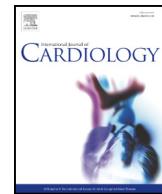




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Spontaneous coronary artery dissections and fibromuscular dysplasia: Current insights on pathophysiology, sex and gender

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ABSTRACT

Spontaneous coronary artery dissections (SCADs) are increasingly recognized as an important cause of acute coronary syndromes in predominantly women below 60 years of age. SCAD patients comprise a heterogeneous group, in which it is estimated that a quarter to one third have underlying fibromuscular dysplasia (FMD). Although the mutual relationship of SCAD and FMD is complex and only partly understood, there seems to be some overlap in genetic background and interaction with endogenous sex-steroids. In this review we provide an update of our current knowledge on these intriguing emerging arteriopathies.

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1. Introduction

An acute coronary syndrome (ACS) caused by a spontaneous coronary artery dissection (SCAD) is less rare than previously considered and occurs 9 times more often in women than in men [1]. A SCAD is defined as an acute development of a false lumen within the coronary artery, either caused by an intimal tear or an acute bleeding within the tunica media of the arterial wall. This leads to a compression of the true lumen, resulting in the clinical characteristics of an ACS. In most cases women between 35 and 65 years are affected, with a peak around 53 years of age [2–4]. It is estimated that up to 25% of all ACS within this age-group are caused by SCAD. Fewer than 10% of all SCADs appear in (late) pregnancy or after delivery (P-SCAD). In clinical practice, a SCAD is diagnosed by acute chest pain, (N)STEMI changes on the ECG, elevation of Troponins and typical characteristics at coronary angiography. The number of SCADs is still underestimated, as the angiographic features may be mistakenly for atherosclerosis [5]. Four major types of angiographic characteristics can be identified: type I with a double lumen, type II with a long and smooth stenosis, type III with an atherogenous-like aspect and type IV as a distal occlusion that becomes clear after reperfusion (with/without wiring) [1,5]. In addition,

increased coronary tortuosity is often present. In case of uncertainty intracoronary imaging with OCT/IVUS can be done to establish the correct diagnosis. In almost 60% the LAD is affected, followed by the RCA (26%) and RCX (19%) [6]. Although hypertension is present in one third of SCAD patients, other traditional cardiovascular disease (CVD) risk factors are less often reported than in traditional ACS [1]. Predisposing factors for the heterogeneous population of SCAD patients are female sex, pregnancy-related factors and hereditary mixed connective tissue disorders, whereas there are possibly associations with hormonal therapy, fibromuscular dysplasia (FMD) and inflammatory disorders. Emotional or physical triggers may act as precipitating stressors [3]. Gender differences in the pathophysiological impact of stress may be one of the reasons why an ACS caused by SCAD is so disproportionately predominant in women [3,7,8]. Fibromuscular dysplasia is the most commonly observed arteriopathy associated with SCAD. Patient series report a wide range in prevalence of FMD, varying between 17 and 86% [9]. As many SCAD patients are not routinely examined for FMD, more precise estimates are lacking. Like SCAD, FMD also has a strong female predominance (>80%) and it affects the renal and carotid arteries in about 75% of patients [10,11]. Fibromuscular dysplasia can manifest as vascular stenosis, aneurysm, dissection, occlusion or arterial tortuosity. Preliminary data from the US registry suggest that women may have more frequently carotid FMD lesions than men (74.9 vs. 44.1%, $p = 0.0004$). On the contrary, renal FMD might be even more frequent in men than in women (89.7 vs. 74.1%, $p = 0.032$) [12]. Up to now the strong female predominance in SCAD and FMD patients suggest that

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sex- and gender related factors are important in both entities and possibly also in their mutual relationship. In this paper we aim to focus on common aspects of SCAD and FMD.

