Review paper

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Fibromuscular Dysplasia – Underrecognized Vasculopathy with Female Preponderance

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Abstract- Fibromuscular dysplasia (FMD) is a non-atherosclerotic, non-inflammatory vascular disease with strong female preponderance. However the diagnosis of the disease is low. FMD affects medium-sized muscular arteries, predominantly renal arteries, but equally carotid and vertebral arteries. It leads to artery stenosis, occlusion, aneurysm or dissection. The clinical picture depends on the affected blood vessels. It is most commonly recognized as a cause of hypertension in young female patients. In the case of involvement of cranial and cervical arteries, the clinical picture is mostly nonspecific, with headache, migraine and tinnitus. In registries, females had more frequent classical symptoms of cerebrovascular FMD like pulsatile tinnitus, cervical bruit and neck pain, and males have more frequently visceral affection (abdominal pain, renal impairment and renal infarction). Also, man had more frequently more sever clinical presentation like arterial dissection or arterial aneurysm. At the age of diagnosis males are younger compared to females. Large cohort studies showed the association of FMD with female sex, migraine, and intracranial aneurysm. FMD is an under-recognized vascular disease, more prevalent in females, but exhibiting more sever clinical presentation in males.

Key words: fibromuscular dysplasia; migraine disorders; sex characteristics; intracranial aneurysm

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Introduction

The European consensus provides a basic description of what constitutes fibromuscular dysplasia (FMD): an idiopathic, segmental, nonatherosclerotic, and noninflammatory disease of the musculature of the arterial walls characterized by abnormal cell proliferation and distorted architecture of the arterial wall, leading to narrowing of small and medium-sized arteries [1-3].

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FMD manifests mostly as beaded (multifocal) or focal lesions in medium-sized or small arteries, primarily in the kidneys and extracranial carotid and vertebral arteries. Almost all arterial beds may be affected, and involvement of multiple vessels is common. The clinical phenotype of FMD has recently been extended to include arterial dissection, aneurysm, and tortuosity [4,5]. However, in the absence of a string-of-beads or focal stenosis, these lesions are not sufficient to establish the diagnosis. In patients with multifocal/focal lesion(s) in at least one vascular bed, multivessel involvement of all affected vascular beds should be considered in the presence of aneurysm, dissection, or tortuosity in another vascular bed

(s) [2,3]. FMD lesions may be either symptomatic or clinically silent and hemodynamically significant or nonsignificant. The diagnosis of FMD requires differential diagnostic workup of other diseases [6]. After evaluation of the FMD diagnosis, involvement of other vascular beds should be investigated.

Discussion

Current knowledge on fibromuscular dysplasia incidence and clinical presentations based on registry data

Until two decades ago, FMD was thought to be a rare cause of renovascular hypertension in young women. The use of imaging techniques, the establishment of FMD registries, led to a number of new findings and now encompass a variety of anatomic and clinical manifestations.

The US Registry for FMD was launched in 2009 and currently includes nearly 3000 patients from 17 specialized FMD clinical centres. New centres have been added across the USA to increase geographical, racial/ethnic, and clinical diversity of the Registry population [7]. The French-Belgian ARCADIA Registry includes expert centres from 16 university hospitals in France and Belgium. It was established by the Hypertension Excellence Centre of the Hôpital Européen Georges Pompidou (Paris, France) [5,8]. The Polish study ARCADIA -POL was initiated in 2015 at the National Institute of Cardiology in Warsaw and now includes more than 300 patients with confirmed FMD referred by 32 centres [9-11]. The ARCADIA - POL study differed from other registries in terms of imaging protocol because CT angiography (CTA) of the intracranial and cervical arteries and CTA of the abdominal aorta, its branches, and upper and lower extremity arteries were performed in all patients during hospitalisation. Systematic and multidisciplinary examination of patients with FMD according to a study protocol revealed a large number of previously undetected typical stenotic lesions as well as other FMD-related lesions such as aneurysms and dissections. Such results indicate that FMD is systemic vasculopathy, and therefore a comprehensive evaluation of all arterial beds is necessary.

