

European consensus on the diagnosis and management of fibromuscular dysplasia

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The main objectives of this expert consensus are to raise awareness about fibromuscular dysplasia, which is more frequent and more often systemic than previously thought and can sometimes have devastating consequences; to provide up-to-date recommendations for the diagnosis, evaluation, and management of the disease; and to identify research priorities. The emphasis has been put on recommendations for daily practice. The main topics covered include definition, classification, diagnosis, and management of fibromuscular dysplasia in adult patients with symptomatic involvement of the renal arteries, supra-aortic trunks, and digestive and peripheral arteries.

Abbreviations: AHA, American Heart Association; CTA, CT-angiography; DSA, digital subtraction angiography; DUS, renal duplex ultrasound; FMD, fibromuscular dysplasia; HTN, hypertension; MRA, MR-angiography; PTA, percutaneous transluminal angioplasty; RAS, renal artery stenosis; SAH, subarachnoid hemorrhage; SCAD, spontaneous coronary artery dissection

Keywords: aneurysm, dissection, fibromuscular dysplasia, renal angioplasty, renal artery stenosis, renovascular hypertension

INTRODUCTION

The prevalence of symptomatic renal fibromuscular dysplasia (FMD) in the general population is approximately 0.4% and cervicocephalic FMD is probably half as common as renal FMD [1]. The most frequent clinical presentation of FMD is renovascular hypertension (HTN) secondary to renal artery involvement [1]. Cervicocephalic FMD can result in ischemic or hemorrhagic stroke, cervical artery dissection, and may be associated with intracerebral aneurysms and risk of subarachnoid hemorrhage (SAH) [2]. In some patients, the diagnosis of FMD can lead to invasive procedures such as percutaneous angioplasty, reconstructive surgery, or intracranial aneurysm clipping. Thus, both the disease and its treatment can lead to significant morbidity and mortality [1].

There are no specific guidelines for the diagnosis and treatment of FMD, which is at least partly explained by the absence of randomized clinical trials. Except for one systematic review and meta-analysis [3] and descriptive data

from the French [4] and US [5] registries, most of the evidence still comes from small and old cohorts and expert opinions.

The origin of this expert consensus is a Belgo-French consensus [6] developed upon request of the French 'Haute Autorité de la Santé' (<http://www.has-sante.fr>). The current version has been thoroughly revised and updated by an enlarged panel including experts from several European countries.

The main objectives of the expert panel were to raise awareness about FMD, which is more frequent and more often systemic than previously thought [1,5]; to provide up-to-date recommendations for the diagnosis, evaluation, and management of the disease; and to identify research priorities. The emphasis has been put on recommendations for daily practice. The main topics covered include definition, classification, diagnosis, and management of FMD in adult patients (≥ 18 years) with symptomatic FMD of the renal arteries, supra-aortic trunks, and digestive and peripheral arteries.

DEFINITION AND CLASSIFICATION

The Medical Subject Headings definition of FMD is 'An idiopathic, segmental, nonatheromatous disease of the musculature of arterial walls, leading to stenosis of small and medium-sized arteries'. The definition indicates that

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FMD induces arterial stenoses, implying that the presence of an aneurysm without stenosing lesions cannot be attributed to FMD. It also mentions the absence of atherosclerosis to exclude the much more frequent atherosclerotic stenoses; however, typical FMD lesions can coexist with atherosclerotic plaques. We propose the following definition: 'FMD is an idiopathic, segmental, nonatherosclerotic and non-inflammatory disease of the musculature of arterial walls, leading to stenosis of small and medium-sized arteries. The diagnosis of FMD requires exclusion of renal artery spasm, arterial diseases of monogenic origin, and inflammatory arterial diseases'.

Three main types of renal FMD have been identified according to the most affected arterial wall layer [7,8]: intimal FMD (5% of renal-artery FMD cases), medial FMD (>85%), and perimedial FMD (10%). These categories are not mutually exclusive, as involvement of more than one layer in the same diseased artery is not uncommon [9]. Although these different subtypes were initially described in patients with renal FMD, similar lesions have been observed in patients with cervical or intracranial FMD [2].

Kincaid *et al.* [8] have proposed an angiographic classification of FMD based upon the pathological–angiographic correlations found in 60 patients who underwent angiography and from whom pathological renal artery FMD specimens were obtained. Three angiographic types of renal artery FMD have been described: multifocal ('string-of-beads' appearance), unifocal (solitary stenosis <1 cm in length), and tubular (stenosis at least 1 cm in length) (Fig. 1). As the two last categories differ only by the length of the diseased segment, it was proposed to group them under the general term unifocal [4].

As FMD-related renal artery stenosis (RAS) is now usually treated by percutaneous transluminal angioplasty (PTA) rather than surgery, histological verification is seldom available and the angiographic classification has progressively replaced the histological classification.

The 'string-of-beads' aspect accounts for more than 80% of cases, and its histological substrate is medial FMD [5]. It affects mainly women between 30 and 50 years of age [5,6,10]. The lesions commonly involve the middle or distal thirds of the main renal artery, and there is often extension into the proximal portion of the first-level branches. Lesions are bilateral in 60% of cases [1]. Although the 'string-of-beads' appearance is almost pathognomonic of multifocal (medial) FMD, similar aspects of multifocal stenosis have

been described after intoxication by sympathomimetic agents and ergotamine derivatives. Mid-aortic syndrome (also called hypoplasia or coarctation of the abdominal aorta), characterized by segmental narrowing of the proximal abdominal aorta [11,12], may also be associated with RAS – particularly in children – and in some cases, histological lesions similar to those of medial FMD may be observed on examination of the aorta or renal artery [13].

