

## Revisiting Fibromuscular Dysplasia Rationale of the European Fibromuscular Dysplasia Initiative

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### • Online Data Supplement

Fibromuscular dysplasia (FMD) has been defined as an idiopathic, segmental, nonatherosclerotic, and noninflammatory disease of the musculature of arterial walls, leading to stenosis of small- and medium-sized arteries.<sup>1,2</sup> Furthermore, to confirm the diagnosis of FMD, arterial diseases of monogenic origin, inflammatory arterial diseases, and the use of arterial vasoconstrictors have to be excluded. Renal FMD may lead to renovascular hypertension, less frequently renal artery dissection, renal infarction, and aneurysm rupture.<sup>1</sup> Cervico-cephalic FMD can result in ischemic or hemorrhagic stroke, cervical artery dissection, and may be also associated with intracerebral aneurysms and risk of subarachnoid hemorrhage.<sup>3</sup> 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.<sup>1</sup>

The French<sup>4-6</sup> and the US<sup>7-10</sup> registries have led to a reappraisal of the frequency, demographic characteristics, classification, pathophysiology, and management of FMD. The face of the disease is evolving from a rare disease of renal arteries accounting for a minority of cases of secondary hypertension in young women to a “systemic” vascular disease affecting renal and also cervico-cephalic, coronary, and iliac arteries<sup>1,11</sup> (Table 1). In various cohorts, despite incomplete exploration, mostly driven by symptoms and clinical complaints, FMD of  $\geq 2$  vascular beds was consistently found in  $>30\%$  of cases.<sup>1,7,12,13</sup> The French ARCADIA (Assessment of Renal and Cervical Artery Dysplasia) registry, which required a standardized vascular work-up in all patients, will soon provide

a more precise estimate of the frequency of diffuse FMD. Besides female sex and repeated mechanical trauma because of increased kidney mobility,<sup>14</sup> recent works suggest a contribution of smoking<sup>5</sup> in progression of the disease, as well as a genetic susceptibility.<sup>15,16</sup> High-resolution cardiac echo-tracking,<sup>17</sup> mechanistic,<sup>18</sup> biochemical, and genetic studies<sup>15,16</sup> will soon lead to a better understanding and classification of the disease. Furthermore, registries should help to identify characteristics of patients likely to develop extensive, progressive, or complicated forms of FMD.

Progresses in the understanding of the disease and research perspectives have been extensively reviewed on the occasion of the First National Meeting on Fibromuscular Dysplasia, endorsed by the European Society of Hypertension, which took place in Brussels on December 12, 2015, (<http://www.saintluc.be/professionnels/agenda/2015/2015-12-12-fibromuscular-dysplasia.pdf>), and summarized for an expert audience on the occasion of the 10th International Workshop on Structure and Function of the Vascular System (Paris, February 4–6, 2016). This short review covers the highlights of these meetings and provides the rationale for the European FMD initiative (see list of centers currently involved in the [online-only Data Supplement](#)).

### Renal FMD

Renal FMD has been for long considered a rare disease with an estimated prevalence of  $\approx 0.02$ – $0.08\%$ .<sup>2</sup> However, recent data suggest that FMD is much more common. A meta-analysis based on kidney donor data found renal FMD in 4% of the potential kidney donor population.<sup>19,20</sup> Along the same

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**Table 1. Five Things All Physicians Should Know About Fibromuscular Dysplasia (FMD)**

Data from kidney donor studies suggest that the prevalence of FMD has been substantially underestimated.
In current cohorts, the mean age at diagnosis of FMD is >50 y.
FMD is more frequent in young to middle-aged women, but may be also diagnosed in men, and at all ages of life, from infancy to the elderly old.
FMD is a systemic disease with frequent involvement of multiple vascular beds, including but not limited to renal and cervico-cephalic arteries.
FMD can be associated with spontaneous coronary artery dissection (SCAD).
FMD has a hereditary component, and the first susceptibility genes are currently being identified.

