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Coronary artery involvement in fibromuscular dysplasia (FMD): a review

Short title: Coronary involvement in FMD

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Abstract

This report reviews the current progress in understanding of clinical manifestation, epidemiology, diagnosis and treatment strategies in fibromuscular dysplasia (FMD) involving coronary arteries.

FMD involving the coronary arteries is believed to be rare but it may lead to serious, life-threating consequences including acute myocardial infarction or sudden cardiac death. The most common coronary manifestations are presented by irregular stenosis, arterial enlargement, dissection, distal tapering, smooth narrowings, and excessive coronary tortuosity with additional markers of tortuosity leading to spontaneous coronary dissection in some cases. The etiology of the disease is poorly understood but presumably the pathogenesis of FMD is associated with combination of genetic and environmental factors. There is limited data on FMD with coronary involvement, management and treatment of the disease, but many acute vascular lesions may heal spontaneously and conservative approach is preferred. The pharmacological management with antihypertensive drugs, especially in patients with

concomitant hypertension, and antiplatelet therapy should be considered in patients with confirmed FMD.

Key words: fibromuscular dysplasia; coronary arteries; hypertension; spontaneous coronary artery dissection

Introduction

Fibromuscular dysplasia (FMD) is an idiopathic, segmental, non-atheroslerotic and non-inflammatory disease of the musculature of arterial wall, most frequently affecting small and medium-sized arteries. The renal, extracranial carotid and vertebral arteries are predominantly involved, but virtually every artery in the body may be affected [1].

The current classification of FMD is based on two types of angiographic appearance: 1. focal FMD and 2. multifocal FMD, with alternating areas of stenosis and dilation (string-of-beads appearance) [1]. In addition, it has been documented that FMD can coexist with arterial abnormalities as arterial aneurysms, dilatation, dissection or tortuosity. It primarily affects young and middle-aged women, but FMD may occur at all ages, both in women and men with wide variety of clinical features and manifestations [1–6]. The clinical presentation of FMD mostly depends on localization of the FMD lesions. It may cause wide range of clinical manifestation, from asymptomatic and clinically silent, through hypertension or headache, to life-threatening complication like transient ischemic attack or even myocardial infarction. The existing data of coronary arteries involvement of FMD is limited and based on case reports and studies encompassing small series of patients, mainly due to rare clinical manifestations of coronary FMD. However, when present, it may lead to serious clinical consequences including myocardial infarction or sudden cardiac death [7–13]. Moreover, there is relatively frequent correlation between FMD and spontaneous coronary artery dissection (SCAD) [14–16]. Likely most of coronary FMD cases may be clinically silent and thus unrecognized, rendering the true prevalence of coronary artery involvement in this disease unknown.

Over the last decades, the progress in research and understanding of FMD have been driven by data from international registries and multicenter research collaborations, including The United States Registry (US Registry for FMD), French FMD Registry (ARCADIA Registry) and Polish FMD Registry (ARCADIA-POL study) [2, 4].

This review summarizes the recent data on coronary artery involvement of FMD to assist physicians in the diagnosis and management of this important condition.

Epidemiology and demographics

In 1938, Leadbetter and Burkland [17] reported the first case report of fibromuscular dysplasia in a 5.5-year-old boy with renovascular hypertension caused by an intra-arterial smooth muscle mass. The first report of coronary artery involvement in patient with confirmed FMD was published in 1965, where Hill and Antonius [18], described the pathology and history of two patients with lesions in coronary arteries corresponding with fibromuscular dysplasia. Up to now, the data on coronary arteries involvement in patients with FMD rely on case reports and studies of small series of patients with clinically overt coronary FMD [8, 10]. Probably, it is due to an absence of specific coronary or cardiac symptoms and findings before a serious, life-threatening complications occur. The true prevalence of FMD, as well as broader diagnostic criteria which would encompass asymptomatic patients remain unknown.

