Fibromuscular dysplasia – underestimated cause of renovascular hypertension?

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Abstract

Based on a current definition, fibromuscular dysplasia (FMD) is an idiopathic, segmental, non-atherosclerotic and non-inflammatory disease of the musculature of arterial walls leading to the stenosis of small and medium-sized arteries. For many decades, FMD was believed to be solely a disease of the renal arteries being a cause of renovascular hypertension in young women, which only occasionally affected the carotid arteries. Over the last years, however there is a growing evidence that FMD is not a local disease of one or two arteries, but in fact a systemic arteriopathy that can affect practically every medium-sized artery. The large international registries and prospective studies not only showed the multivessel involvement of stenotic FMD lesions but also proved frequent coexistence of vascular complications such as dissections and aneurysms in FMD patients. Also tortuosity and S-shaped cervical arteries were documented to be highly frequent in FMD patients. Recent study showed that FMD patients had smaller visceral arterial diameters when compared to patients without FMD. If all these findings reflect a new phenotype of FMD, as a generalized arteriopathy, needs further investigation and confirmation in larger cohorts. Also there is a need to conduct further research on the genetic background as well as the emerging biomarkers of the disease to better characterize the pathophysiology of FMD.

Introduction

Fibromuscular dysplasia (FMD) is an idiopathic, non-atherosclerotic and non-inflammatory disease of the musculature of arterial walls and is regarded as a generalized vascular disease, as it may affect all vascular beds [1].

FMD has been reported in virtually every arterial territory. It most commonly affects the renal and extracranial carotid and vertebral arteries but has been also described in intracranial, lower and upper extremity arteries and is also prevalent among patients with spontaneous coronary artery dissection (SCAD). FMD may result in arterial stenosis, occlusion, aneurysm or dissection [1-3].

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Recent advances in the understanding of the natural history of FMD have been mostly driven by data from international FMD patient registries, such as the United States (US), the ARCADIA registries, and the most recent European/International FMD registry [4-7].

Definition, classification and differential diagnosis

Based on a current definition, FMD is an idiopathic, segmental, non-atherosclerotic and non-inflammatory disease of the musculature of arterial walls leading to the stenosis of small and medium-sized arteries [1].

FMD, with the highest prevalence in renal arteries, may be clinically silent and diagnosed incidentally and most common manifestation of FMD is hypertension, with different severity and onset. When carotid or vertebral artery are involved FMD may lead to dizziness, pulsatile tinnitus, transient ischemic attack (TIA) or stroke [1].

The diagnosis of FMD requires evaluation for other diseases and conditions on differential diagnosis, such as arterial spasm, atherosclerosis, monogenic, and inflammatory arterial diseases [1].

FMD is currently classified by angiography into 2 subtypes, multifocal and focal. Multifocal FMD, with a typical string-of-beads pattern affects mainly women between 30 and 50 years of age and usually occurs in the mid and distal portions of the artery. This type is the angiographic presentation of medial FMD and is at least 4x more frequent than focal FMD.Focal FMD, present in young (<30 years) can be found at the ostium, the trunk or the bifurcation of the renal arteries with no signs of atherosclerosis [1].

Of note, the angiographic features of carotid and vertebral artery FMD are very similar to those described in renal FMD and patients may have simultaneous multifocal and focal disease in different vascular territories[1,8].

FMD is primarly a stenotic disease with lesions classified according to angiographic appearance as described above. It is also increasingly recognized that aneurysm, dissection, and arterial tortuosity occur frequently in affected patient. According to the First international consensus on the diagnosis and management of fibromuscular dysplasia: "if a patient has a focal or multifocal lesion in one vascular bed to establish the diagnosis of FMD, the presence of an aneurysm, dissection, or tortuosity in another/other vascular beds is considered multivessel involvement of all affected vascular beds" [1].

Etiological factors of FMD

Although a variety of genetic, mechanical and hormonal factors have been proposed, the cause of FMD is still poorly understood. Its development is likely related to a combination of genetic and environmental factors.