Unifocal FMD can be found at the ostium, the trunk, or the bifurcation of the renal arteries. As this feature lacks specificity, the diagnosis can be established in young (usually <40 years old) patients with no atherosclerosis or other less frequent diseases. The differential diagnosis of unifocal FMD includes compression of the proximal renal artery by the median arcuate ligament; Takayasu or giant cell arteritis, usually associated with biological inflammation and vascular thickening; and rare monogenic or congenital diseases (type 1 neurofibromatosis, tuberous sclerosis, pseudoxanthoma elasticum, vascular Ehlers–Danlos syndrome, Alagille syndrome, Williams syndrome, and Turner syndrome) [1].

The angiographic features of carotid and vertebral artery FMD are very similar to those described in renal FMD. However, atypical forms of FMD exist, with diaphragmatic stenoses because of intimal dysplasia at the origin of the internal carotid artery [2] (Fig. 2).

The diagnosis of **multifocal FMD** can be established when a 'string-of-beads' appearance is observed on a medium-sized artery, in the absence of aortic involvement or exposure to vasoconstrictor agents. This angiographic aspect is strongly correlated with medial FMD lesions on histological examination. The diagnosis of **unifocal FMD** can be established in young patients (usually <40 years) in the absence of atherosclerotic plaque, multiple vascular risk factors, inflammatory syndrome or vascular thickening, and familial or syndromic disease.

SCREENING AND DIAGNOSIS

Screening for fibromuscular dysplasia

Renal artery fibromuscular dysplasia

The most common presentation of renal artery FMD is renovascular HTN. In the general population, the

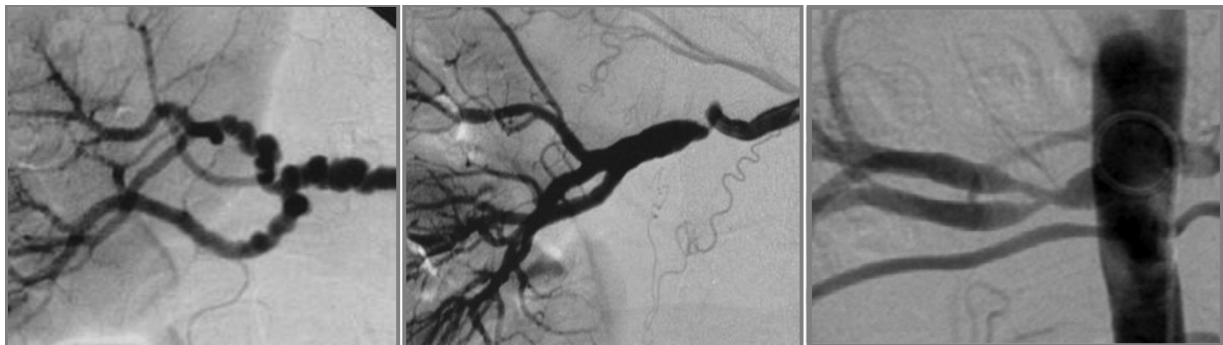


FIGURE 1 Angiographic classification of fibromuscular dysplasia (FMD) of the renal arteries. From left to right, 'string-of-beads' appearance of multifocal FMD, unifocal FMD, and tubular FMD (adapted from ref [1]).

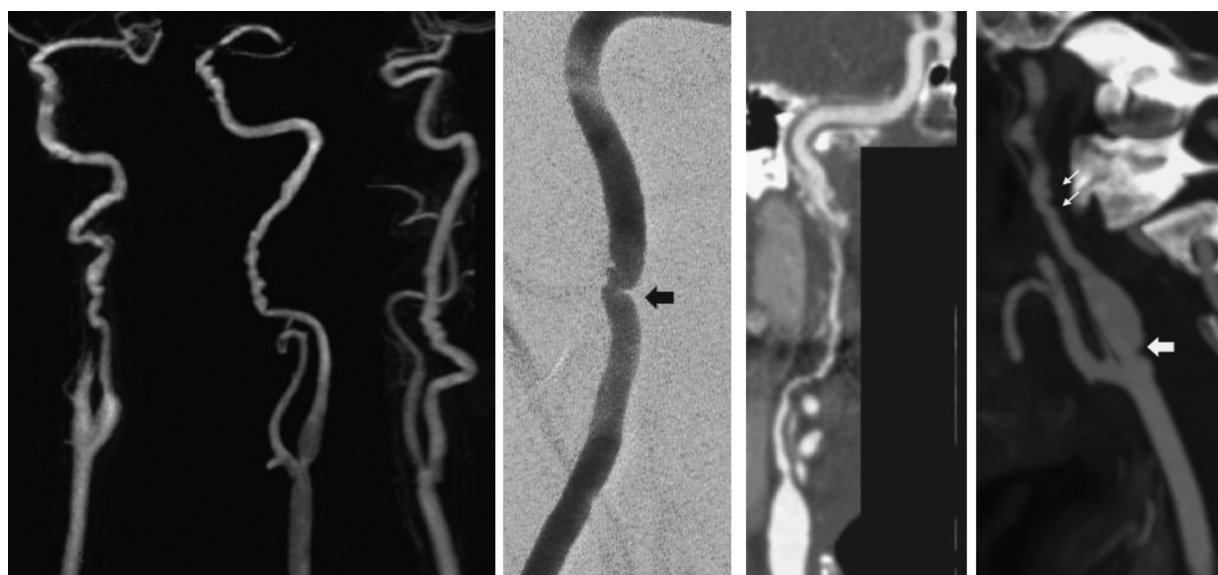


FIGURE 2 Classification of fibromuscular dysplasia (FMD) of the cervicocephalic arteries. From left to right, 'string-of-beads' appearance of multifocal FMD (MRA), unifocal FMD (conventional angiography), tubular FMD (CTA), and atypical form of FMD with a diaphragmatic stenosis at the internal carotid artery origin (large arrow; associated typical string-of-bead lesions are indicated by thin arrows) (adapted from ref. [2]). CTA, CT-angiography; MRA, MR-angiography.

prevalence of this presentation is roughly four of 1000 [1]. The majority of patients are women between 15 and 50 years of age [10].