2. Role of sex steroids and TGF-beta in arterial malformations

Both estrogens and androgens are involved in the development of CVD and hypertension. Estrogens have complex but important regulating effects on vascular reactivity, blood pressure, endothelial relaxation and cardiac/vascular remodeling through genomic and non-genomic effects [13–15]. Rapid actions of estrogens include the ability to stimulate endothelial NO synthase (eNOS) in vascular endothelial cells and the inhibition of proliferation of smooth muscle cells (SMC). Estrogens also modulate angiogenic factors, such as matrix metallo-proteinases (MMPs) and tissue growth factor- β (TGF- β). Elevated levels of TGF- β have been found in patients with the Marfan syndrome and in patients with FMD [16,17]. Estrogen decreases deposition of collagen and increases deposition of elastin, whereas testosterone has an opposite effect [18]. This is mediated by the expression of important MMPs including collagen, elastin, and fibrillin-1 and their regulators. In contrast, progesterone attenuates the increase in elastin deposition observed with 17 β -estradiol alone. A possible consequence is that high cyclic progesterone levels in premenopausal women may attenuate the beneficial effects of 17 β estradiol on the elastin/collagen ratio of the vascular wall. Cyclic symptoms in women before/after SCAD have been reported [19]. After menopause low 17 β estradiol levels enhance vascular stiffness and lower arterial compliance, resulting in more stiffened arteries and higher pulse pressure in elderly women than in age-matched males [20,21]. Modulation of sex steroid levels with ageing are therefore likely to interact with important sex differences in arterial stiffness across the lifespan. While a small study performed in a limited number of samples suggests that progesterone receptors are expressed in the nuclei of vascular smooth muscle cells of renal arteries from patients with FMD ($n = 6$) but not from controls ($n = 3$) [22], the role of sex hormones including progesterone in the pathophysiology of arterial changes in FMD needs to be further explored.

TGF- β enhances the production of collagen and the remodeling of the extracellular matrix [23]. Overproduction of TGF- β in Marfan patients reduces connective tissue elasticity and leads to weakness of the vascular wall. Aortic manifestations of the disease occur predominantly in male patients [24]. Arterial tortuosity in the coronary arteries is often present in SCAD patients (Fig. 1) and is a major though insufficiently studied vascular phenotype of FMD [25]. Increased TGF- β activity has been postulated to affect the degree of arterial tortuosity [26]. Accordingly, genetic syndromes in which arterial tortuosity is at the forefront, such as the Loeys Dietz syndrome and the rare Aneurysms Osteoarthritis Syndrome, are due to mutations in genes involved in the TGF- β pathway (*TGFB1/TGFB2* and *SMAD3*, respectively) [27,28]. Hypertension is in part regulated by steroid sex hormones and probably plays an important role in the pathophysiology of arterial tortuosity [29,30].

3. SCAD in pregnancy

Although SCAD was once considered primarily a peripartum condition, it is now clear from large multinational registry studies that pregnancy-associated SCAD (P-SCAD) accounts for a minority ($\leq 10\%$) of women with SCAD [2,3,7,31–33]. However SCAD accounts for around a quarter of ACS occurring during pregnancy and half of ACS in post partum patients [34,35]. Most P-SCAD events occur in a period from the third trimester of pregnancy peaking in the early (up to 6-months) post partum period but cases have been reported throughout gestation and late (up to 2-years) post partum, including in association with breast feeding (or the recent cessation of breast feeding) [36–38]. At present it is unclear if these very early or very late events represent true P-SCAD or are due to sporadic SCAD recurrence occurring by coincidence at these times. The true at-risk period