Smoking

In some previous observational studies smoking was identified as a potential factor contributing to FMD but this association in this group of patients remains undefined.

Savard et al. reported that among patients with multifocal FMD, current smokers experienced an earlier diagnosis of both hypertension and FMD than other patients, a greater likelihood of kidney asymmetry and further renal artery interventions [9].

However, since approximately 50% of patients with FMD have never smoked, cigarette smoking cannot be considered as a prerequisite for the development of the disease. Nonetheless, it was postulated that smoking might provoke development of FMD lesions in susceptible individuals and therefore increase the true incidence of the disease. On the other hand, smoking may only worsen pre-existing arterial lesions and thus increase the likelihood and magnitude of clinical consequences of the disease [9].

Bofinger et al. showed that cigarette smoking was associated with an earlier onset and increased severity of the disease in a subgroup of patients with multifocal renal FMD [10].

In the US Registry 37% of patients had a history of ever smoking tobacco and it has been reported that those subjects had a significantly higher rate of

all aneurysm, cerebral aneurysms and aortic aneurysms than those who had never smoked. There was also a trend toward increased prevalence of major vascular events in smokers [11].

The US Registry found also that smoking patients with FMD were more likely to have claudication symptoms or to have undergone a vascular procedure. However, observations from US Registry might rather be attributable to premature atherosclerosis and its consequences including aortic aneurysm formation or symptomatic peripheral vascular disease. On the other hand, there is no clear cut explanation as to how smoking may trigger vascular changes and progression of FMD [11].

In contrast to other studies, in the ARCADIA-POL study any association was found between smoking and the extent of FMD nor the presence of renal artery stenosis, history of intervention and renal asymmetry. Moreover, this study did not show that smoking is associated with the presence of vascular complications - aneurysms and dissections [12].

The analysis of ARCADIA-POL study for the first time provided 'negative' findings in respect of the association of smoking with FMD. This observation is corroborated by the design of the study. The strengths of this study are as follows: a group of patients with FMD was evaluated in one clinical centre; it was a prospective study, systematically assessing smoking habits, presence of FMD and its complications in several vascular beds; the rate of smokers in FMD patients was compared to the rates observed in the matched control groups from the general population assessed in a nationwide survey [12].

Hormonal factors

Environmental factors such exposure to endogenous or exogenous estrogens has also been associated with FMD, but the exact association remains unclear. Also the disease is more prevalent in women, no clear-cut causative link has been identified in individuals who have used oral contraceptives or exogenous hormones. It should be noted, however, that most of these studies are very small and in reality there has been very little research done to investigate the pathogenesis of FMD. There is little supporting evidence for the role of female hormones beyond the sex and age distribution of FMD. However, no link

was found between FMD and estrogen exposure in a case-control study of 33 patients with renal FMD. Also in the US Registry, in which 91% of registrants were female, FMD has not been associated with the number of pregnancies or the use of oral contraceptives or other hormones[13-16].

Mechanical factors

Environmental factors such as repeated stretching of the renal artery as in kidney mobility has also been associated with FMD, but the exact association remains unclear.

The available study do not support the notion that renal mobility is an important etiologic exposure for the development of FMD. There was a modest trend toward increased postural nephroptosis in kidneys with diseased renal arteries, but the association was not statistically significant, was not seen during respiratory displacement, and was not impressive enough to substantiate previous suggestions of a causal relation between nephroptosis and FMD induced hypertension [17].

Other

It is hypothesized that FMD may have overlapping features with vascular connective tissue diseases, such as Ehlers-Danlos syndrome. However, the prevalence of genetic mutations associated with connective tissue disease was negligible in a cohort of clinically confirmed FMD patients who underwent genetic testing [18].