In agreement with the American Heart Association (AHA)/American College of Cardiology [14], we propose the following indications of RAS screening [4]:

In a patient with HTN, screening for FMD-related RAS is recommended in any of the following cases:

1. Age <30 years, especially in women
2. Grade 3 ($\geq 180/110$ mmHg), accelerated or malignant HTN,
3. Resistant HTN (blood pressure target not achieved despite triple therapy at optimal doses including a diuretic)
4. Small kidney without history of uropathy
5. Abdominal bruit without apparent atherosclerosis
6. FMD in at least another vascular territory

However, these practice guidelines are derived only from an expert consensus and are not specific to FMD. In individuals aged less than 50 years, screening for FMD may also be considered in milder HTN cases.

Fibromuscular dysplasia of the cervicocephalic arteries

The frequency of symptomatic FMD of cervicocephalic arteries is lower than that of renal FMD. The mean age at diagnosis in most series of patients with cervical FMD was over 50 years [2].

Cervicocephalic FMD can be found in patients with focal retinal or cerebral ischemic symptoms owing to either a thromboembolic mechanism or a hemodynamic compromise of the distal circulation. Some patients also develop complications including spontaneous dissection, intracranial aneurysms and carotid-cavernous fistulas, or vertebral arteriovenous fistulas, all of which being sometimes

associated with focal neurological deficits. SAH usually results from intracranial aneurysm rupture, but has also been reported in patients with cervicocephalic FMD but no detectable aneurysm at angiography [15].

Cervical artery dissection is a classical complication of FMD, but its incidence in patients with FMD remains unknown. In the US FMD registry [5], approximately 20% of patients suffered from arterial dissection, the most common dissection site being carotid arteries. Conversely, it has been reported that up to 20% of patients with cervical artery dissection have signs of FMD on imaging [2]. However, the diagnosis of FMD can be challenging in case of acute cervical artery dissection, as angiographic features of both entities can be similar. One series reported a higher rate of recurrence of cervical artery dissection in patients with FMD [16,17]. Finally, some patients hear pulsatile tinnitus or have a cervical bruit on physical examination [5].

Screening for FMD of the cervicocephalic arteries should be considered in case of retinal or cerebral ischemic events, intracranial aneurysms, subarachnoid hemorrhage, cervical or intracranial dissections, or pulsatile tinnitus.

However, it should be kept in mind that none of these symptoms are specific of FMD. In particular, the existence of intracranial aneurysms is not sufficient to establish the diagnosis of FMD.

Fibromuscular dysplasia of other vascular territories

FMD lesions most commonly involve the renal arteries and the extracranial portion of the cervicocephalic arteries. However, involvement of the mesenteric, axillary, iliac, hepatic, intracranial, and, in a few cases coronary arteries has also been reported [1,10]. The frequency of lesions of different vascular beds in an old series from Switzerland [18] and more recent cohorts from France (P.F. Plouin, personal

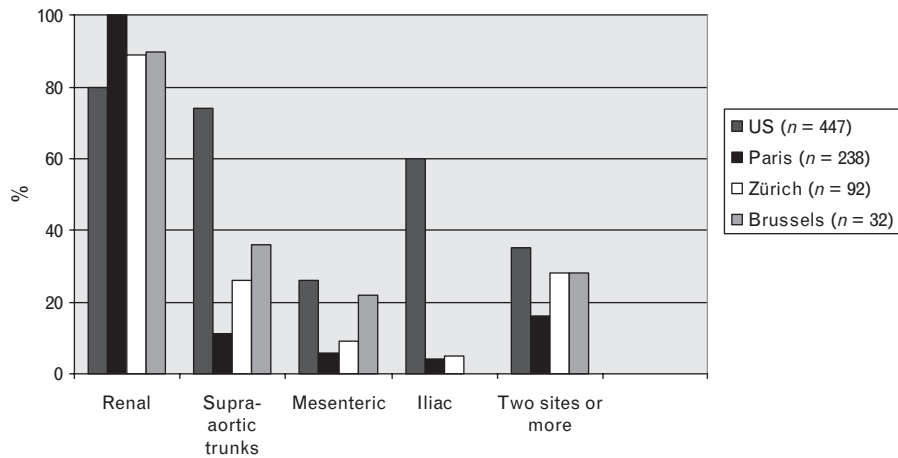


FIGURE 3 Frequency (%) of involvement of different vascular beds and of multiple-site involvement in series of patients with fibromuscular dysplasia (FMD) from the US registry (5) and cohorts of FMD patients from Paris (Hôpital Européen Georges Pompidou, P.-F. Plouin, personal communication), Zürich (15), and Brussels (16). The percentages provided for the three European cohorts correspond to the proportion of patients in whom FMD lesions of each vascular bed were found. As not all vascular beds were imaged in all patients and different imaging methods were used, the percentages may correspond to an underestimation. By contrast, the percentages provided in the US registry (5) correspond to the ratio of patients with FMD lesions of the corresponding vascular beds to the number of patients imaged for these vascular beds. This may lead to a substantial overestimation in some cases, as imaging of rarely involved vascular beds was targeted according to symptoms. In particular, imaging of lower limbs was performed only in a minority of patients ($n=70$), mostly in presence of claudication. In addition, for the US registry (5), the column 'supra-aortic trunks' refers to extracranial carotid artery involvement. The corresponding percentage for vertebral arteries was 36.6% (adapted from ref [6]).

communication) Unites States [5], and Belgium [19] are indicated in Fig. 3. In these series, the prevalence of FMD lesions affecting two or more vascular beds was in the range of 16–35%. These figures are likely underestimated and biased by indication, as vascular investigations were neither systematic nor standardized for all vascular beds. Notably, although FMD of the renal artery was usually considered as the most frequent localization of the disease, in the US registry [5], the prevalence of FMD of the renal arteries and that of FMD of the extracranial carotid arteries were similar (79.7 and 74.3%, respectively). As expected, the most frequent association was that of renal and cervicocephalic FMD [18,19].