lines, in the CORAL trial (Cardiovascular Outcomes in Renal Atherosclerotic Lesions), where FMD was an exclusion criteria, the prevalence of FMD was 5.8%.<sup>20</sup> Three main histopathologic types of renal FMD have been described according to the arterial wall involved, that is, intimal FMD (5%), medial FMD (>85%), and perimedial FMD (10%).<sup>21</sup> However, nowadays, as few cases of FMD require surgery, and pathological documentation is lacking, this classification has become largely obsolete. Based on pathological–angiographic correlations, Kincaid proposed 3 types of renal artery FMD: multifocal (string-of-beads appearance), unifocal (solitary stenosis <1 cm in length), and tubular (stenosis at least 1 cm in length) FMD.<sup>22</sup> As the 2 last categories differ only by the length of the diseased segment, Savard et al have proposed to group them under the generic term "unifocal."<sup>4</sup>

Hypertension of variable severity is the most common clinical presentation of FMD. Occasionally, an epigastric or flank bruit at physical examination can also lead to the diagnosis. Flank pain may be a manifestation of renal artery dissection or aneurysm. FMD-associated arterial aneurysms at any location have been reported in 17% (33% in renal artery) and dissections in 19.7% (22% in renal artery) of patients in the US registry.<sup>7</sup> Renal insufficiency is uncommon and often due to renal artery dissection and renal infarction. Progression to end-stage renal disease is very rare.

The diagnosis of renal FMD can be made by using non-invasive imaging studies, including duplex ultrasonography, and angiography by computed tomography or magnetic resonance. However, the gold standard remains catheter-based angiography.<sup>23</sup> In equivocal cases, intravascular ultrasound and pressure measurements can help to assess the hemodynamic significance of a stenosis and the anatomic success after percutaneous intervention.<sup>1</sup>

The treatment of patients with renal FMD may include medical therapy with surveillance, endovascular therapy (angioplasty without stenting), or surgery. The decision depends on the nature and location of vascular lesions (stenosis/dissection/aneurysm), the presence and severity of symptoms, prior vascular events related to FMD, and comorbid conditions.<sup>1</sup> Medical therapy includes antihypertensive drugs, preferably blockers of the renin–angiotensin system, treatment of other cardiovascular risk factors, and antiplatelet or anti-thrombotic drugs after angioplasty or in case of renal artery

dissection or thrombosis. Hypertension cure after revascularization varies between 30% and 50%. The younger the patient, the more recent the hypertension, the higher the cure rate. The rate of success is also higher in unifocal than in multifocal forms.<sup>1,24</sup> Indefinite, yearly follow-up of blood pressure, kidney function, and kidney length appears appropriate.<sup>1,25</sup>

### Cerebrovascular FMD

FMD of the carotid and vertebral arteries has long been considered less frequent than renal FMD, but recent observational studies and registries<sup>3,7</sup> suggest that the prevalence of both entities may be similar. Furthermore, renal and cervical FMD frequently coexist, with a prevalence of 65% of carotid FMD lesions in patients with renal FMD according to the US registry.<sup>7</sup> Though interventional treatment is only seldom required, detection of cervical FMD has implications for the patients as it may help to improve primary and secondary prevention of cerebrovascular events and lead to the diagnosis of FMD of renal or other vascular beds.<sup>1</sup> The main circumstances of diagnosis of cervico-cephalic FMD include incidental diagnosis, screening in patients with renal FMD, pulsatile tinnitus, cervical artery dissection, cerebral ischemia, subarachnoid hemorrhage, unruptured intracranial aneurysm, and rarely arterio-venous fistula or Moyamoya syndrome.<sup>3</sup> Another symptom frequently associated with cerebrovascular FMD in the US FMD registry<sup>7</sup> is headache (60% of patients, with 32% reporting classical migraines). This finding is in agreement with previous reports, also discussed by Olin et al.<sup>7</sup> However, in the absence of demonstrated causal link between both entities, the association of migraine with cervico-cephalic FMD may partly reflect an exploration bias as up to 25% of females experience migraines during their life,<sup>26</sup> which may lead to cerebrovascular imaging and incidental finding of FMD lesions. FMD of supra-aortic trunks has been also associated with the presence of arterial tortuosities.<sup>27</sup> In the US FMD registry,<sup>7</sup> ischemic stroke was reported in ≈10% of patients and transient ischemic attack in ≈20%. Ischemic symptoms are due either to a thromboembolic mechanism or to hemodynamic compromise of the distal circulation. FMD is also associated with first ever, multiple and recurrent cervical artery dissection.<sup>3</sup> Coexistence with atherosclerotic lesions is common, especially in cases diagnosed after 50 years.