The European/International FMD registry was launched in Brussels in year 2015 and endorsed by the European Society of Hypertension (ESH) in 2016 [12,14]. It forms the nucleus of the wider European/International FMD Registry and Initiative (FEIRI) as of now, it enrolled about 1800 patients from 47 centres in 23 countries, also including Argentina, China, and Japan. Current knowledge on demographic data of the FMD at the time of disease recognition and clinical picture derive from these registries. From these registries it is clear that FMD is a disease that affects populations on all continents, equally and all races, without exception.

Although the incidence of FMD in the general population is unknown, it was found to be present on renal angiogram in up to 10 % of healthy kidney donors [14,15]. Most FMD patients are women (82 - 95 % in current registries), but FMD can occur in men, too. FMD can occur at any age, including in children and elderly patients, but most commonly occurs in young and middle adulthood. The average age at diagnosis of FMD is estimated to be 43 - 53 years in the different registries [16].

FMD patients in all registries had body mass index (BMI) within normal limits: in US Registry for FMD BMI was 26, in European/International Registry 25, in ARCADIA 24, in ARCADIA/POL 25, and were diagnosed at middle age, at age of 53 years, 46 years, 53 years, and 43 years, respectively. Hypertension was present in 67-91 %, with values varying according to presentation and the specialist's sensitivity to a particular clinical presentation. However, hypertension was diagnosed more than ten years earlier, at age of 36 - 45 years. FMD is mostly multifocal disease, in up to 95 % of patients. In most registries with one exception, the disease affects multiple vessels or vascular beds in about half of the patients.

Although the disease has a strong female preponderance, the clinical manifestation of disease vary by patient sex. While females have

mainly cerebrovascular disease and a nonspecific clinical presentations (Figure 1.), males have a more aggressive course with a higher frequency of aneurysms and dissections [12,17]. In US registry women were significantly more likely to have a family history of hypertension or stroke, but there were no differences in family history of aneurysm, dissection, or sudden death. Hypertension and headache were the most common symptoms leading to a diagnosis of FMD in both sexes, but women were significantly more likely to have other signs and symptoms of carotid and/or vertebral artery involvement than men, with higher rates of pulsatile tinnitus (35.7 % vs. 9.1 %), cervical bruit (26.8 % vs. 4.5 %), and neck pain (28.6 % vs. 13.3 %). Men compared with women were significantly more likely to have signs and symptoms of renal artery involvement, including flank and/or abdominal pain (43.8 % vs. 14.3 %), azotemia/renal insufficiency (9.1 % vs. 2.2 %), and renal infarction (42.9 % vs. 4.3 %). Renal and extracranial carotid arteries were the most commonly affected arterial beds in all registries, and also in this overall cohort which analysed sex differences (two thirds in both sexes), but there were significant differences between the sexes: Men were more likely to have renal involvement (89.7 % vs. 74.1 % in women), whereas women were more likely to have extracranial carotid involvement (74.9 % vs. 44.1 % in men). In a cohort of consecutive patients with first-ever cervical artery dissection (CeAD), enrolled in the setting of the multicentre IPSYS CeAD study (Italian Project on Stroke in Young Adults Cervical Artery Dissection), in multivariate analyses of putative risk factors, female sex, migraine, presence of intracranial aneurysm and familial history of arterial dissection showed association with cerebrovascular FMD [18].

Arterial dissections and aneurysms were common among patients in the US registry, with 21.7 % of patients having at least one dissection and 22.2 % of patients having one or more arterial aneurysms [6]. Men had a higher prevalence of aneurysms (40.8 % vs. 20.4 % in women) and dissections (39.6 % vs. 20.0 % in women). The most common sites of dissection in both sexes were the carotid artery (15.7 %), vertebral artery (4.2 %), and renal artery (4.1%). Renal artery dissections occurred significantly more frequently in men (18.5 % vs. 2.7 % in women).