In addition to the usual angiographic features of cervicocephalic FMD, patients with renal artery FMD often show abnormal echographic patterns at the common carotid artery, a site that is usually not affected by macroscopic FMD lesions [1,20]. This observation, made using high-resolution echotracking, suggests that arterial abnormalities without concomitant clinical or angiographic manifestations are common during the course of FMD.

In view of these elements, it appears appropriate to screen for cervicocephalic FMD in patients with renal FMD and vice versa, provided there are arguments that identification of lesions in the second vascular bed could modify management. In particular, in patients with renal artery FMD, screening for asymptomatic cervicocephalic lesions may help to establish the diagnosis of FMD, and have practical implications in cases of intracranial aneurysm (see *infra*). Conversely, screening for renal FMD in hypertensive patients with cervicocephalic FMD may lead to revascularisation of an FMD-related RAS.

In patients with renal artery FMD, it is recommended to screen for asymptomatic cervicocephalic lesions, if it is likely that identification of lesions will alter future management.

Hypertensive patients with cervicocephalic FMD should be screened for renal FMD.

FMD stenotic lesions of the mesenteric territory may cause nausea, postabsorptive abdominal pain suggesting ischemia, and weight loss. Severe forms have been reported in a few cases [13,21]. Some cases of claudication of the upper or lower limbs have been associated with FMD in the subclavian or aortoiliac arteries. An abdominal bruit in a patient without apparent atherosclerosis should also alert the physician on the possibility of FMD.

In patients with renal artery and/or cervicocephalic FMD, screening of other, less often involved vascular beds should be considered in presence of suggestive symptoms or medical history.

Fibromuscular dysplasia in patients with spontaneous coronary artery dissection

Spontaneous coronary artery dissection (SCAD) is a rare cause of acute coronary syndrome usually affecting young women without coronary risk factors [22]. Recently, Saw *et al.* [23] reported six cases of concomitant renal FMD. Toggweiler *et al.* [24] identified FMD lesions of renal arteries in three of 12 patients with SCAD. In a retrospective cohort of 87 patients diagnosed with SCAD, FMD of iliac ($n=8$) and carotid ($n=2$) arteries was incidentally found in 11% of patients [25]. Finally, in a prospective cohort of 50 patients with SCAD, Saw *et al.* [26] identified lesions of FMD in at least one extracoronary vascular bed in 86% of cases, and at least two vascular beds in 42% of cases. This association suggests that SCAD may result from weakening of the vessel wall by underlying coronary FMD lesions [27]. Irrespective of the mechanism, existing data are convincing enough to

advise screening for FMD of the renal, iliac and cervicocephalic vascular beds in all patients with suspected or diagnosed SCAD, especially in case of HTN or other suggestive symptoms.

Screening for FMD of the renal, iliac and cervicocephalic arteries is also recommended in case of spontaneous coronary artery dissection, particularly in presence of HTN or other suggestive symptoms.

Screening for intracranial aneurysms

Renal artery aneurysms were identified in four of 716 (0.6%) potential kidney donors, all four presenting with lesions suggestive of FMD [28]; furthermore, 12 of 125 (9.6%) patients with symptomatic renal artery FMD also had renal artery aneurysms [8].

Similarly, the prevalence of intracranial aneurysms in patients with cervicocephalic FMD was estimated to be 5.1–9.5% [29], that is, higher than in the general population. The ad-hoc committees of the AHA Stroke Council Guidelines [14] recommend that magnetic resonance angiography (MRA) of the head should be performed in all patients with cervical FMD.

An association between renal artery FMD and cerebral aneurysm was also documented [30]. However, there are no data on the prevalence of this association.

Algorithms for the treatment of unruptured intracranial aneurysms have been proposed, taking into account factors such as the size of the aneurysm and its location, as well as the patient's preferences [31]. A recent review showed that age, HTN, history of SAH, aneurysm size, aneurysm location, and geographical region were the main predictors of rupture [32]. However, randomized controlled trials are still lacking, and no study has been specifically devoted to the management of FMD-related aneurysms.

Patients with cervicocephalic FMD should be screened for intracranial aneurysm, if it is likely that identification of intracranial aneurysm(s) would modify management.

Screening for fibromuscular dysplasia in first-degree relatives

No systematic imaging screening has been performed in family members of patients with renal or cervical FMD. However, a retrospective analysis of 104 patients with renal artery FMD revealed that 11% had familial FMD, as documented by a history of renal artery FMD lesions detected by arteriography in at least one other first-degree family member [33]. In cases of hereditary FMD, renal artery lesions were usually multifocal and more often bilateral compared with sporadic FMD cases. Furthermore, a familial resemblance was observed in 47 relatives of 13 FMD cases using high-resolution echotracking of the carotid artery as a surrogate marker for the disease and segregation analysis was compatible with an autosomal dominance of the trait [34]. Finally, in the first report of the US FMD registry including 447 patients [5], the existence of at least

another relative affected with FMD was reported in 7.3% of cases.

Conducting FMD screening among asymptomatic relatives of a patient with established FMD remains a research topic. However, if the relative is symptomatic, that is, if she or he has early-onset or resistant HTN or unexplained neurological symptoms, the presence of FMD within the family may provide an etiological clue.

It is recommended to ask a patient with FMD about history of early-onset HTN, dissection, aneurysms, or cerebral hemorrhage among his or her first-degree relatives. If there is a positive answer to at least one of these questions, the patient may inform the respective relative(s) about the possibility of hereditary FMD.