Ganesh et al found elevated secretion of transforming growth factor (TGF)-beta1 and TGF-beta2 by fibroblasts derived from FMD patients compared with matched controls. FMD patients also had elevated plasma levels of circulating TGF-beta1 and TGF-beta2 relative to matched controls. The potential involvement of TGF-beta pathways in the pathogenesis of FMD is an area for future investigation [19].

In FMD-associated visceral artery aneurysms (VAAs), the accumulation of lysoPC in the visceral arteries may reflect predisposition for the development of aneurysms. One study demonstrated the differences in the distribution patterns of lipid molecules, such as CE and lyso PC, between FMD-associated VAAs and atherosclerotic VAAs [20].

Genetics of FMD

Based on available reports FMD appears to be both sporadic and familial - several lines of evidence indicate that inherited factors contribute to FMD and indicate the occurrence of FMD in the first-degree relatives of affected individuals.

One study using angiographic definitions estimated familial cases to represent 7% to 11% of all FMD patients. Also of 447 patients who enrolled to the US Registry, only 7.3 % of subjects reported a confirmed diagnosis of FMD among family member [7].

Of note, evidence supports a genetic basis for susceptibility to FMD and a complex genetic basis for FMD is being suspected. Based on the genome-wide association study a common genetic risk variant has been identified, a single nucleotide polymorphism (SNP) rs9349379-A, in the PHACTR1 locus (6p24) conferring an odds ratio of approximately 1,4 for FMD. The risk variant resides within the intron of the PHACTR1 gene being associated with PHACTR1 transcript expression levels in dermal fibroblasts [21].

Further genetic studies are required for identification and characterization of genes that may contribute to FMD, including candidate gene evaluation and genome-wide association studies.

Historical perspective and the present status of FMD registries

FMD was first described in 1938 by Leadbetter and Burkland in a 51/2-year-old boy with severe hypertension and a renal artery stenosis. Since the early publications in the 1970s and 1980s, subsequent publications have almost all been confined to case reports or small case series. Therefore there has been very little new information published about FMD in the past three decades.

Significant advances in understanding of FMD required collaboration across a large network of research and clinical centers in the United States and Europe and gave a stimuli to launch large-scale registries including the US Registry for FMD, the French Registry for FMD and European/International FMD Registry [4,5-7].

The US Registry for FMD, started in 2009, has currently enrolled almost 2000 patients at 13 active clinical centers based on centralized data coordination in an online platform[7].

The French FMD Registry, coordinated by P.F. Plouin, was created in 2010 to merge existing local FMD databases. It includes over 50 items covering demographic and clinical characteristics of FMD, family history, type, localization, associated complications, and interventions selected from the larger dataset used in the French ARCADIA registry [6].

The European/International FMD Registry endorsed by the European Society of Hypertension, was launched in 2015 in parallel with the Belgian FMD initiative and was adapted from the French FMD Registry. Since beginning the registry included so far 675 FMD [1].

The prospective ARCADIA-POL Study was instituted in January 2015 on the basis of Polish-French collaboration in the Institute of Cardiology, Warsaw, Poland. In all patients CTA of intracranial and cervical arteries as well as CTA of abdominal aorta and its branches including celiac trunk, mesenteric arteries, common hepatic artery, splenic artery, renal arteries and iliac, femoral arteries were performed during one hospital stay [22].

The main results of the study published in Hypertension in 2020 proved that systematic and multidisciplinary evaluation of FMD patients according to an uniform protocol based on whole-body CTA scans has an impact on the clinical management of patients. Out of 232 FMD patients included to the registry in years 2015-2018 systematic evaluation of FMD patients revealed newly diagnosed FMD lesions in 34.1% of patients and previously undetected vascular complications in 25% of patients. Among all FMD patients included in the study, one out of every four evaluated patients qualified by multidisciplinary team for interventional treatment due to newly diagnosed FMD lesions or vascular complications. ARCADIA-POL study proved the necessity the systematic evaluation of all vascular beds in FMD patients, regardless of initial FMD involvement [22].