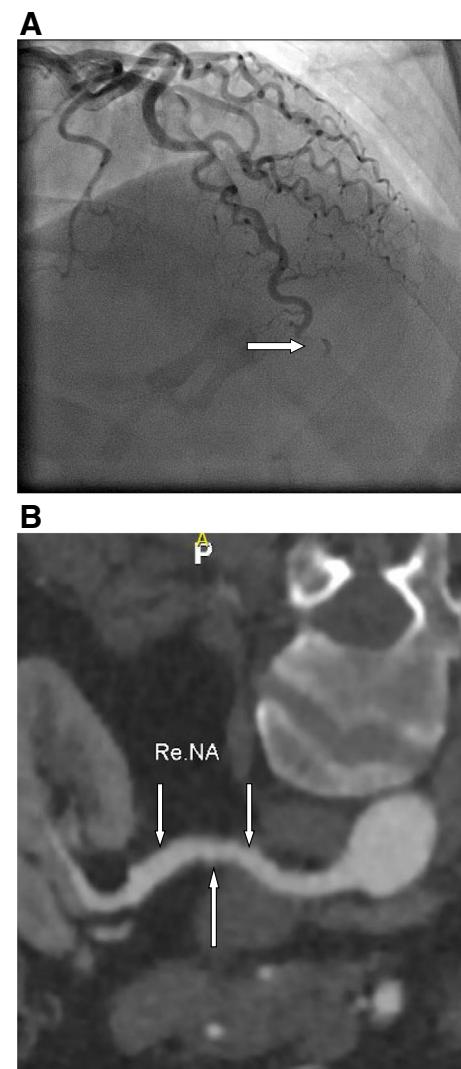


Fig. 1. Woman 53 years, known with premature hypertension and migraine in her teens/twenties, presents with SCAD- distal LAD (panel A). CT scan of her renal arteries reveals signs of FMD (string-of-beads) in the right renal artery (panel B).

for P-SCAD therefore remains ill-defined. Despite a hypothetical mechanistic association with increased coronary sheer stress, delivery per se does not appear to be a prime driver of P-SCAD events [38]. The very high progesterone-levels during pregnancy and the rapid hormonal changes thereafter may be an important reason why SCADs occur more often during or shortly after pregnancy. Up to now there are no other data suggesting that P-SCAD patients are different from other SCAD patients. More research is needed on potential triggers for SCAD during pregnancy.

Acute management of P-SCAD presents a unique series of challenges and requires a careful multidisciplinary approach with close monitoring of mother and fetus [39]. There is growing evidence that P-SCAD patients present with a more extreme SCAD phenotype characterized by more proximal coronary involvement and a higher proportion of ST-elevation myocardial infarction (STEMI), cardiogenic shock, arrhythmia (including as a cause of maternal death) and a reduction in post infarct ejection fraction [38,40,41]. The suggested approach to coronary management in P-SCAD is based on expert consensus [36,37,39]. The benefits of an accurate angiographic diagnosis and risk stratification outweigh the fetal X-ray exposure, which is manageable with contemporary techniques [39]. In line with general recommendations in patients with SCAD, a conservative approach to revascularization is favored, reserving percutaneous coronary intervention (PCI) for cases

with poor or absent coronary flow, ongoing evidence of significant ischaemia or infarction and a large myocardial area in jeopardy [36,37,39,42]. Coronary bypass surgery may be a useful bail-out in extremely high risk scenarios such as unstable proximal dissections or a failure of PCI to restore flow to a large myocardial territory but increased late graft failure following healing of the native coronary circulation has been reported [2]. Timing and mode of delivery should be an individualized multi-disciplinary decision [42]. Time interval since SCAD, left ventricular function, use of antiplatelet therapy and presence of a known connective tissue disorders or aortopathy will impact on this decision. Operative delivery is not mandatory in all cases and consideration of supported vaginal delivery with measures to minimize cardiac demand has been advocated [39]. There is currently very limited data on the risk of pregnancy in survivors of SCAD. Recurrence is well recognized in SCAD and is a potential additional concern over and above the issues of teratogenicity, the impact of left ventricular impairment and the risk of stent thrombosis on pregnancy risk [37,39,43]. A single series of nine pregnancies in survivors of SCAD reported a single recurrent SCAD occurring 9 weeks post partum [44]. It is not currently clear to what extent pregnancy per se constitutes an additional risk over and above the background recurrence risk in SCAD. However, patients should avoid unplanned pregnancy and those contemplating planned pregnancy should be carefully counseled [42].