The data of patients with confirmed FMD enrolled in U.S. Registry and European Registries for FMD share many similarities in terms of demographics and clinical characteristics. The mean age at diagnosis for FMD was 51.9–53 ± 13.4 years and 84–91% were females, respectively [2, 4]. The most common cardiovascular risk factor was hypertension or receiving antihypertensive medication (72%) [4] due to renal FMD. In comparison, in 2016 Saw et al. analyzed 32 patients with confirmed FMD with coronary artery manifestation, most of the patients were females (88%) and the mean age was 59.4 ± 9.9 years [8]. The cardiovascular risk factors were relatively infrequent, and included hypertension in 56.3%, dyslipidemia 37.5%, current smokers 12.5% (8). In a series of 7 patients with coronary artery presentation of FMD, all were women between 42 and 56 years of age [10]. Two of the patients received antihypertensive therapy, one was active smoker, two were ex-smokers [10]. In a study with 50 patients with SCAD, in which 86% had confirmed FMD, 49 patients were women and the mean age was 51 ± 9.6 years, similarly to the data mentioned earlier, the prevalence of cardiovascular risk factors was relatively low [14]. In the Canadian Registry, 411 of 750 enrolled patients with SCAD, were systematically evaluated and FMD was found in 56.7% of them. The mean age was 51.8 ± 10.2 and the majority were women (88.5%) and Caucasian (87.7%). Moreover, 33.9% patients had no cardiac risk factors, 32.1% has hypertension and 20.3% dyslipidemia [19].

Etiology

The etiology of FMD and its coronary manifestations remain unclear. It is believed that combination of genetic and environmental risk factors may play a causal role in this condition.

Genetic factors

The first family-based genetic reports, published decades ago, was difficult to conduct due to relatively low frequency of well-described multiplex pedigrees, incomplete penetrance (∼0.5) and also absence of symptoms in most patients and their relatives [20–23]. Based on the pedigree studies, it has been suggested that autosomal dominant inheritance with incomplete penetrance may play role in FMD pathology [20, 24]. The data from international FMD Registers documented that only 1.9–7.3% of patients had FMD diagnosed among any family member [2, 4]. In 2016, Kiando et al. presented a genome-wide association study where a common genetic risk variant was identified of a single nucleotide polymorphism (SNP) rs9349379-A, located on chromosome 6 in the phosphate and actin regulator 1 gene (PHACTR1), which increases the risk of FMD by ∼ 40% [25]. The same variant has been correlated with SCAD [26]. Additional data suggest that the same SNP regulates endothelin-1 (EDN-1) expression, which has multiple vascular effects on arterial remodeling [27]. The mentioned above PHACTR1 FMD rs 9349379-A risk-allele has pleiotropic effects, presented with SCAD, carotid artery dissection, hypertension, and migraine headache, but has protective effects on coronary atherosclerotic arterial disease and myocardial infarction [26, 28–33] and may play important role in genetic predisposition to FMD [25].

Molecular factors

There are two hypotheses of molecular pathogenesis of FMD. The first is based on the role for altered TGF-beta signaling pathway [34, 35], which causes known connective tissue disorders including Marfan syndrome (MFS), Loeys-Dietz syndrome (LDS) or vascular Ehlers-Danlose syndrome and may also cause FMD. In addition, some patients with established diagnosis of FMD may present connective tissue disorders with arterial abnormalities like dilatation, aneurysm, tortuosity, but also joint laxity, scoliosis, degenerative disease in the spine, early onset arthritis [34]. The study of 38 FMD patients reported increased circulating transforming growth factors (TGF) TGF-β1 and TGF- β2 plasma levels [34]. In other cohort of 35 FMD patients that underwent genetic testing for mutations, two variants in the *TGFBR1* gene (c.611 C>T, p.Thr204lle and c.1285 T>C, p.Tyr429His) were identified [35]. The second hypothesis

of molecular background of FMD involved mutations in a pathway driven by platelet-derived growth factor (PDGF) receptor beta (encoded by the *PDGFRB* gene). PDGFRB play a role in angiogenesis, and its overactivation in vascular mural cells leads to their migration and proliferation [36]. Some data suggest that mutation in PDGFRB gene and overexpression of PDGF receptor beta is associated with aneurysms located in various arteries in the body [37–40]. The precise link between FMD and TGF-β signaling and PDGFB and *PDGFRB* genes and their involvement in FMD pathophysiology remains unclear and need further investigations.