European/International Fibromuscular Dysplasia Registry showed similar more aggressive affection of male patients compared

CARDINAL SYMPTOM OR SIGN

- Severe and/or chronic migraine headaches (> 15 days/month for > 3 months, which on at least 8 days/month), especially in the presence of other suggestive symptoms or signs
- Pulsatile tinnitus
- Cervical bruit on exam
- Stroke, TIA, or amaurosis fugax
- Unilateral head/neck pain or focal neurologic findings (e.g. partial Horner's syndrome with ipsilateral ptosis and miosis) suggestive of a cervical artery dissection

POSSIBLE SYMPTOM

- Headaches (not chronic migraine or not migraine-type)
- Tinnitus (not pulsatile)
- Dizziness/light-headedness

Figure 1. Clinical signs/symptoms of cerebrovascular fibromuscular dysplasia

to females (12). Compared with women with FMD, men were significantly younger at diagnosis of both FMD (42 ± 17 vs 47 ± 16 years) and hypertension (34 ± 16 vs 38 ± 15 years), were more likely to have focal FMD (46 % vs 23 %), and had fewer bilateral cerebrovascular lesions (17 % vs 26 %). In addition, men had a higher prevalence of arterial dissections than women (14 % vs 4 %), whereas no significant difference was found in the prevalence of arterial aneurysms (19 % in men vs 22 % in women). Similar results were obtained in IPSYS CeAD study where migraine was more common in the CeAD ischemic stroke group compared to ischemic stroke of other causes in young adults (30.8 % vs 24.4 %), and the difference was mainly due to migraine without aura [19]. Compared with migraine with aura, migraine without aura was independently associated with CeAD ischemic stroke (OR 1.74; 95 % CI 1.30 - 2.33) [12]. The strength of this association was higher in men (OR 1.99; 95 % CI 1.31 - 3.04) and in patients younger than 39.0 years (OR 1.82; 95 % CI 1.22 - 2.71).

All Registers showed the presence of aneurysm in approximately 20-31% of FMD patients, with most aneurysms located in the cerebrovascular bed [6,7,9,12]. This prevalence of unruptured intracranial aneurysms in FMD patients is higher than in the general population with has a life time incidence of 3-4 % [19]. Because of the risk of subarachnoid haemorrhage due to aneurysm rupture, surgical and endovascular aneurysm management are considered. The risk of complications from preventive aneurysm occlusion has decreased in recent decades, not only due to the advent of endovascular treatment but also due to a lower risk of complications from surgical treatment [20]. These data suggest that the balance of benefits and risks of screening has changed in favour of screening.

The ARCADIA (Assessment of Renal and Cervical Artery Dysplasia) registry analysed factors associated with carotid artery dissection ([21]. Patients with cervical artery dissection were younger, more often male, had a history of migraine, and less often had a history of hypertension than patients without cervical artery dissection. A systematic review was performed to establish an association between sex and CeAD [21]. Therefore, the additional data on sex from two previously published studies and unpublished data from the US Fibromuscular Dysplasia Registry and the European/International FMD Registry were used. In the pooled analysis that included almost 2000 patients of which 289 with CeAD, male sex was significantly associated with CeAD (OR 2.04; 95 % CI 1.41 - 2.95). This male predominance of (mostly carotid) dissection is in sharp contrast with the overwhelming female predominance of spontaneous coronary artery dissection, a disease often associated with extra-coronary FMD showing that the association between dissection and sex may be vessel-specific [12,22,23]. Although previous reports and registry results indicated an incidence of FMD of about 15-20 % in patients with craniocervical artery dissection, ARCADIA - POL results showed an incidence of up to 40 % [24]. Such results may indicate that FMD is mostly under-recognized disease, even in centres of excellence.