Clinical manifestations of FMD

Unlike previous reports from 70ties and 80ties of XX century suggesting that FMD is a disease of

young women, the reports from current registries indicate that FMD is predominantly diagnosed in the middle-aged subjects although it may be present at any age [1].

The clinical manifestations of FMD are variable and depend on a number of factors, including vascular bed involvement, the type and severity of the vascular lesions.

Recent estimates showed that FMD primarily affects the renal arteries and in the US and AR-CADIA registries, FMD involvement was found in approx. 75% of patients. However, some current reports that include systematic imaging of arterial beds beyond the initial site of diagnosis have revealed similar rates of cervical artery and renal artery disease [1].

In all registries the majority of patients presented with at least 1 clinical symptom or sign and the most frequent presenting signs and symptoms of FMD were hypertension, headaches (especially migraines), dizziness, pulsatile tinnitus, transient ischemic attack (TIA) or stroke which may be a hall mark of cerebrovascular FMD [1].

However a number patients had no signs and symptoms and were discovered incidentally when the imaging was performed for another reason.

FMD may be clinically silent and discovered incidentally but in available registries the most common manifestation of renal artery FMD is hypertension (67.3% - 91.7%), the severity and onset of which are variable. FMD should be suspected as a potential diagnosis particularly in the patient with early-onset hypertension or in subjects with drug-resistant hypertension. In recently reported large ARCADIA Registry patients were characterized by high prevalence of history of hypertension (81.2%) and by relatively low BP at FMD diagnosis (139/83 mmHg) [6]. In the group of patients enrolled to the ARCADIA-POL study, hypertension was relatively well controlled (133.8/82.2 mmHg) with a median of 2.1 (interquartile range 1-3) medications required for hypertension treatment [23].

This lower BP values observed in ARCADIA and ARCADIA-POL study stay in line with reports of Giavarini et al. who analysed medical records of hypertensive patients diagnosed with FMD at a single referral center from 1986 to 2012. Accordingly, patients diagnosed with FMD after 2000 have lower BP levels than those diagnosed before 2000, and this difference is not fully explained by more stringent definition of hypertension since early 1990s. In parallel, the authors observed a time-dependent increase in the use of medical treatment alone for these patients with a milder clinical phenotype. This confirms a temporal trend towards lower BP at FMD diagnosis, at least partly independent of the lower BP goals. It should also be taken into consideration that significant RAS was diagnosed only in a subset of subjects supporting the concept that patients with renal FMD may also have in fact essential hypertension with a string of beads as an innocent 'bystander' [24].

Of note, in ARCADIA-POL well characterized group, blood pressure was also evaluated by ABPM supporting good BP control. The non-dipping pattern of BP during the night has been reported as a feature of patients with atherosclerotic RAS. However, in ARCADIA-POL large sample size patients with FMD, values of 24-h ambulatory BP and nocturnal dipping pattern did not differ between patients with renal FMD as compared with those with essential hypertension, showing no association between higher ambulatory BP levels nor nocturnal dipping pattern and the presence of FMD [5, 7, 12, 14, 23-29].

Pathophysiological mechanisms causing hypertension in FMD patients ?

In contrast to atherosclerotic renal artery stenosis, little is known about the pathophysiological mechanism causing hypertension in FMD patients. Until now, renal FMD was believed to cause hypertension through a decrease in renal blood flow, which subsequently leads to increased renin secretion similar as in patients with RVHT caused by ARAS [30].

The recent findings of van Twist et al. argue against the hypothesis that FMD induces hypertension via similar pathophysiological mechanism as in ARAS and indicating that renal blood flow was significantly higher in FMD as compared with ARAS. Moreover, no differences in mean RBF were found between affected and unaffected kidney in patients with unilateral multifocal RAS suggesting that "string of beads" does not seriously affect local

RBF. These authors also documented that glomerular filtration rate was comparable between kidneys of patients with renal FMD and essential hypertension.Also in patients with unilateral ARAS renin secretion was increased in the affected kidney as compared with the unaffected kidney. This lateralization in renin secretion was not found in unilateral FMD and systemic and local renin secretion was lower in FMD as compared with ARAS [31,32].