Environmental factors

Tobacco smoking has been identified as one of the potential contributing factors related to FMD. Some data indicated increased proportion of current smokers or ever smokers in FMD patients as compared to matched hypertensive controls [41]. In US Registry, history of cigarettes smoking was correlated with a higher rate of prevalence of aneurysm in patients with FMD and increased number of major vascular events [42]. Dobrowolski et al. showed no difference in the rate of ever smokers among FMD patients as compared to the groups of general population and hypertensive subjects [43]. The studies associating smoking with pathogenesis of FMD are equivocal and further studies are needed to clarified this issue.

Manifestation

According to recent data, the majority of FMD patients with coronary artery involvement presented with irregular stenosis, arterial enlargement, dissection, distal tapering or smooth narrowings and excessive coronary tortuosity with additional markers of tortuosity: the intravessel and multivessel symmetry sign, corkscrew appearance (Fig. 1). Typical for FMD “string of beads” appearance is rather uncommon in coronary arteries, if ever, arises in this localization. The most common feature of coronary manifestation of FMD is coronary tortuosity; however, the diagnostic criteria applied across studies are hard to clearly define [8, 16, 44, 45]. The most frequently used definition of tortuosity is the presence of ≥ 3 consecutive curvatures of 90° to 180° measured at end-diastole in a major epicardial coronary artery ≥ 2 mm in diameter. Severe tortuosity was defined as ≥ 2 consecutive curvatures of ≥180° in a major epicardial coronary artery ≥ 2 mm in diameter. Mild tortuosity was defined as either ≥3 consecutive curvatures of 45° to 90° in a major epicardial coronary artery, or ≥ 3 consecutive curvatures of 90° to 180° in an artery [16]. Following markers of tortuosity were identified: (1) Intravessel symmetry sign, as the presence of symmetrical curvatures of similar

angle throughout the course of a coronary artery; (2) multivessel symmetry sign, as the presence of symmetrical curvatures of similar angle throughout the course of multiple coronary arteries, with an angiographic appearance resembling the tentacles of a Portuguese Man of War; (3) corkscrew sign, as helical course of a coronary artery ≥ 360° pendicular to the epicardial plane [16].

Previously, it has been believed that the most common phenotype corresponding to coronary involvement of FMD manifests with main epicardial coronary artery or its major branch dissection [10–13].

The first report presenting the angiographic appearance suggestive of coronary FMD in patients with extracoronary FMD was published in 2016. The study presents 32 patients who underwent coronary angiography for cardiac symptoms. The majority of patients (30 of 32) had > 1 coronary artery abnormality, the most frequent abnormality was tortuosity, present in each of the patients. The second most common coronary abnormality was irregular stenosis, observed in 19 (59%) analyzed subjects. Arterial enlargement was also common, present in 18 (56%) patients, with the majority having mild dilatation ≤ 1.5 times the adjacent coronary artery segments. Ectasia with enlargement > 1.5 times the adjacent coronary segment was much less frequent. SCAD was present in 13 (41%) patients, with 16 dissected arteries [8].

Similarly, the recent data confirmed that coronary tortuosity was the most common manifestation of FMD coronary involvement [46]. In a case series of five patients, in whom diagnostic studies for FMD were initiated because of coronary tortuosity, the presence of renal and/or cervical FMD was confirmed in all of them [9]. These results were based on limited data and potential selection bias.

The clinical manifestation of coronary artery involvement of FMD leads to wide range of presentations from asymptomatic, through exertional chest pain, to serious life-threatening events, such as myocardial infarction, left ventricular dysfunction or sudden cardiac death mostly due to SCAD. Moreover, it has been documented that severe coronary tortuosity is associated to an increased risk of recurrent coronary dissection in SCAD [16]. The pathomechanism includes the increased number and degree of coronary curves translating into higher transcoronary gradient, causing myocardial ischemia and increased local shear stress, leading to dissections [47–49].