Anatomic and clinical manifestations of fibromuscular dysplasia/arterial structure and function

To establish a diagnosis of FMD arterial lesion should be classified according to angiographic appearance as focal FMD or multifocal FMD [2,3,6]. Besides angiography, non-invasive ultrasound techniques have been widely used as a primary screening method in assessment of patients suspected on FMD. Ultrasound screening methods have lower sensitivity for FMD detection due to localization of the disease which is mostly located in distal parts of internal carotid or vertebral artery or branches of the renal artery. Lesions usually do not cause significant stenosis, so it is difficult to identify them, especially on the basis of hemodynamic features.

There is insufficient awareness of the existence of vasculopathic findings, as each finding is presumed to be an atherosclerotic lesion. Also, lesions that do not cause significant

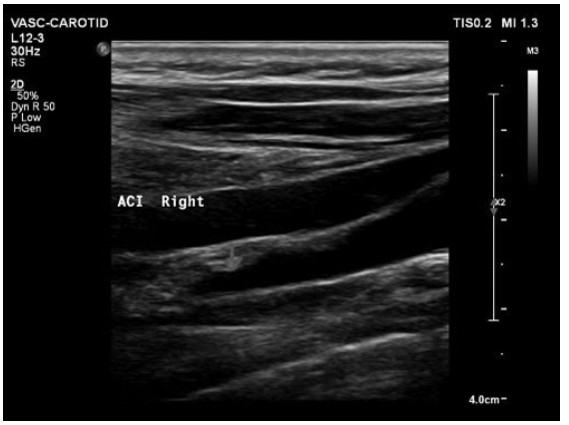

Figure 2. Ultrasound findings showing subtle luminal changes of mild beaded appearance of the distal part of internal carotid artery

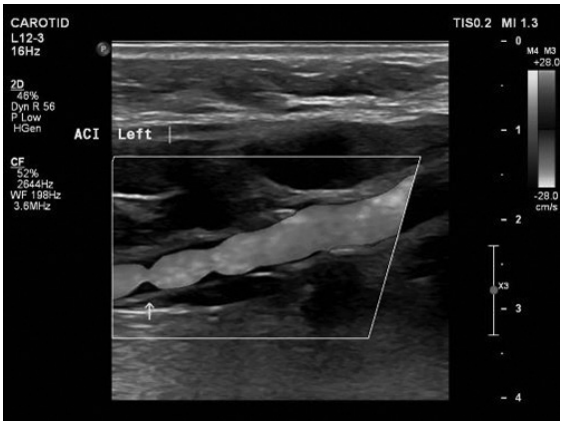

Figure 3. Ultrasound finding of multifocal stenosis of internal carotid artery

stenosis are insufficiently expressed, as is the finding of angiographic findings. High detection of FMD in patients with craniocervical artery dissection has been demonstrated from ARCAIDA - POL registry [10]. Such a finding suggests the possibility of insufficient recognition of lesions in other centres that are FMD focused, and especially in other centres that do not have as much expertise in diagnosis. A high volume neurosonology laboratory in out of 15 000 patients detected only 0,14 % FMD [24]. Therefore, expertise in lesion recognition is important [25,26]. Ultrasound detection may reveal a whole spectrum of findings ranging from subtle luminal changes of mild beaded appearance (Figure 2) to focal of multifocal stenosis (Figure 3). Concentric stenosis may be visible (Figure 4), as well as focal or diffuse increase of carotid intima-media thickness (IMT) (Figure 5), also called a "carotid marker". Tortuosity is found in one third of FMD patients (Figure 6). However, it's a