Diagnosis of fibromuscular dysplasia

Renal artery fibromuscular dysplasia

Duplex ultrasound

Duplex ultrasound (DUS) is time-consuming, highly operator-dependent, and less sensitive than CT-angiography (CTA) and MRA for detecting atherosclerotic [10,14] and FMD-related [10] artery lesions, especially of accessory or polar arteries. Much difficulties arises in obese patients or in those who cannot hold their breath. However, DUS is widely available, less expensive, nonirradiating and can be more easily repeated than other imaging tests. Furthermore, in addition to the location of RAS, DUS provides information about the hemodynamic impact of the stenosis [35,36], kidney size, and associated renal disease. Therefore, it remains a reasonable first-line screening technique (Fig. 4).

When there is a clinical suspicion of RAS, duplex ultrasound remains a reasonable first-line screening test to detect RAS in most cases. However, the results should be confirmed by another imaging technique:

1. in the case of positive findings;
2. in the case of negative results despite a high clinical suspicion.

CT-angiography and MR-angiography

CTA and MRA display a good sensitivity and specificity in detecting renal artery FMD [37,38], especially of the multifocal subtype [39] and are thus the recommended imaging techniques to confirm the diagnosis. They can also be considered as a screening test when the results of DUS are expected to be suboptimal (obese patients, apnea difficult or impossible, low echogenicity, or poor local expertise), especially if the degree of clinical suspicion is high (Fig. 4) and in few severe cases in which the diagnosis cannot be overlooked (very young age, malignant or complicated HTN, complications in another territory, increase in plasma creatinine). However, they are less accurate for quantification of the degree of stenosis and do not provide information on its hemodynamic impact.

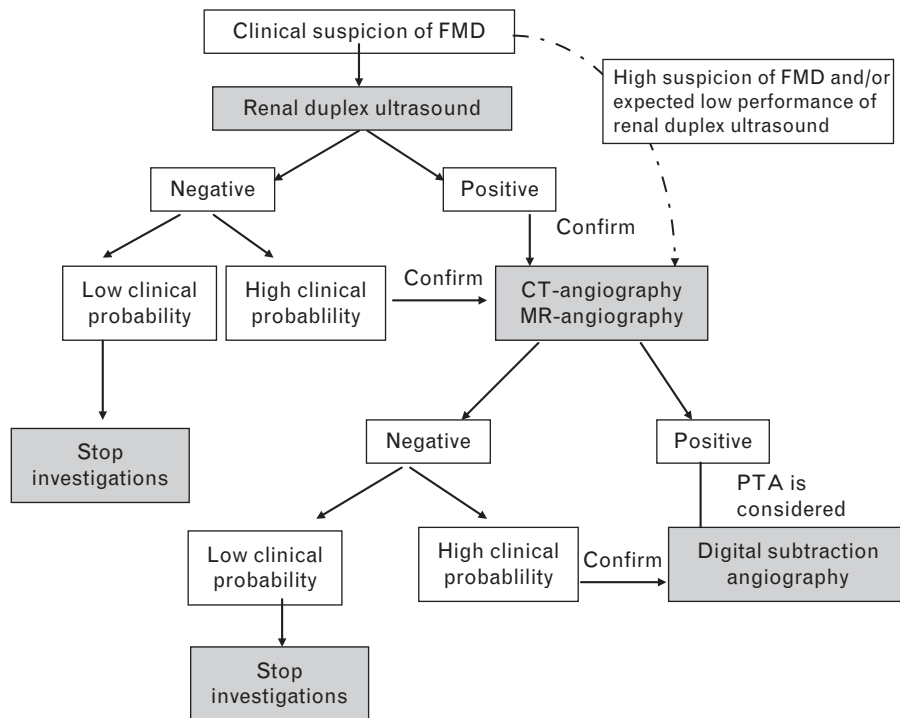


FIGURE 4 Proposed algorithm for establishing the diagnosis of fibromuscular dysplasia (FMD) of the renal arteries. Renal duplex ultrasound remains a reasonable first-line screening test to detect renal artery stenosis in most cases. However, CT-angiography or MR-angiography are recommended as first screening test when the results of renal duplex are expected to be suboptimal (obese patients, apnea difficult or impossible, low echogenicity, or poor local expertise) and/or when the degree of suspicion is high or the diagnosis of FMD would have major clinical implications (very young age, malignant or complicated hypertension, complications in another territory, increase in plasma creatinine). CT-angiography is preferable to MR-angiography because of its higher spatial resolution, especially for distal lesions. In practice, the choice between CTA and MRA will take into account local expertise, individual risk of nephrotoxicity and irradiation, and patients' preference. CTA, CT-angiography; MRA, MR-angiography; PTA, percutaneous transluminal angioplasty (adapted from ref [6]).

CTA has a better spatial resolution than MRA [39,40], especially for distal lesions, [41] and can visualize small calcifications, providing a better discrimination of atherosclerotic vs. FMD lesions in older patients, and may thus be preferred to MRA. However, it has the disadvantage of exposing patients to irradiation, nephrotoxicity, and allergic reactions to iodinated contrast medium.

MRA has slightly less spatial resolution than CTA [40–42], may lead to stenosis overestimation [27], and occasionally show an aspect of pseudobeading, falsely suggestive of multifocal FMD [10]. Gadolinium used for MRA has less renal toxicity than iodinated contrast, but was occasionally associated with catastrophic nephrogenic systemic fibrosis in patients with severe renal insufficiency [43,44].

In practice, the choice between CTA and MRA will take into account local expertise, individual risk of nephrotoxicity and irradiation, and patients' preference.

MRA or preferably CTA are the recommended imaging techniques to confirm the diagnosis of renal artery FMD. They are also recommended as first-line screening test:

1. When the results of DUS are expected to be suboptimal (obese patients, apnea difficult or impossible, low echogenicity, or poor local expertise)
2. When the degree of suspicion of FMD is high and/or a diagnosis of FMD would have major clinical implications (very young age, malignant or complicated HTN, complications in another territory, increase in plasma creatinine)

Renal scintigraphy

Quantification by renal scintigraphy is based on the detection of asymmetric renal plasma flow at baseline or after administration of a single oral dose of captopril and applies particularly to unilateral RAS. However, the kidneys are often asymmetric in patients with essential HTN [45], and FMD-related RAS is often bilateral [1]. According to the AHA guidelines [14], renal scintigraphy is no more considered for the diagnosis of RAS. We did not identify a scintigraphic study specifically dedicated to FMD. For the aforementioned reasons, renal scintigraphy has little room in the diagnosis of FMD-related RAS and was not included in the proposed algorithm.