Diagnosis

Based on current recommendations from First International FMD Consensus [1], the diagnosis and classification of FMD is based on imaging studies including computed

tomography angiography (CTA), magnetic resonance angiography (MRA) and/or catheter-based angiography, and angiographic confirmation of multifocal or focal FMD lesions in at least one arterial bed. The presence of aneurysm, dissection, or tortuosity without typical patterns of FMD (multifocal or focal lesion) is not sufficient to diagnose FMD [1].
Multivessel involvement should be considered in patients with multifocal or focal lesions in at least two different arterial beds, or if FMD-related stenosis in one vascular bed and other FMD-related lesions as aneurysm, dissection, or tortuosity is present in other vascular beds. The cerebrovascular, renal, visceral, upper and lower extremity arteries are taken into account [1].
When FMD is suspected, firstly, a non-invasive imaging study should be performed to confirm or exclude diagnosis of FMD. The type of the imaging examination depends on the suspicion of localization were FMD has arisen [1].
For suspected renal FMD involvement, according to the consensus of the scientific committee that CTA is the appropriate modality for initial test. The contrast-enhanced MRA is an option when CTA is contraindicated. Duplex ultrasound is recommended only in specialized centers with extensive experience in duplex ultrasound for evaluation of FMD [1].
For cerebrovascular FMD involvement there are inadequate data to recommend a specific imaging modality over any other. The gold diagnostic standard remains catheter-based angiography, but it is typically reserved for complicated cases that may require intervention (aneurysm or pseudoaneurysm related to dissection). In most centers, this modality has been replaced by CTA or contrast-enhanced MRA as the initial diagnostic imaging modality.
There are no studies comparing the accuracy of diagnostic imaging modalities for visceral, coronary or lower, upper extremity FMD [1]. It is recommended, that regardless of initial site of vascular bed involvement, patients with FMD should undergo imaging of all vessels “from brain to pelvis” to identify other potential areas occupied by the disease [1].
At present, coronary artery imaging for potential manifestations of FMD is not recommended in the absence of symptoms. There are data that the systemic evaluation of FMD patients reveals 34% newly diagnosed FMD lesions in different areas [50]. Previously undetected vascular complications were found in 25% of the patients, and one out of every 4 evaluated patients qualified for interventional treatment [50]. Based on these data, the multidisciplinary approach of patients with confirmed FMD has a significant impact on their clinical management.

Differential diagnosis

The differential diagnosis of FMD and particularly of its coronary artery manifestation is challenging and includes many arterial pathologies such as arterial spasm, atherosclerosis, monogenic arterial diseases or others. The diagnosis is based on detailed analysis of the imaging examinations, family history and risk factors. of which all importantly contribute to differential diagnosis. Williams syndrome (WS) is a congenital arteriopathy involving the cardiovascular, connective tissue, and central nervous systems, affecting 1/10,000 live births (51). Patients with confirmed diagnosis clinically has typical facial features including characteristic 'Elfin face' with broad forehead, upturned nose, pointed chin, developmental delay, hypercalcemia and congenital heart defects [51]. Cardiovascular defects are the most common cause of death in patients with WS [52]. The supravalvular aortic stenosis (SVAS) is the most frequent cardiovascular abnormalities and seen in up to 45% of patients, also coronary artery anomalies were present [53] and likely contribute to sudden death in patients with WS [54]. The standard method for establishing the diagnosis is demonstrate hemizygosity of the *ELN* locus in patients [55]. Ehlers-Danlos syndrome type IV, the vascular subtype, is clinically characterized by four clinical criteria: easy bruising, thin skin with visible veins, characteristic facial features (large eyes, small chin, thin nose and lips, lobeless ears), and rupture of arteries, uterus, or intestines [56]. It may also present as coronary artery dissection [57, 58]. This condition has usually more serious course than FMD involving coronary arteries; more than 80% of the patients have at least one vascular complication by the age of 40. The calculated median survival of the entire cohort was 48 years [59]. Presence of the mutation in type III procollagen gene (*COL3A1*) establish the diagnosis [59]. Takayasu arteritis and giant cell arteritis represent large- and medium-vessel vasculitis respectively, that mostly appear in the aorta and its branches, and also can impact coronary arteries [60, 61]. Primarily it affects women, usually between 10 and 40 year-old [60–62]. Cardiac involvement presents with dyspnea, palpitations, angina, myocardial infarction, heart failure or sudden death. The coronary involvement is detected in 10–30% of the cases and the most frequent finding is occlusion of the ostia of the left main coronary artery and of proximal segments of the coronary arteries [63–64]. Segmental arterial mediolysis (SAM) is a non-inflammatory and non-atherosclerotic disease, which occurs in epicardial coronary arteries and in the abdominal splanchnic arteries. Coronary SAM manifests in neonates, children, and young adults [65] and may present as spontaneous arterial dissection, rupture, occlusion, or aneurysm. The diagnosis requires histopathological examination establishing vacuolar degeneration of the artery media. Cocaine use may also be taken into consideration in the differential diagnosis. It has been documented that cocaine users were young, mostly male,