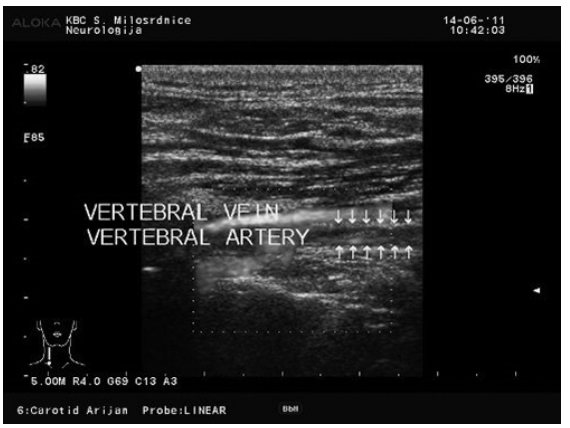

Figure 4. Ultrasound finding of concentric stenosis of the vertebral artery

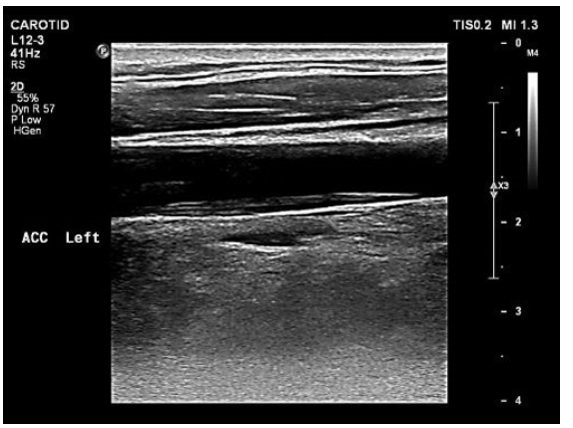

Figure 5. Carotid "marker" - increase of carotid intima - media thickness (IMT)

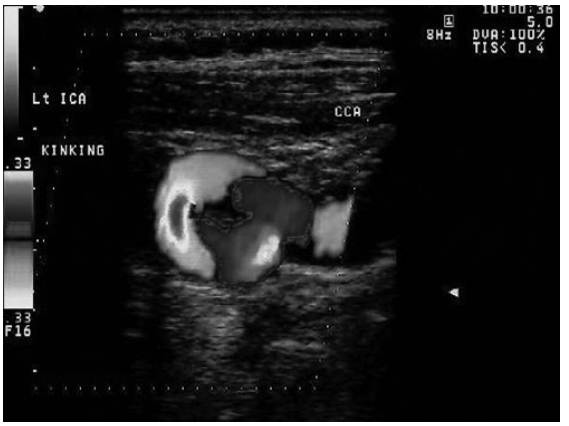

Figure 6. Tortuosity of internal carotid artery

nonspecific findings, since it can be detected in genetically mediated arteriopathies, as well as during aging, in longstanding hypertension, atherosclerosis or increased BMI. It is a sign of affection of another vessel only if a beaded or focal lesion is found in another artery.

Other forms of dysplastic lesions are recognized, which are classified as fibromuscular dysplasia. Carotid webs (CW) are endoluminal projectile fibrotic mass that generates flow stagnation and, consequently, thromboembolic events [27].

Case - control studies have found that CW are present in 9 % to 37 % of patients younger than 60 years with cryptogenic stroke, and that a CW increases the risk of ischemic stroke approximately 10- to 20- fold [28-30]. The risk of recurrent stroke is also high, ranging from 17-56 % [32,33]. Optimal treatment of this lesions are unknown.

Although patients with FMD may also have atherosclerotic lesions, they are less common than in the rest of the population, and found to be present in about 33 % of patients older than 65 years in European/International FMD registry [12]. Compared to Cardiovascular Health Study, including 5888 participants older than ≥ 65 years showed a prevalence of carotid atherosclerotic plaques in 77 % [33]. Due to lower cardiovascular events of the FMD patients in the registry, this may reflect survival or inclusion biases, or support the common belief that patients with FMD are somehow protected from atherosclerosis.

In the end, we can conclude that FMD is an under-recognized vascular disease. It includes a wide variety of anatomic and clinical presentations and is more prevalent in females, but exhibiting more sever clinical presentation in males.

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Conflict of interest

None to declare.

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