In contrast with cervical FMD, intracranial FMD is very rare and usually corresponds to an extension of the extracranial disease. However, the prevalence of the disease may be underestimated as diagnosis of minor form or unifocal forms of FMD is challenging. Moreover, intracranial aneurysms, sometimes multiple, are common (≈6%) in FMD patients.<sup>28</sup> While the classification of FMD in multifocal and unifocal forms<sup>4</sup> also applies to cervical FMD, an atypical form of FMD characterized by the presence of a diaphragm at the origin of the internal carotid (bulb) has been described in young patients of African descent with stroke.<sup>29</sup> So far, all pathologically confirmed cases were intimal FMD.<sup>29</sup> Whether this subtype corresponds to the same disease as "classical" unifocal or multifocal FMD is still unclear, notably because it has no equivalent in the renal territory.

The natural history of cervical and intracranial FMD is unknown. Old series of patients with cervical FMD found

rates of recurrent stroke/transient ischemic attack in the range of 0% to 5%, but populations are heterogeneous.<sup>3</sup> FMD seems to increase the risk of recurrent cervical dissection,<sup>30,31</sup> but no data exist on intracranial aneurysms.

Carotid duplex is often used as diagnostic test for internal carotid FMD and is a primary tool for surveillance of carotid FMD lesions. Nevertheless, as cervical FMD is often distal, in a substantial proportion of cases, diseased vessel segments may be overlooked by ultrasounds. Furthermore, carotid duplex does not allow detection of associated cerebral aneurysms. Accordingly, the European FMD consensus has recommended magnetic resonance angiography or preferably computed tomographic (CT) angiography as the first-line screening test for cerebrovascular FMD, especially in patients with renal artery FMD.<sup>1</sup> In most cases, treatment of cervicocephalic FMD is conservative, including antithrombotic drugs in patients with cerebral ischemia and control of cardiovascular risk factors (especially smoking). In the absence of specific evidence, the management of FMD-related aneurysms—including endovascular or surgical treatment—does not differ from that of aneurysms of other origin. Rarely, severe stenotic cervical FMD lesions with ischemic or hemodynamic manifestations (pulsatile tinnitus) may require angioplasty stenting.<sup>3</sup>

### Spontaneous Coronary Artery Dissection and FMD

While multifocal FMD lesions of the coronary arteries appear to be exceptional,<sup>32</sup> recent works suggest the existence of a tight link between FMD and another rare vascular disease, spontaneous coronary artery dissection (SCAD). SCAD is caused by dissection or hematoma formation within the vessel media, causing luminal compression and obstruction. The diagnosis of SCAD should be considered in case of acute coronary event occurring in young or middle-aged women with few cardiovascular risk factors. Notably, the age at diagnosis of SCAD is similar to that of FMD—in the range of 50 years—while the female prevalence is even higher (>90%).<sup>33</sup> Intense physical and psychological stress, including childbirth delivery, are well-known triggers, but appear to be less frequent than initially reported.<sup>33</sup> More recently, a frequent association between SCAD and FMD of extracoronary vessels has been demonstrated in several single-center patient series, with prevalence varying from 52% to 86%.<sup>33–37</sup> The largest and best explored series included 168 patients with SCAD, of which 72% had FMD of the renal, iliac, or cerebrovascular arteries.<sup>33</sup> In an earlier series of 50 patients published by the same group, lesions of  $\geq 2$  noncoronary vascular beds were found in 42% of patients.<sup>35</sup> Finally, in another series of 115 patients, 9/40 patients who underwent brain imaging had intracerebral aneurysms.<sup>36</sup> SCAD has been also associated with connective tissue disorders and inflammatory vascular diseases.<sup>36,37</sup> The diagnosis can be established during a coronary angiogram in presence of contrast dye staining of arterial wall with multiple radiolucent lumen (SCAD type 1). However, in many cases, this typical aspect is missing. More often, SCAD may be suspected in presence of smooth narrowing or tortuosity or coronary arteries (type 2) or even mimic atherosclerosis, with focal or tubular stenosis (type 3).<sup>38</sup> The diagnosis of SCAD type 2

and even more so type 3 is difficult, but can be ascertained by intravascular ultrasound or optical coherence tomography showing the presence of hematoma or double lumen.<sup>39</sup>

