



Male Sex Is Associated With Cervical Artery Dissection in Patients With Fibromuscular Dysplasia

Charlotte Arnaud, Marion Boulanger, Aurélien Lorthioir, Laurence Amar,
Arshid Azarine, Louis Boyer, Gilles Chatellier, Silvia Di Monaco, Xavier
Jeunemaitre, Adrian Kastler, et al.

► To cite this version:

Charlotte Arnaud, Marion Boulanger, Aurélien Lorthioir, Laurence Amar, Arshid Azarine, et al.. Male Sex Is Associated With Cervical Artery Dissection in Patients With Fibromuscular Dysplasia. Journal of the American Heart Association, 2021, pp.e018311. 10.1161/JAHA.120.018311 . hal-03236182

HAL Id: hal-03236182

<https://hal.univ-lorraine.fr/hal-03236182>

Submitted on 26 May 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.









L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

ORIGINAL RESEARCH

Male Sex Is Associated With Cervical Artery Dissection in Patients With Fibromuscular Dysplasia

Charlotte Arnaud, MD*; Marion Boulanger , PhD*; Aurélien Lorthioir , PhD; Laurence Amar , PhD; Arshid Azarine , PhD; Louis Boyer, PhD; Gilles Chatellier, PhD; Silvia Di Monaco, PhD; Xavier Jeunemaitre, PhD; Adrian Kastler, PhD; Elie Mousseaux , PhD; Catherine Oppenheim, PhD; Frédéric Thony, PhD; Alexandre Persu , PhD*; Jeffrey W. Olin , PhD*; Michel Azizi, PhD*; Emmanuel Touzé , PhD; on behalf of the ARCADIA Co-investigators[†]

BACKGROUND: Cervical artery dissection (CeAD) is a frequent manifestation of fibromuscular dysplasia (FMD). However, risk factors for CeAD are unknown. We investigated factors associated with CeAD in the ARCADIA (Assessment of Renal and Cervical Artery Dysplasia) registry.

METHODS AND RESULTS: The ARCADIA registry includes women or men aged ≥ 18 years, with a diagnosis of renal, cervical, or intracranial artery FMD, who were prospectively recruited at 16 university hospitals in France and Belgium. Diagnosis of acute or past CeAD at inclusion was established on imaging according to standard diagnostic criteria. Associations between potential determinants and CeAD were assessed by logistic regression analyses. Among 469 patients (75 men) with FMD, 65 (13.9%) had CeAD. Patients with CeAD were younger, more likely to be men, have a history of migraine, and less likely to have a history of hypertension than patients without CeAD. In the multivariable analysis, male sex (odds ratio [OR], 2.66; 95% CI, 1.34–5.25), history of migraine (OR, 1.90; 95% CI, 1.06–3.39), age ≥ 50 years (OR, 0.41; 95% CI, 0.23–0.73), history of hypertension (OR, 0.35; 95% CI, 0.20–0.64), and involvement of ≥ 3 vascular beds (OR, 2.49; 95% CI, 1.15–5.40) were significantly associated with CeAD. To validate the association between CeAD and sex, we performed a systematic review. We collected additional data on sex from 2 published studies and unpublished data from the US Registry for Fibromuscular Dysplasia and the European/International FMD Registry. In the pooled analysis (289 CeAD, 1933 patients), male sex was significantly associated with CeAD (OR, 2.04; 95% CI, 1.41–2.95; $I^2=0\%$).

CONCLUSIONS: In patients with FMD, male sex and multisite involvement are associated with CeAD, in addition to other previously known risk factors.

REGISTRATION: URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT02884141.

Key Words: cervical artery dissection ■ fibromuscular dysplasia ■ sex

Fibromuscular dysplasia (FMD) is an idiopathic, systemic, noninflammatory, and nonatherosclerotic vascular disease of small to medium-size arteries, primarily affecting the renal and cervical arteries.^{1,2}

Involvement of the cervico-encephalic arteries is now considered as frequent as that of renal arteries,^{3,4} and the latest international consensus guidelines on the diagnosis and management of FMD recommend

Correspondence to: Emmanuel Touzé, PhD, Université Caen-Normandie, CHU Caen Normandie, Avenue de Côte de Nacre, 14000 Caen, France. E-mail: emmanuel.touze@unicaen.fr

*C. Arnaud, M. Boulanger, A. Persu, J. W. Olin, and M. Azizi contributed equally.

[†]A complete list of co-investigators in the ARCADIA (Assessment of Renal and Cervical Artery Dysplasia) study is provided in the Appendix at the end of the article.

For Sources of Funding and Disclosures, see page 10.