The risks of pregnancy in patients with FMD are less well studied. However, several elements should be kept in mind. First, patients with FMD may harbour aneurysms of renal or visceral arteries, with a potentially increased risk of rupture during pregnancy [45,46]. Second, a retrospective study by Vance et al. suggests a substantially increased risk of preeclampsia in women with FMD [47]. Finally, in some instances, hypertension due to renal artery FMD may become refractory during pregnancy [48]. Accordingly, screening for renal artery FMD using sensitive methods such as CT- or MR-angiography is worth considering in all hypertensive women planning a pregnancy. In case of FMD lesions of renal arteries requiring revascularization, percutaneous angioplasty should be performed before pregnancy, and a comprehensive vascular screening (from brain to iliac arteries) should be foreseen, in order to rule out the existence of aneurysms or dissections of other arterial beds. Finally, patients with known FMD who decide to become pregnant should be followed in a high volume obstetrical centre with expertise in at-risk pregnancies [42], in tight collaboration with a specialist in vascular medicine or FMD expert.

4. Risk factors and precipitators for SCAD

A large number of conditions have been described in case reports or small case series in patients with SCAD [36,37]. However, many of these are probably simply co-incident conditions rather than true risk factors. It is now well-recognized that SCAD is not confined to women of child-bearing potential but that its incidence extends well into the post-menopausal years [36,37]. Furthermore, although exogenous sex hormones (i.e. hormonal contraception and hormone replacement therapy) are frequently considered a risk, [3,31,49–51] given the highly prevalent population use of these drugs, an association with either SCAD or SCAD recurrence has yet to be clearly established and the relative risk or benefit of specific hormone treatment strategies is unknown.

The precise relationship between exercise and SCAD is also complex. It is clear that extreme (and particularly isometric) exercise can rarely trigger SCAD, [52–56] with an association reportedly more frequent in men [8]. There also seem to be a subset of SCAD patients who exercise to a high (if not elite) level. In these patients the temporal association between specific exercise episodes and the onset of SCAD-related symptoms does not suggest that exercise is acting as a trigger [43]. There is no evidence that exercise is a precipitating factor for SCAD recurrence and whilst avoidance of extreme exercise seems sensible, cardiac rehabilitation is reportedly beneficial [57,58].

It is increasingly recognized that SCAD is one of a series of partially overlapping disorders. These include hereditary connective tissue disorders (CTD), FMD, cervical and intracerebral dissection, migraine and pre-eclampsia (Fig. 2) [36,37]. These associations may be partly genetic (see below) but the precise mechanisms explaining the interrelationship between these conditions remain to be elucidated. In some series the occurrence of SCAD has been associated with (systemic) inflammatory disorders and autoimmune diseases, but this has not been reported by others [3,4]. Thus far, inflammation has not been found to be associated with FMD [10].

5. Psychosocial stress-related factors and SCAD

Severe emotional distress is a potential trigger for an ACS in both women and men, but coping with stress is importantly different among both genders [3,59,60]. Psychosocial stress is often reported by SCAD patients in the months/weeks before the acute event. This may act as a 'trigger' for SCAD. One working hypothesis in SCAD patients is that (prolonged) emotional distress leads to endothelial dysfunction and low-thresholds for vascular spasm. These pathophysiological processes may create a substrate that increases the vulnerability for a sudden intimal tear in the vessel wall that is triggered by physical and emotional stressors, resulting in a SCAD. As a SCAD usually occurs in previously 'healthy' young women, the impact of such an event is huge. The use of antidepressants/anxiolytic agents has been reported in >30% of patients after SCAD [61]. Mental stress-induced ischemia occurs twice as often in women after ACS than in men [62]. This may account for the relative high percentage (>50%) of reported residual symptoms in predominant women after SCAD [63]. Patients with FMD also report an array of psychological symptoms and concerns [64]. Whether the latter are secondary to the announcement of the disease, severity of complications and related anxiety or, at least in some patients, may be part of the disease spectrum is the object of current investigations.