While SCAD accounts for <0.5% of unselected acute coronary events<sup>40</sup> in women aged <50 years, the prevalence of SCAD was estimated to 5.7% in our retrospective monocentric cases series (n=336),<sup>41</sup> 8.7% in a large French database, including 11 605 patients (10.8% in case of ST-segment-elevation myocardial infarction),<sup>40</sup> and up to 24% in an expert, highly focused Canadian center.<sup>42</sup> While the high prevalence of SCAD in the latter may partly reflect a referral bias, it is clear that SCAD is frequently overlooked due to poor awareness, lack of standardized diagnostic criteria, and absence of optical coherence tomography or intravascular ultrasound. Still, the diagnosis of SCAD is of clinical relevance. Indeed, in contrast with atherosclerosis-related coronary events, management is usually conservative, in view of the high probability of spontaneous healing (>50%) and poor results of percutaneous coronary intervention and coronary artery bypass grafting.<sup>33</sup> Furthermore, as mentioned higher, SCAD may indicate the existence of an underlying vascular disease, usually FMD, and lead to detection of abnormalities of other vascular beds.<sup>1</sup> Whether SCAD results from coronary FMD lesions or reflects the presence of an underlying vascular abnormality common to both entities and whether the noncoronary FMD lesions documented in patients with SCAD have the same pathophysiology as "classical" FMD remain to be clarified.

### Genetics of FMD

The presence of FMD in siblings and twins has been reported as early as the years '60 to '70 of the last century.<sup>43–46</sup> More recently, familial cases of the related SCAD entity have also been documented.<sup>47</sup> In 1980, based on interviews of relatives of 20 index patients with FMD, Rushton suggested an autosomal dominant inheritance of the trait.<sup>48</sup> However, in the absence of vascular imaging in family members, the reliability of these findings is questionable. In a French cohort of 100 index patients, angiographically documented FMD was diagnosed in at least another relative in 11% of cases.<sup>49</sup> Along the same lines, the prevalence of self-reported FMD in relatives was 7.3% (26/354) in the US registry.<sup>7</sup> In 2015, Kiando et al performed the first whole exome study in 7 pedigrees, each of them including at least 2 relatives with demonstrated FMD.<sup>15</sup> Unfortunately, none of the 3971 genes screened showed variation in >3 of the 7 pedigrees under scrutiny, suggesting genetic heterogeneity of the trait.<sup>15</sup>

Another pitfall of familial studies is the risk of misclassifying young relatives of FMD patients without overt FMD lesions as unaffected, while they may in fact harbor the trait, thereby decreasing statistical power to identify susceptibility genes. This difficulty may be partly overcome by the identification of subclinical lesions using high-resolution echographic analysis of the common carotid vascular wall. In the study conducted by Boutouyrie et al,<sup>17</sup> carotid arteries of controls were typically characterized by a double signal corresponding to the blood-intima and media-adventitia interfaces, whereas in FMD patients, an additional interface was often observed, leading to a "triple signal" pattern, either continuous or discontinuous. In other cases,

the blood intima interface itself was discontinuous ("dotted" aspect).<sup>17,50</sup> These abnormalities were incorporated in a score, with the continuous signal corresponding to the highest score (2–7). A score >3 was associated with a sensitivity of 73% and a specificity of 81% for the diagnosis of FMD.<sup>17</sup> Notably, in first-degree relatives of patients with FMD (6 families, 47 relatives), the score was slightly lower than that in index cases (4.17 versus 4.61;  $P=0.01$ ), but much higher than in unrelated controls (2.52;  $P<10^{-5}$ ).<sup>50</sup> Furthermore, segregation analysis was consistent with autosomal dominant inheritance of the trait.<sup>50</sup> Admittedly, however, these findings need further investigation and replication in other cohorts. The triple signal aspect is also found—though less frequently—in some patients with essential hypertension and may be a marker of vascular hypertrophy rather than a hallmark of FMD per se. Still, there is no doubt that the technical advances made in noninvasive arterial imaging should provide further insights into the pathophysiology of FMD, help to correctly classify relatives of FMD patients without overt FMD lesions, and may serve as a surrogate marker in intrafamilial studies.