Digital subtraction angiography

Renal digital subtraction angiography (DSA) is the gold-standard technique for imaging the site and morphology of FMD, although the estimate of RAS is quite variable among different operators [46,47]. A global aortic angiography should initially be obtained for diagnosis purposes, evaluation of the extent of the renal artery lesions, visualization of the two nephrograms and detection of renal embolic complications, and artery dissection or infarction in delayed sequences. It may also allow detection of FMD in other visceral arteries.

As FMD is associated with spontaneous dissections [2], the risk of renal artery dissection may be increased. However, as FMD lesions are usually distal, they are probably unaffected by DSA. Thus, in patients with FMD, the risk of the procedure is probably low. Nevertheless, it is

recommended to reserve DSA for patients in whom performing a simultaneous PTA is justified.

Renal DSA is also advised in the case of a high clinical suspicion of FMD-related stenosis, when the diagnosis remains uncertain after performing noninvasive tests [14] (Fig. 4).

It is recommended to perform renal DSA:

1. in cases of FMD confirmed by CTA or MRA, provided revascularization is medically justified
2. in cases of high clinical suspicion of FMD-related stenosis when the diagnosis remains uncertain after performing noninvasive tests

Fibromuscular dysplasia of the cervicocephalic arteries

Thus far, no study has compared the performance of non-invasive tests with DSA for the diagnosis of cervicocephalic FMD. DUS may reveal an irregular stenosis of the carotid or vertebral arteries compatible with FMD. However, CTA and MRA are likely to perform better, especially because FMD usually affects the middle and distal portions of the carotid and vertebral arteries, which are less accessible to DUS [10]. Moreover, CTA and MRA have the advantage to allow the detection of associated intracranial aneurysms.

MRA or CTA are the recommended techniques to establish the diagnosis of FMD of the cervicocephalic arteries and to detect associated intracranial aneurysms. Cervical artery DSA may be indicated in case of atypical clinical presentation and in patients who may require endovascular therapy.

Fibromuscular dysplasia of other vascular territories

In patients with mesenteric or limb ischemic symptoms, the corresponding vascular beds should be explored by DUS or preferably CTA to detect FMD lesions [48]. Although this strategy was recommended for detecting atherosclerotic stenoses, it can be logically extrapolated to the rarer cases in which dysplasia-induced stenosis is suspected.

Diagnosis of significant stenosis

The definition and best way to diagnose a hemodynamically significant stenosis are still controversial issues, especially for multifocal FMD. Some elements of discussion are provided below. For a more detailed discussion, please refer to the online supplement of the Belgo-French consensus [6].

Renal artery fibromuscular dysplasia

Usually, revascularization of FMD lesions is considered only if there are arguments in favor of a hemodynamically significant stenosis, that is, responsible for downstream reduction of renal artery flow and subsequent renal ischemia, activation of the renin–angiotensin system, and renovascular HTN. Although of the utmost practical importance, the diagnosis of significant RAS in humans remains elusive, especially in patients with FMD.

The threshold proposed by the AHA [49] and European Society of Cardiology [50] to confirm the existence of a hemodynamically significant RAS is a decrease in renal artery luminal diameter of at least 60% [49], which corresponds to an 80% reduction of the luminal surface area. This applies to both atherosclerotic and unifocal FMD-induced RAS, which are generally localized to a short segment of the renal artery. In contrast, assessment of luminal diameter reduction is imprecise in multifocal FMD, owing to the frequent absence of a normal reference renal artery segment and the difficulty in visualizing precisely and quantifying string-of-beads diaphragmatic stenoses. Furthermore, given a similar reduction in the luminal diameter, the downstream hemodynamic consequences may be less or more severe according to the length of the FMD lesions and the number of diaphragms. The quantification of multifocal FMD-related RAS is therefore particularly difficult [8,10].

Renal scintigraphy and/or measurement of plasma renin activity or concentration in renal veins before and after captopril are no more recommended in the assessment of RAS, in view of their poor diagnosis performance in bilateral RAS [14], which is often the case for FMD [1]. Transstenotic gradient measurements may help to localize the hemodynamic obstacle. However, the significance of such measures is unclear because of high intrarenal resistances frequently observed in this setting, which also depend on the duration of HTN and glomerular filtration rate [51,52]. Indirect radiological signs such as whole lesion length, number of diaphragms or pseudoaneurysms, the presence of a collateral circulation or a jet image, or small downstream kidney, may all be taken into account. However, these criteria are poorly defined and not based on consensus.

Fibromuscular dysplasia of the cervicocephalic arteries

A cervicocephalic stenosis can be considered significant, if it leads to downstream ischemic consequences. For atherosclerosis, a threshold of 50–70% is generally accepted [53]. As in atherosclerosis, techniques assessing cerebral perfusion, such as transcranial DUS, MRA, or cerebral scintigraphy can be used. However, the prognostic value of potential abnormalities in the context of FMD has not been established.

PREVENTION

Savard *et al.* [54] analyzed a retrospective series 337 patients diagnosed with FMD.

The proportion of current smokers was significantly higher in patients with FMD than in matched controls (30 vs. 18%; $P < 0.001$). Furthermore, among patients with multifocal FMD, HTN and FMD were diagnosed earlier in current smokers, and smokers had a greater likelihood of renal artery interventions and kidney asymmetry than non-smokers. Although a causal relationship cannot be formally established, these findings suggest that smoking maybe associated with a more aggressive course of the disease. Accordingly, it appears appropriate to encourage strongly smoking cessation in patients with FMD.