6. Genetic aspects of SCAD and FMD

There is evidence for a genetic component for SCAD and FMD but the identification of the genetic causes has been a challenging task. Familial

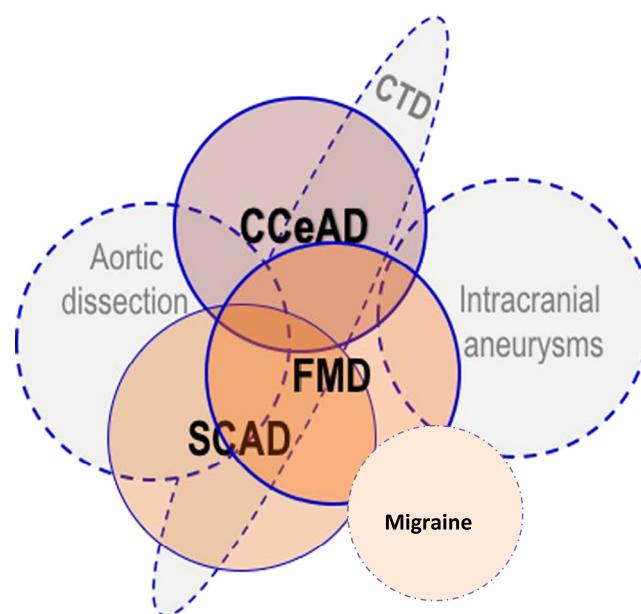


Fig. 2. Overlapping disorders related to SCAD and FMD. CCeAD: Cervico-cerebral artery dissection CTD: connective tissue diseases SCAD: spontaneous coronary artery dissection FMD: fibromuscular dysplasia.

recurrence was investigated in a series of ~100 FMD patients and their hypertensive relatives and concluded to the presence of familial FMD in ~11% of cases, with no evidence for a more severe presentation among familial versus sporadic cases [65]. However, such familial cases may be overrepresented in a highly specialized FMD center. By contrast, in registries, familial FMD was reported in only 2.8–2.9% of symptomatic cases, though admittedly systematic screening of asymptomatic family members may have led to a higher prevalence [30,66]. Familial cases of SCAD were reported to be rare (<2%) in series of over 400 patients and were limited to siblings or mother-daughter pairs [67]. SCAD and FMD were considered for long time rare vascular diseases and their clinical overlap with some rare CTD suggested that a similar genetic model might apply to their mode of inheritance. Features of CTD appear to be more frequent in patients with FMD, though data on the prevalence of such systemic manifestations are conflicting [17]. Notably however, such patients generally do not harbour mutations in genes causative for vascular and connective tissue Mendelian disorders (e.g. Marfan, Loeys-Dietz, vascular Ehlers Danlos syndromes among others) [16]. This finding further supports a previous investigation that showed low yield of genetic testing in patients with FMD for most of known vascular and connective tissue genes [68]. More recently, among 44 SCAD patients who underwent cardiovascular genetics testing in a prospective setting, 6 patients (~8%) had an identifiable genetic cause, with 3 patients carrying mutation in *COL3A1*, the causative gene for vEDS [69]. Overall, SCAD and FMD patients only exceptionally carry mutations for known genes of inherited vascular diseases and CTD. This motivates and encourages specific genetic investigation to understand the etiology of FMD and SCAD. The investigation of the exomes of 16 FMD related patients showed genetic heterogeneity and made unlikely the existence of a major gene for FMD, although this study was underpowered and large-scale exome studies are still missing [70]. A recent study identified the genetic cause of the Grange Syndrome, a rare autosomal-recessive disorder characterized by severe and early onset vascular abnormalities, comparable to focal FMD [71]. In this study, the author reported mutations in *YY1P1* encoding a protein involved in transcription regulation, DNA repair and replication and provided evidence for this gene to be important for the proliferation and TGF-beta mediated differentiation of vascular smooth muscle cells [71]. Given the rarity of this syndrome, only 1 frameshift mutation was found in *YY1P1* in non syndromic FMD and this gene is thus unlikely to be at the origin of common forms of FMD [71]. On the other hand, increasing epidemiological evidence supports FMD and SCAD to be neglected rather than rare and alternative strategies to genetic testing or exome studies to decipher their genetic causes proved to be informative. The study of 26,000 common genetic variants in ~250 FMD patients and followed up in >900 patients and ~2500 controls supported the association with FMD of *PHACTR1/EDN1* [72], a genetic locus on chromosome 6q24 reported to confer risk for Coronary Artery Disease and Acute Myocardial Infarction, but in an opposite directional effect of the risk allele compared to FMD [73,74]. *PHACTR1/EDN1* risk allele for FMD is also associated with migraine [75] and cervical artery dissection [76], supporting shared genetic control between these cardiovascular and neurovascular diseases (Fig. 2). The putative causal genetic variant at the *PHACTR1* locus has recently reported to lie in a putative enhancer for *EDN1*, the endothelin-1 gene [77]. However, this locus only contributes to a ~40% increased risk for FMD and the mechanism that may link a decrease in endothelin-1 circulating levels with an increased risk for FMD is still to be determined. These genetic findings suggest that FMD and likely SCAD, are under the control of numerous genetic variants, with weak to moderate individual effects. We expect that genetic studies, including well-powered full exome and genome-wide association studies will shed light on the full picture of the genetic makeup of FMD and SCAD patients, and potentially enhance our scarce knowledge about the underlying biology of these atypical and women-specific vascular diseases.