As far as we know, the clinical,<sup>49</sup> radiological, and histological characteristics of rare familial cases of FMD and of the more common apparently sporadic presentation do not differ. Furthermore, similar scores were found by echotracking in sporadic and familial forms of FMD.<sup>50</sup> Finally, autosomal dominant transmission of echographic subclinical abnormalities<sup>50</sup> suggests that the prevalence of inherited forms may be underestimated due to low penetrance. Accordingly, it may be postulated that there is a continuum between both forms and that, alongside with environmental factors, genetic factors may also contribute to the pathogenesis of apparently sporadic FMD. Earlier case–control studies failed to show an association between FMD and variants of genes coding for components of the renin–angiotensin system<sup>51</sup> and extracellular matrix,<sup>52</sup> including  $\alpha$ -1 antitrypsin.<sup>53</sup> However, a large association study looking for enrichment in gene variants in patients with sporadic FMD compared with controls disclosed a significant association between multifocal FMD and 3 genes coding for muscle proteins (OBSCN, DYNC2H1, and MYLK), one of them (MYLK) also involved in familial thoracic aortic dissection, and a fourth one associated with susceptibility to Moyamoya disease (RNF213).<sup>15</sup> Finally, the first genome wide association study performed in the field has identified a locus on chromosome 6, associated both with FMD and with vascular phenotypes, such as intima–media thickness or arterial wall/lumen ratio.<sup>16</sup> In the future, genetic dissection of FMD may lead to identification of patients at risk of complications deserving a closer follow-up and possibly to targeted therapies, allowing to slow down the progression of the disease.

### Patient's Perspective: The Experience of FMDSA

Though less rare than previously thought, FMD is frequently overlooked, and when the diagnosis is made, management is highly variable and often not evidence-based. Only a limited number of physicians have seen more than a few isolated cases of FMD, and until recently, few researchers were interested

in this condition. As a matter of consequence, the time lag between the first manifestations of the disease and the diagnosis may be long, leading to anxiety, depression, and fear of the unknown. Many patients feel isolated and report that they are not understood, or worse dismissed, not only by medical professionals but also by family and friends. These elements provided the incentive for the foundation of the Fibromuscular Dysplasia Society of American (FMDSA; [www.fmDSA.org/](http://www.fmDSA.org/)) in 2003.<sup>54</sup> Patients found each other on a support group site and shared their frustrations, personal stories, and their perspective of what was lacking in their care. Admittedly, the most severe cases may be over-represented in websites of patient associations and patient-led discussion groups. This may lead to unnecessarily raising the level of alarm of individuals with minimal, stable forms of the disease. However, we feel that these shortcomings do not outweigh the aforementioned advantages of patient groups and remain limited, provided information released is regularly reviewed by an expert medical advisory board.

Initially, the organizers of FMDSA never dreamed that in a decade they would grow to the influential organization they have become and that so many patients in the United States would be getting diagnosed with FMD. Today, through the internet and social media, FMDSA is able to connect with patients, researchers, and organizations from around the world, raising awareness and funding and helping to educate medical professionals. Among other achievements, FMDSA was successful in obtaining recognition of FMD by the National Organization for Rare Diseases and for getting the National and American Stroke Associations to recognize FMD as a cause of stroke. One of its greatest accomplishments is the United States Registry for FMD, coordinated by Jeffrey Olin, Heather Gornik, and Pam Mace, which currently includes over 1400 patients recruited within 13 centers and has already led to publication of over 20 abstracts and peer-reviewed papers. In Europe, following the successful example of FMDSA, a Dutch patient association has been established in 2014 (<http://www.fmdgroep.nl/>), and a Belgian association is on its way (Alexandre Persu, personal communication). The final aim is to foster the creation of a European FMD patient association, which may provide support and information to patients, physicians, and researchers and serve as an interface with scientific societies and health authorities all over Europe.