Smoking cessation should be strongly encouraged in patients with FMD. Patients should enter a smoking cessation program using all the available means according to the guidelines for smoking cessation [55].

TREATMENT

There are no randomized controlled studies comparing revascularization to medical treatment only, or revascularization by PTA to surgical revascularization in patients with FMD. Usually, revascularization is considered in cases of symptomatic FMD (renovascular HTN for renal FMD, ischemic symptoms for FMD in other vascular beds). In the absence of evidence-based recommendations, the best therapeutic option should be discussed within a multidisciplinary team including clinicians (HTN specialists, internists, nephrologists, neurologists, cardiologists), interventional radiologists or cardiologists trained in peripheral interventions, and vascular surgeons with experience of FMD management.

Revascularization of FMD-related lesions is recommended only in cases of symptomatic FMD with direct or indirect signs of organ ischemia downstream of the lesion. The therapeutic decision should take into account the symptomatology, the type, localization and extent of the arterial lesions, the presence of associated aneurysms in the same or other territories than the primary lesion, the experience of the center, as well as the age and preferences of the patient. It should be performed by a multidisciplinary team with an extensive experience of the disease.

Renal artery fibromuscular dysplasia

Indications of revascularization

In contrast with atherosclerotic RAS, HTN cure is fairly common following revascularization of FMD-related RAS (30–50% according to the definition of normotension) [3]. In addition, in the absence of associated risk factors or atherosclerotic lesions, patients with FMD-related RAS do not require any cardiovascular or renal prevention once HTN has been cured. As shown by a recent meta-analysis [3], recovery rates are higher in younger patients (Fig. 5), those with more recent onset of HTN and in unifocal FMD compared with multifocal FMD.

Therefore, it appears appropriate to propose revascularization in hypertensive patients with FMD-related RAS, especially if HTN is of recent onset or in case of drug-resistant HTN. By contrast, in FMD without HTN and with normal renal function, the value of revascularization has not been established [1,53]. However, if there is a downstream reduction in renal size exceeding 10 mm during two successive examinations by DUS, CTA or MRA (excluding a congenital asymmetry in kidney size), revascularization may be justified as well [56].

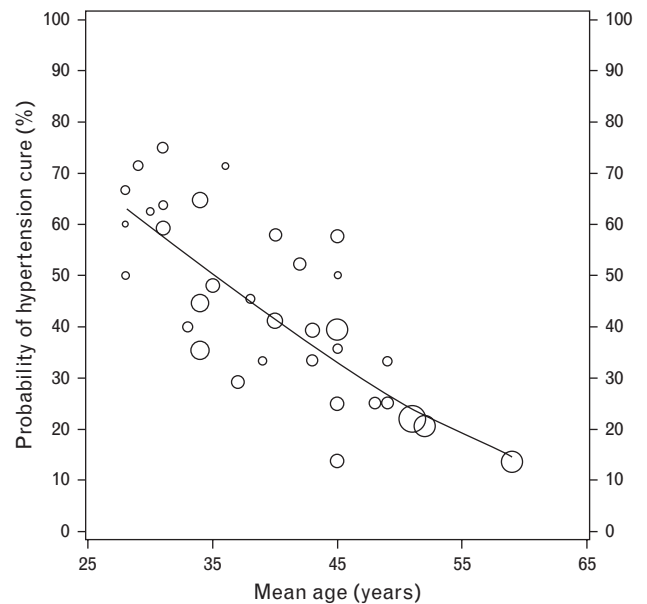


FIGURE 5 Meta-regression analysis assessing the relationship between the hypertension cure rate following percutaneous angioplasty and mean age (adapted from ref. [3]).

In hypertensive patients with FMD-related RAS, revascularization is recommended:

1. in the case of HTN of recent onset, as a first-line treatment to normalize blood pressure
2. in cases of medical treatment failure (drug resistance or intolerance)
3. in case of renal insufficiency or deterioration of renal function especially after administration of an angiotensin converting enzyme inhibitor, an angiotensin II receptor blocker or a renin inhibitor
4. in case of renal size reduction downstream of the stenosis.

The two options available for renal artery revascularization are balloon PTA and renal artery surgery. It is impossible to reliably compare the results of both revascularization techniques because they are not performed in patients with similar characteristics. Furthermore, surgical revascularization has been performed for a longer time than PTA revascularization, and the assessment methods therefore also differ in series using surgery or PTA.

In view of its less invasive character and of the large experience acquired, PTA without stenting is currently the first-line revascularization technique in FMD-related RAS. Indeed, there is no evidence of superiority of renal artery PTA followed by stenting vs. PTA alone in FMD patients. Furthermore, several cases of stent fracture have been reported in patients with renal FMD [57], possibly owing to an increased kinetic stress related to severe kidney ptosis [57,58]. Accordingly, stenting is not indicated after primary PTA unless needed because of a significant per-procedural dissection [57]. It may also be considered in case of PTA failure [57], in the absence of vascular surgeon with expertise in FMD.

Surgery remains the primary approach for patients with complex lesions of arterial bifurcation or branches, stenoses associated with complex aneurysms, or following PTA failure [4,7,59]. A second PTA may be attempted following PTA failure, but a third PTA is not recommended so as to prevent arterial trauma, which could jeopardize surgical results [60].

Cutting balloons, proposed by some authors as an alternative to surgery in case of PTA failure [61,62], are not recommended in patients with FMD because of the risk of renal artery rupture [63–65] and subsequent pseudoaneurysm formation [66].

In patients with significant FMD-related RAS, renal PTA is the first-line revascularization technique. Stenting following PTA is not recommended, unless needed because of a per-procedural dissection.