7. Connective tissue diseases (CTD) in FMD and SCAD: similarities and differences

Several arguments suggest the existence of an overlap between FMD and CTDs: (i) FMD is associated with a wide spectrum of vascular abnormalities, including aneurysms, dissections and arterial tortuosity [10,78], which are also part of the phenotype of inherited CTDs such as vascular Ehlers-Danlos [79] and Loeys-Dietz syndrome [27]; (ii) both FMD and less often CTD can be associated with SCAD [1,8]; (iii) FMD is a systemic vascular disease, with two or more vascular beds involved in over 50% of cases [30] and (iv) cases of patients with Ehlers-Danlos type IV or Marfan syndrome coexisting with FMD-like abnormalities [68], or FMD patients with features suggestive of CTD have been occasionally reported [80,81].

Screening for systemic features suggestive of CTD in patients with FMD (mostly females with multifocal FMD) was performed in two cohorts, both from the United States. In 47 FMD patients explored at the National Institute on Ageing (NIA, Baltimore) 4 or more features suggestive of mild CTD were documented in 95.7% of patients, including hyperlaxity (Beighton score ≥ 5 in 57.4% of patients), early onset degenerative spine disease (95.7%), pectus deformity (40.4%) and various craniofacial abnormalities [17,82]. In contrast, in a cohort of 139 patients followed at the Cleveland Clinic [80], only 18.7% of patients harboured ≥ 4 features suggestive of CTD, hyperlaxity (Beighton score ≥ 5) was rare (2.9%), pectus deformities were present in only 7.2% of patients, and other classical CTD features such as hypertelorism or cleft palate were not or seldom observed. Still, compared to historical control populations, several characteristics were more often encountered. Besides pectus deformities, the latter include palatal abnormalities (56.1%), dental crowding (29.7%), moderately severe myopia (29.1%), and early onset arthritis (15.6%). Furthermore, in the same cohort [80], several CTD features such as high palate, pneumothorax and atrophic scarring tended to be more frequent in patients harbouring at least one arterial dissection or two aneurysms ("high risk vascular group"). Discrepancies between both studies [17,80] may reflect differences in patient characteristics and disease severity: in the NIA cohort [16], 21.3% of patients underwent open surgery and 48.9% had a cerebrovascular event, while patients from the Cleveland cohort [68] appeared more representative of patients included in the US registry. Interestingly, compared to age and gender-matched controls, patients with FMD included in the NIA study ($n = 38$) had evidence of increased inflammatory markers, including TGF-beta 1 and 2 [17]. In particular, plasma levels of TGF-beta1 were similar to those observed in patients with Marfan syndrome [83], while, in multivariable regression, plasma TGF-beta2 levels were predictive of the number of arterial beds affected by FMD (string-of-beads, aneurysms, stenosis or tortuosity). As mentioned above, TGF-beta 1 and TGF-beta 2 secretion in dermal fibroblast cell lines of patients with FMD ($n = 16$) was higher than in age and gender-matched controls. Finally, in a series of 35 patients with FMD, two variants in the transforming growth factor beta receptor 1 (*TGFBR1*) gene were identified in two unrelated patients, both with medial fibroplasia