### The European FMD Consensus: A Brief Update

In 2015, a European panel published a consensus paper on the diagnosis and management of FMD<sup>1</sup> (see key messages in Table 2). Screening for renal FMD has been advocated in hypertensive patients <30 years old, particularly women.<sup>1</sup> While this target group remains a priority, the authors of this short update feel that, in women, the upper age limit for screening should be at least 50 years, which corresponds to the mean age at diagnosis of FMD, both in the US registry<sup>7</sup> and in ongoing French studies (P.-F. Plouin, personal communication). Along the same lines, while, in the consensus, screening by renal duplex was still recommended, CT angiography is increasingly considered as a reasonable first-line imaging

**Table 2. The Updated European Consensus on Fibromuscular Dysplasia (FMD) in a Nutshell**

Screening for renal FMD should be considered in hypertensive women aged 20–50 y old and at all age irrespective of sex in case of severe or resistant hypertension.
Screening for cervico-cephalic FMD is indicated in case of pulsatile tinnitus, cervical or intracranial dissection, intracranial aneurysms, subarachnoid hemorrhage and retinal or cerebral ischemic events.
CT angiography (or MR angiography if contraindicated) is the preferred imaging modality for detection of cervico-cephalic FMD and is increasingly proposed as first-line screening test for renal FMD.
Screening for renal FMD should be considered in patients with cervico-cephalic FMD and vice versa.
Patients with documented or highly suspected SCAD should undergo screening for renal, cervico-cephalic, and iliac FMD.
In case of FMD-related renal artery stenosis in a hypertensive patient, the preferred revascularization approach is angioplasty without stenting.
In the absence of aneurysms, the treatment of cervico-cephalic FMD is usually conservative.
Indefinite annual follow-up is recommended in all FMD patients.

CT indicates computed tomography; MR, magnetic resonance; and SCAD, spontaneous coronary artery dissection.

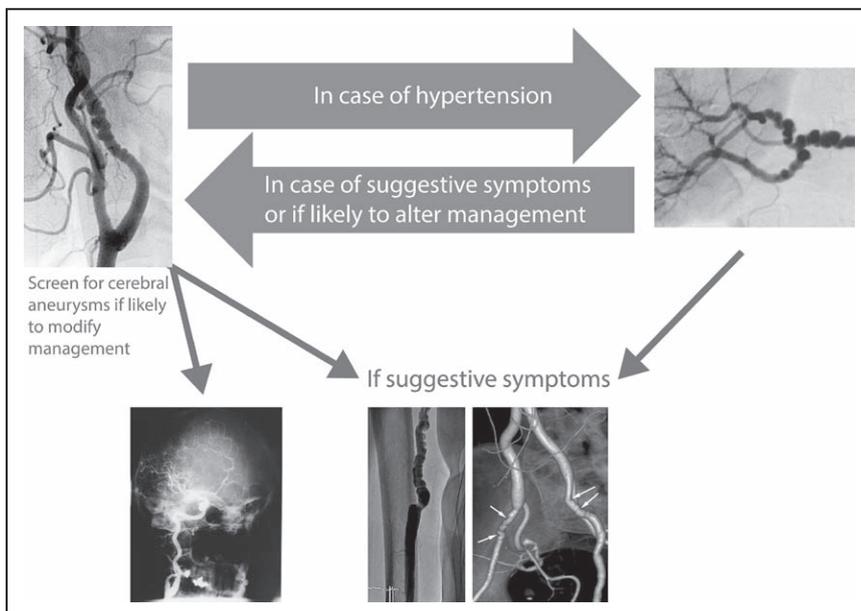
modality, in view of its higher resolution, especially for distal lesions, ability to detect FMD lesions without hemodynamic consequences, and decreasing costs and radiation exposure. This is especially true in case of high diagnostic probability or expected low performance of renal duplex (obese or hypoechogenic patients, lack of local expertise, etc).<sup>1</sup> As mentioned earlier, the case for CT angiography is even stronger for detection of carotid and vertebral lesions, which are often located in intracranial segments and may, thus, escape to carotid duplex.<sup>1,3</sup> Furthermore, CT angiography also allows detecting associated cerebral aneurysms.