cigarettes smokers with cardiac symptoms [66, 67]. The diagnosis of cocaine ingestion was confirmed by urine toxicology screening test. Among patients with cocaine abuse the history of myocardial infarction, coronary artery aneurysms and ectasia is frequent [68, 69]. The consequences of cocaine use in patients may also be cardiac hypertrophy, dilated cardiomyopathy and myocarditis [70, 71]. Atherosclerosis should be taken into consideration in older age patients with cardiovascular risk factors including hypertension, hyperlipidemia, obesity, diabetes or tobacco use. It may affect any arterial bed but predominantly involves the origin and proximal part of arteries. Atherosclerotic plaque with or without calcification may be diagnosed on CTA, MRA, or duplex ultrasound. Finally, imaging artefacts appearing in an image but not present in the original object, may be mistaken for multifocal FMD. Patients motion during examination may result in areas of luminal irregularity of an examined vessel.

Spontaneous coronary artery dissection (SCAD)

Spontaneous coronary artery dissection (SCAD) is defined as the acute development of a false lumen within the coronary artery wall which may compromise coronary flow by external compression of the true lumen [72]. Patients with confirmed SCAD are mostly women, aged 18–84 years, with the mean age from 44 to 53 years [72–77] and often with no cardiovascular risk factors.

The association between FMD and SCAD was first published in 2005 (10) and in 2012, in a series of 6 women with SCAD and concomitant fibromuscular dysplasia (FMD) [15]. In another series of 12 patients with SCAD, 2 women presented with a “string of beads” angiographic appearance of the renal artery, suggesting FMD [78]. The prevalence of FMD in SCAD population is hard to determine due to the proportion of patients screened in each study, the screening protocol used (e.g., imaging technique, vascular beds, screening according to symptoms or systematic assessment) and diagnostic criteria of FMD. In some studies, less than 50% of patients with SCAD were screened against coexistence of FMD lesions. Thus, the data of true prevalence of FMD in SCAD population could be underestimated [16, 73, 79].

In the remaining data, it has been documented that the prevalence of FMD in SCAD patients ranges from 41 to 86% with the most often affected vascular beds being the cervical, renal, and ilio-femoral vessels [14, 74–76, 80] with the multifocal subtype. Fibromuscular dysplasia of extra-coronary vascular beds was frequently confirmed in SCAD population with a higher coronary tortuosity score [16]. Also, coronary artery tortuosity is associated with recurrent SCAD [16].

In comparison, SCAD is present in only 2,7% of FMD patients, according to US Registry for FMD report [6]. The FMD manifestation in SCAD patients was rather benign and non-progressive in short- or medium-time observation [5, 72, 81].
Moreover, similarly to FMD, another extracoronary vascular abnormalities in SCAD population including aneurysm, dissections, tortuosity, irregularities or undulations have been reported. However, the association and clinical overlap between FMD and SCAD remains unclear and further studies are required to better understand the pathophysiology and establish clinical management of these significant conditions [76, 80, 82].

