not a single disease but rather overlapping disorders [19]. Further research is in progress [97].

Treatment

Overall, based on expert opinion and observational data, a conservative approach is preferred in patients with SCAD when possible [84, 85, 98]. A treatment algorithm is proposed in the recent ESC guidelines [98].

CONCLUSIONS

FMD is an idiopathic, segmental, nonatherosclerotic, non-inflammatory disease of the musculature of small to medium-sized arteries. It cannot be considered a rare disease of young women anymore. Indeed, though predominant in female sex, it may be diagnosed both in men and women and at any age. While renal and cervical arteries are the most frequently affected, FMD may be found in all arterial beds and multivessel involvement is common. FMD primarily manifests as multifocal ('string-of-beads') or focal lesions, but arterial aneurysms, dissections and tortuosity are frequent manifestations of the disease. The clinical course of FMD is highly variable, from incidental findings to life-threatening lesions. Confirmation of the diagnosis requires CT-, MR- or catheter-based angiography. Regardless of the initial site of vascular bed involvement, imaging of all vessels from brain to pelvis should be performed at least once. Treatment depends on the clinical presentation and can be conservative as well as invasive. Ongoing research is promising for our patients.

Article information

Conflict of interest: None declared.

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