For standardization purposes, the simplified dichotomic classification of FMD proposed by Savard et al<sup>4</sup> recommended in the European FMD consensus<sup>1</sup> and subsequently endorsed by the

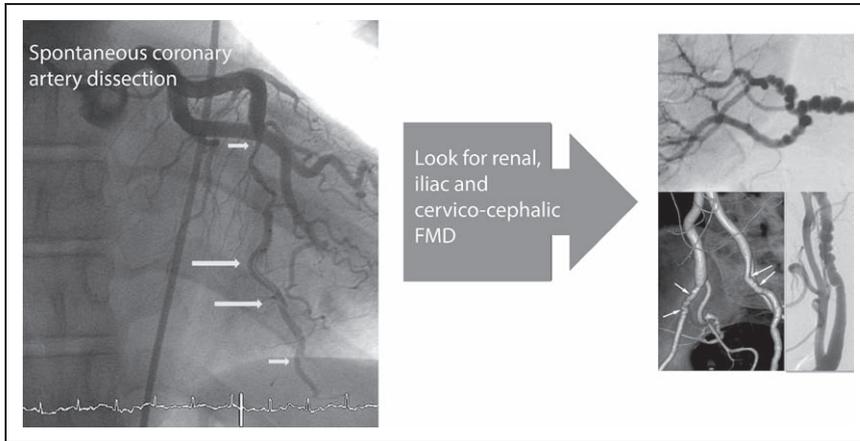
American Heart Association<sup>24</sup> should be widely diffused. In particular, radiologists are encouraged to use the terms "multifocal" and "unifocal" FMD rather than "irregularities" or "stenosis" in their protocols to draw the attention of the clinician on the possibility of a systemic vascular disease requiring a more extensive vascular work-up and, at times, interventional treatment.

In view of the frequent association of renal and carotid FMD lesions, the diagnosis of cervical FMD in a patient with hypertension warrants exploration of renal arteries. Conversely, in patients with renal FMD,<sup>1</sup> it is recommended to explore supra-aortic trunks and to screen for cerebral aneurysms in case of suggestive symptoms or if identification of lesions would be likely to alter management (Figure 1). Finally, in view of the strong association between SCAD and FMD,<sup>33–37</sup> in case of SCAD, imaging of renal, cervico-cephalic arteries (including search for cerebral aneurysms)<sup>36</sup> and iliac arteries should be considered according to patient's symptoms, medical history, and preferences (Figure 2). Exploration of other vascular beds or vascular imaging of family members may also be considered in case of suggestive symptoms.<sup>1</sup>

Finally, while renal angioplasty is not the panacea, especially in older patients who might suffer from essential hypertension with incidentally associated FMD lesions,<sup>1,55</sup> it may lead to hypertension cure in a substantial proportion of cases<sup>55</sup> and, thus, deserves to be proposed, especially in young hypertensive patients or in case of severe or difficult-to-treat hypertension. In contrast with atherosclerotic renal artery stenosis, stenting is usually not recommended in patients with FMD because of the risk of stent kinking<sup>56</sup> or fracture,<sup>57</sup> probably due to repeated mechanical stress induced by increased kidney mobility.<sup>14</sup> In case of recurrent stenosis, despite 2 attempts of angioplasty, surgery is probably the best option in order to avoid arterial trauma, inflammation, and fibrosis, which may jeopardize subsequent interventions.<sup>1</sup> The therapeutic attitude is less clear for cervico-cephalic lesions and should be discussed on a case-by-case basis in expert centers.<sup>1,3</sup> In the absence of severe stenosis or associated aneurysms, conservative management is usually recommended.



**Figure 1.** Recommended vascular screening in patients with renal or cervico-cephalic fibromuscular dysplasia (FMD) according to the European FMD consensus.<sup>1</sup> The panel showing iliac FMD comes from Figure 7 of Varennes et al.<sup>23</sup>



**Figure 2.** Recommended vascular screening in patients with spontaneous coronary artery dissection (SCAD).<sup>1</sup> The panel showing iliac FMD comes from Figure 7 of Varennes et al.<sup>23</sup>

### The European FMD Initiative and Registry

The main objectives of the European FMD initiative as presented at the Brussels FMD meeting are (1) to standardize screening and management of FMD in Europe; (2) to establish a network of expert centers; (3) to promote the creation of a European patient association; (4) to establish a European FMD registry; (5) to set up large genome wide association study/whole exome study likely to identify genes underlying the heritable component of the disease; and (6) to offer a platform of discussion and collaboration for transnational FMD-related projects.