Medical therapy

There were no placebo-controlled studies evaluating medical therapy in FMD population. Medical management in patients with coronary arteries may be challenging, because there are limited data to guide therapy with no precise recommendation.
It has been documented that patients with FMD may show with thromboembolic complications and manifest vascular abnormalities including dissections or aneurysms. In the absence of contraindication, antiplatelet therapy (i.e., aspirin 75–100 mg) is reasonable for symptomatic or asymptomatic patients with FMD [1, 6, 83]. The benefits and risks of antiplatelet treatment should be considered in an individual patient, taking into account prior thromboembolic events, arterial dissection, or revascularization procedures as well as risk factors for bleeding (e.g., prior history of subarachnoid hemorrhage or other bleeding events, large intracranial aneurysm). According to data from US Registry, 72.9% of patients use antiplatelet therapy and aspirin is the most frequently prescribed medication [83].
The majority of patients with FMD receive antihypertension therapy [4, 83]. It is important to control hypertension, especially in FMD patients with essential or renovascular hypertension due to renal artery involvement. Antihypertensive therapy, with beta-blocker as a first-choice drug (if not contraindicated), may have protective effect on SCAD patients [84, 85] and may be considered as preventive therapy for migraine. It is important for patients with intracranial aneurysms, as well as aneurysms at other locations.
Statins are recommended for patients with FMD with hyperlipidemia or concomitant atherosclerosis. They should not be prescribed routinely in this population [1, 86].
In acute phase of SCAD, conservative strategy is preferred in stable patients, as SCAD heal spontaneously within 3–6 months in most cases. The results of percutaneous coronary intervention (PCI) seem to be worse than for patients with atherosclerotic disease, mostly due to the propensity to extension of the intramural hematoma or increased risk of iatrogenic left

main dissection [74, 77, 87–89]. Early outcomes on coronary artery bypass grafting in SCAD are good, but in follow-up, the US Mayo Clinic series reported high ratio of graft failure, probably as a result of healing of the native coronary artery leading to competitive flow and conduit thrombosis [87]. Nevertheless, coronary artery bypass grafting (CABG) as a therapeutic strategy should not be excluded, as it can be used as temporizing intervention to effectively reduces serious clinical complications during the process of vascular healing.

Conclusions

Despite advancements in clinical and radiological characterization of coronary involvement in FMD in the last decade, there are significant approaches to investigate. It is important to precisely identify the correlation of SCAD, coronary involvement and FMD, also to estimate its true prevalence, determine further treatment and raise awareness among physicians and patients about this important condition. It is hoped that the next years will bring the progression with the effective management in patients with coronary manifestations of FMD and deliver clinical practice guidelines.

Author contributions

All authors were engaged in creation process of this article.

Conflict of interest

None declared.

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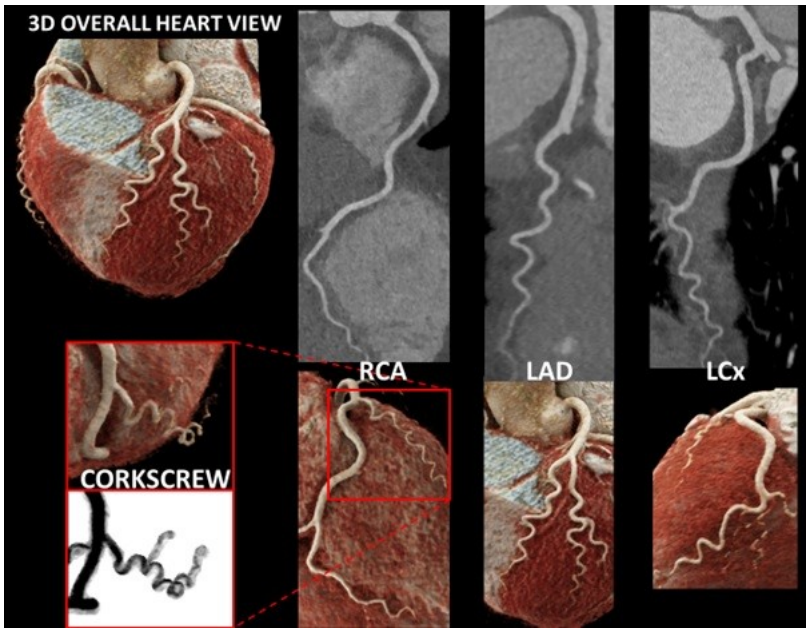

Figure 1. Overall volume rendered (3D) view, and curved multiplanar reformatted, contrast enhanced images of coronary arteries and heart in a patient with FMD involvement within a renal artery. Excessive tortuosity is seen in mid and distal **segments of le**

Figure 2. A young female patient diagnosed in the 1st line with coronary computed tomography angiography (CCTA) due to atypical chest pain. The examination revealed a narrowed proximal part of right coronary artery (RCA) with intramural hematoma **(dashed r**