In patients with significant FMD-related RAS, surgery should be considered in the following cases:

1. Stenosis associated with complex aneurysm(s)
2. Restenosis despite two unsuccessful attempts of PTA
3. Complex lesions of arterial bifurcation or branches (rare)

Fibromuscular dysplasia of the cervicocephalic arteries

FMD of the cervicocephalic arteries has a good long-term prognosis, and its presence alone should thus not be considered as an indication for prophylactic surgery. The situation is more complex for symptomatic lesions. The risk of recurrence with medical treatment alone is probably low. Furthermore, the causal role of carotid FMD in case of neurological symptoms is difficult to establish in some patients, especially with cardiac source of embolism or concomitant atherosclerosis. Some symptoms, which are not threatening but debilitating, such as pulsatile tinnitus, may be considered as an indication for revascularization. Endovascular approaches are less invasive than surgery. However, there are no large case-series and no randomized trials. Thus, indications of revascularization are mainly based on individual decisions and patient's preference [2].

It is recommended to revascularize only symptomatic carotid FMD lesions. The indication should take into account the severity of symptoms, the causality of the relation between lesions and symptoms, the experience of each center, and the patient's preferences.

Fibromuscular dysplasia of other territories

FMD lesions of other sites are rarely symptomatic. For symptomatic stenoses of digestive or limb arteries, the first-line treatment is usually PTA.

FOLLOW-UP

In the absence of revascularization

Renal artery fibromuscular dysplasia

If renal artery revascularization is not considered, because the RAS is not deemed hemodynamically significant, the patient declines intervention or for other reasons, the duration of clinical (monthly blood pressure measurements until target blood pressure values are reached, then every 3 months) and biological (annual monitoring of plasma creatinine) follow-up is indefinite, as for any HTN with renal involvement [67]. Slovut and Olin [10] also recommend annual DUS monitoring of kidney length. This may be especially useful in cases of bilateral or unifocal FMD, which are more likely to progress [68,69]. In the latter, indefinite ultrasound monitoring is probably useful. Failing that, an annual surveillance for 2 years, reconducted in cases of blood pressure or creatinine elevation, is acceptable.

If revascularization does not seem justified in renal artery FMD patients with HTN, clinical (monthly blood pressure measurements until target blood pressure values are reached, then at regular intervals) and biological (annual assessment of plasma creatinine) monitoring is recommended, as well as monitoring of kidney length (annual DUS).

Fibromuscular dysplasia of the cervicocephalic arteries

In asymptomatic cervical and intracranial artery FMD, an annual check of cervical and intracranial vessels (MRA and DUS, followed by CTA if necessary) is recommended. In the absence of lesion progression, the frequency of imaging may be decreased.

In FMD diagnosed after an ischemic cerebral event, a new arterial evaluation is usually necessary approximately 3 months after diagnosis in case of acute dissection and after 6 months, in the absence of dissection, and then annually (MRA and DUS, followed by CTA if necessary). In the absence of lesion progression, monitoring visits may occur less frequently.

In symptomatic FMD revealed by meningeal hemorrhage, no specific recommendation exists. Aneurysm follow-up options depend on the specific primary treatment implemented. Other FMD lesions are checked on an annual basis. In the absence of progression, monitoring visits may occur less frequently.

After revascularization

Renal artery fibromuscular dysplasia

An early assessment at 1 month allows antihypertensive treatment to be adjusted, often by reducing doses or discontinuing treatment. As restenoses mostly occur within the first 6 months [70], it is recommended to perform a DUS within this period. This check is performed before 6 months in case of blood pressure or plasma creatinine elevation. If the 6-month follow-up is satisfactory, subsequent

monitoring is similar to that of FMD without significant stenosis.

Blood pressure and renal function should be checked at 6 months and at regular intervals thereafter. Not infrequently, blood pressure may rise again after that period, necessitating drug adaptation [71].

After revascularization of FMD-related RAS, it is recommended to measure blood pressure and estimate glomerular filtration rate at 1 month and to check renal imaging at 6 months, or earlier in case of blood pressure or plasma creatinine elevation.

Fibromuscular dysplasia of the cervicocephalic arteries

Arterial imaging by MRA, CTA, or DUS is usually performed in the days following the intervention, then again at 3–6 months. The arterial imaging technique used depends on the revascularization approach (surgery or PTA). The frequency of follow-up visits may be similar to that of nonrevascularized FMD, also depending on postoperative evolution. Usually, after aneurysm embolization, noninvasive imaging by CTA is recommended every 5 years.

PERSPECTIVES

One of the major aims of current research is to identify the genetic and environmental factors involved in the pathogenesis, progression, and clinical spectrum of FMD. In addition to this candidate gene studies, which have proven disappointing thus far [1], nonhypothesis-driven strategies such as genome-wide association studies performed in large discovery and replication cohorts and whole exome sequencing in selected familial, severe, early-onset cases, may contribute to unravel the genetic determinants of the disease. Environmental factors, including tobacco and hormones, and possible gene–environment interactions also need further evaluation.

Additional research efforts should be devoted to accurate assessment of the risk of disease progression, extension to other vascular beds, and occurrence of complications such as vessel dissection or aneurysms; identification of the disease subtypes more likely to progress; and definition of an evidence-based screening and follow-up algorithm. To achieve these objectives, a research program combining imaging techniques, noninvasive vascular evaluation, new biomarkers of vascular smooth muscle cell dysfunction, inflammation, fibrosis, and genetic markers is currently underway.

Other important research aims include improvement in the detection and quantification of FMD-related RAS for diagnosis, therapeutic, and prognosis purposes. The latter may include evaluation of the relative performance of intravascular ultrasound, optical coherence tomography, trans-stenotic pressure gradient, and fractional flow reserve. Several projects exploring these topics are already in progress.

A common prerequisite of most of these investigations is to collect systematically and prospectively all FMD cases

into national and international registries such as the ongoing French [4] and US [5] registries, which further highlights the need for standardized clinical practice and research coordination at the European level and beyond.

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Conflicts of interest

There are no conflicts of interest.

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