The European FMD registry (Figure 3), coordinated by A. Persu (Brussels) in tight collaboration with P.-F. Plouin, M. Azizi, and X. Jeunemaitre (Paris), is at the crossroads of these



**Figure 3.** Map of the centers already contributing or in the process of joining the European fibromuscular dysplasia (FMD) registry. The list of participants can be found in the [online-only Data Supplement](#). The Paris and Warsaw centers coordinate the ARCADIA-PROFILE (Assessment of Renal and Cervical Artery Dysplasia–Progression of Fibromuscular Lesions) and ARCADIA-POL (Assessment of Renal and Cervical Artery Dysplasia–Poland) networks, respectively.

different objectives. It will contribute to standardize clinical practice. It requires the contribution of expert centers and patient associations and, on the other hand, will provide them with new evidence likely to improve detection and management of the disease.

Inclusion in the registry will be linked with optional contribution to genetic studies, as well as a comprehensive research program addressing the clinical, imaging, mechanistic, biochemical, and molecular aspects of the disease. Currently planned or ongoing studies include comparison of the performance of echo-Doppler and CT angiography for the detection of FMD lesions; evaluation of the added value of optical coherence tomography, intravascular ultrasound, and pressure gradient measurement for identification and hemodynamic characterization of renal FMD lesions; identification of predictive factors of disease progression; multicentric evaluation of the feasibility, sensitivity, and specificity of carotid echo-tracking for detection of subclinical FMD; identification and evaluation of novel biomarkers (markers of smooth muscle phenotype and differentiation, renin–angiotensin system, microRNAs, urinary proteomic classifiers); and identification of genes over- and underexpressed in vascular walls of patients with FMD. The registry will also facilitate more in-depth study of environmental factors likely to be involved in the pathogenesis or progression of the disease, such as exposure to estrogens, smoking, cardiovascular risk factors, and associated atheroma lesions. The current version of the registry has been adapted from the French FMD registry (coord. P.-F. Plouin), which was created in 2010 to merge existing local FMD databases, to feed the French National Rare Vascular Diseases database<sup>58</sup> and to share data semantics with the US registry.<sup>59</sup> It includes a set of over 50 items covering demographic and clinical characteristics of FMD, family history, type (uni- versus multifocal FMD), localization of FMD, associated features (aneurysm and dissection), and interventions (angioplasty, surgery, etc; Table 3). A flexible, user-friendly online version has been developed (L. Toubiana), allowing to add an indefinite number of new events/visits. Finally, specific modules can be developed according to local interests. The Belgian, French, and Dutch platforms are already operational. The countries and investigators already contributing or in process of joining the registry are listed in the [online-only Data Supplement](#).

**Table 3. Short Outline of the European Fibromuscular Dysplasia Registry**

General characteristics
Year of birth; sex; ethnicity; number of pregnancies; oral contraception
Characteristics of FMD
Year of diagnosis; type of FMD (multi- vs unifocal); associated atheroma lesions; clinical presentation (hypertension; neurological signs/symptoms; other); family history
Clinical and biological assessment*
Smoking; antihypertensive medication; body mass index; blood pressure; renal function
Vascular imaging*
Localization of FMD lesions (renal, cervico-cephalic, mesenteric, lower limb, coronary); imaging modality (ultrasound, CTA, MRI, angiography); side (left/right); type of lesion (stenosis, occlusion, aneurysm, dissection)
Interventions*
Localization; side; procedure (angioplasty, angioplasty+stent, aneurysm repair, surgical revascularization)

This table provides an idea of the organization of the registry. An exhaustive list of items is available on request. CTA indicates computed tomographic angiography; FMD, fibromuscular dysplasia; and MRI, magnetic resonance imaging.

\*To be filled at each visit.

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## Disclosures

None.

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