and a history of multivessel dissection [68]. Both variants induced an amino acid substitution in a highly conserved region of *TGFBR1*, however their role is unknown. These findings are of interest, since both Loeys-Dietz syndrome, due to mutations in genes encoding TGF-beta receptors 1 and 2, and the very rare Aneurysms Osteoarthritis Syndrome, due to mutations in *SMAD3*, are associated with aneurysms, arterial tortuosity and for the latter early-onset osteoarthritis [27,28]. Still, as mentioned above, the yield of genetic screening oriented by clinical indications (including genes such as *TGFBR2*, *COL3A1*, *FBN1*, *ACTA2*, or *SMAD3*) was low [17,68].

As a whole, while arterial aneurysms, dissections and arterial tortuosity may occur both in FMD and several inherited CTDs, the typical string-of-beads (Fig. 1) is almost pathognomonic of multifocal FMD [10,78]. Even in FMD patients with extra-vascular features suggestive of CTD, mutations in genes at the origin of inherited CTDs are seldom

identified. Still, CTD clinical features are probably more frequent in patients with FMD than in healthy controls, but their exact prevalence remains to be determined in larger and more diverse cohorts, compared with matched controls from the same populations. Whatever their prevalence, CTD-like extravascular abnormalities identified in patients with FMD appear to be milder than those observed in CTDs. Thus, major complications suggestive of CTD such as hollow organ rupture associated with a history of arterial aneurysms or dissection should prompt genetic screening for CTDs, even in presence of vascular images compatible with FMD [68].

SCAD has also been associated with CTD, especially Marfan syndrome and vascular Ehlers–Danlos syndrome [84,85]. In clinical practice genetic screening is not routinely performed in SCAD patients and often randomly done in those who have signs of hypermobility or Marfan-like physical characteristics. Data from a single center patient series showed that 3 out of 59 patients had a clear CTD mutation (*FBN1* and *COL3A1*), 20.3% had genetic variants of unknown significance, but a distinct vascular phenotype was not identified [86]. Further genetic studies are warranted in SCAD patients to unravel potential CTD abnormalities.

8. Conclusion

The vast majority of patients diagnosed with SCAD and FMD are women below 60 years of age. Although the mutual relationship of both entities is complex and only partly understood, there seems to be some overlap in genetic background and interaction with endogenous sex-steroids. A variety of external factors and co-morbidities interfere with their occurrence. A diversity of phenotypes of FMD are expressed in individuals, leading to a heterogeneous group of patients. Identification of susceptibility genes and associated biomarkers, as well as careful study of hormonal profile, in correlation with various clinical presentations will help unraveling the pathophysiology and improving the classification of this intriguing group of diseases. The final aim would be to individualize management and follow-up according to each patient's specificities, with particular attention to sex and gender-related issues such as pregnancy, breastfeeding or exogenous hormonal intake.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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