These results challenge the earlier study of Higashi et al. who showed that patients with renal artery stenosis are characterized by higher activity of renin angiotensin system and that both in patients with FMD and atherosclerotic renal artery stenosis renal artery angioplasty resulted in the decrease in the activity of renin angiotensin system [33].

Imaging and diagnosis of FMD

According to the current knowledge on FMD summarized in the First International Consensus regardless of initial site of vascular bed involvement, patients with FMD should undergo imaging of all vessels from brain to pelvis, at least once and usually with CTA or contrast-enhanced MRA, to identify other areas of FMD, as well as to screen for occult aneurysms and dissections. Imaging-based evaluation for renal FMD should be considered in patients with suggestive symptoms (young patients with hypertension, severe hypertension with sudden onset, resistant hypertension, abdominal bruit, renal assemtry, renal aneurysm or dissection, confirmed FMD lesions in other vascular bed). For patients with suspected renal artery FMD, CTA is the initial imaging modality of choice. Contrast-enhanced MRA is an alternative to CTA when CTA is contraindicated. Duplex ultrasound may be used as the first diagnostic procedure for renal FMD only in specialized centers with extensive artery expertise in duplex ultrasound for FMD. Regardless of initial site(s) of vascular bed involvement, patients with FMD should undergo at least one-time assessment for intracranial aneurysm with brain CTA or MRA. Whether brain CTA or MRA should be repeated after a period of time for patients without detected aneurysm on the initial study is unknown [1].

The recent analysis of the ARCADIA-POL study proved that that systematic and multidisciplinary evaluation of FMD patients according to an uniform protocol based on whole-body CTA scans has a substantial impact on the clinical management of patients [22].

Management of fibromuscular dysplasia

Despite the lack of prospective clinical trials on pharmacological treatment in FMD, experts point out the benefits of antiplatelet drugs, especially in the context of preventing the occurrence of thrombotic and thromboembolic complications in FMD patients. In the absence of contraindications, antiplatelet therapy (e.g. 75 mg - 100 mg / day acetylsalicylic acid) should therefore be used in all patients with FMD to prevent thrombotic and thromboembolic complications in patients with FMD [1].

Other important aspect of FMD management is interventional treatment in patients with renal FMD. Although classic renal artery angiography remains the gold standard for assessing the location and FMD lesions morphology, it is only recommended when angiographic results may affect patient management. Renal artery angiography is most often performed in patients with significant renal artery stenosis suspected on the basis of non-invasive tests. Measurement of a pressure gradient, usually with a flow wire, is necessary to avoid angioplasty of lesions, especially of the multifocal type, that are not hemodynamically significant [1].

Summary

For many decades, FMD was believed to be solely a disease of the renal arteries being a cause of renovascular hypertension in young women,, which only occasionally affected the carotid arteries. Over the last years, however there is a growing evidence that FMD is not a local disease of one or two arteries, but in fact a systemic arteriopathy that can affect practically every medium-sized artery. The large international registries and prospective studies not only showed the multivessel involvement of stenotic FMD lesions

but also proved frequent coexistence of vascular complications such as dissections and aneurysms in FMD patients. Also tortousity and S-shaped cervical arteries were documented to be highly frequent in FMD patients. Recent study showed that FMD patients had smaller visceral arterial diameters when compared to patients without FMD [34]. If all these findings reflect a new phenotype of FMD, as a generalized arteriopathy, needs further investigation and confirmation in larger cohorts.

Also there is a need to further conduct further reasearch on the genetic background as well as the emerging biomarkers of the disease to better characterize the pathophysiology of FMD.

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Conflict of interest

The authors confirm that there are no conflicts of interest.

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