© 2021 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Recent data from international registries of patients with fibromuscular dysplasia show that involvement of the cervico-encephalic arteries is as frequent as that of renal arteries. Dissection is also a frequent manifestation of fibromuscular dysplasia.
- In this prospective international study, the prevalence of cervical artery dissection averages 14% in patients with fibromuscular dysplasia.
- Male sex, age <50 years, history of migraine, involvement of ≥ 3 vascular beds, and absence of history of hypertension are independent risk factors for cervical artery dissection in fibromuscular dysplasia.

What Are the Clinical Implications?

- Demographic characteristics and severity of the disease can help stratify patients with fibromuscular dysplasia with high risk of cervical artery dissection.
- Clinicians should be aware of the increased risk of cervical artery dissection in young patients and men with fibromuscular dysplasia.
- Neck strain from activities or manipulative therapy of the neck should be avoided in these high-risk subgroups.

Nonstandard Abbreviations and Acronyms

ARCADIA	Assessment of Renal and Cervical Artery Dysplasia
CeAD	cervical artery dissection
FMD	fibromuscular dysplasia

systematic vascular screening from head to pelvis in all patients with FMD.¹ Although neurological manifestations of FMD are rare and generally considered as benign, severe complications, including ischemic and hemorrhagic stroke, may occur.^{3,5}

Symptomatic or asymptomatic cervical (carotid or vertebral) artery dissection (CeAD) is a frequent manifestation of FMD. Thus, recent data from the United States Registry for Fibromuscular Dysplasia (US FMD Registry) show that the prevalence of CeAD is estimated to be 21%, with a higher prevalence of carotid (16%) than vertebral (5%) artery dissection. Additionally, among patients with a neurological presentation leading to diagnosis of FMD, the prevalence of CeAD is even greater, being 27% in the ARCADIA (Assessment of Renal and Cervical Artery Dysplasia) registry.⁶ In

addition, cervical arteries remain the main location of arterial dissections in FMD. Among patients with FMD with an arterial dissection in the US FMD Registry, carotid artery dissections accounted for 64% of all dissections, and vertebral artery dissections accounted for 21% of all dissections. The presence of multiple CeADs is not uncommon in patients with FMD and is estimated to be up to 37%.^{4,7} However, in patients with FMD, the absolute risk of and risk factors for CeAD remain unknown.

In patients with CeAD, the overall prevalence of cervical FMD is estimated to be as high as 15% to 20%,⁶ and the diagnosis of FMD is more frequently reported in patients with multiple CeAD⁸ or recurrent CeAD.⁹ Several other factors including younger age, migraine (especially migraine without aura), mechanical trigger events, and infections have been reported to be associated with CeAD.¹⁰ In contrast, the presence of high body mass index or hypercholesterolemia is less commonly reported in patients with CeAD compared with controls, whereas the association with hypertension remains controversial.¹¹

In this study, we aimed to investigate factors associated with CeAD in patients with renal or cervico-encephalic FMD using the ARCADIA French and Belgium registries.

METHODS

Any anonymized data not published within the article can be shared at the request of other investigators for purposes of replicating procedures and results.

The design and methods of the ARCADIA study have been published elsewhere.⁶ In brief, included patients were women or men aged ≥ 18 years diagnosed with renal, cervical, or intracranial artery FMD, who were prospectively recruited at 16 university hospitals in France and Belgium from 2009 to 2014. The diagnosis of FMD had to be established in the vascular bed, where the condition was presumed to be symptomatic, by recent (within 2 years before inclusion) computed tomography angiography, magnetic resonance angiography, or digital subtraction angiography. FMD was diagnosed as nonatherosclerotic arterial encroachment or stenoses affecting the trunk or branches of medium-size arteries, in the absence of aortic wall thickening, inflammation, and known syndromic arterial disease.^{1,12} Patients with isolated artery aneurysms or isolated artery dissections (ie, without artery stenosis) were not considered to have FMD. Circumstances leading to the diagnosis of FMD were either (1) renal presentations including hypertension, acute kidney infarction, and miscellaneous conditions leading to renal artery imaging or (2) neurological presentations, among which were acute cerebrovascular events (stroke, transient ischemic

attack, subarachnoid hemorrhage, and acute CeAD), migraine, unruptured intracranial arterial aneurysm, and other neurological signs or symptoms, such as cervical bruit, cervical pain, nonmigraine headache, pulsatile tinnitus, and nonspecific symptoms such as dizziness or light-headedness. We collected information on sex, age at FMD diagnosis and at inclusion, ethnicity, FMD type (multifocal or focal), history of hypertension, diabetes mellitus, migraine, and smoking (former or current smoker), family history of FMD, and body mass index. Hypertension was defined as known history of hypertension or current use of antihypertensive medication(s), and diabetes mellitus was defined as known history of diabetes mellitus or current use of antidiabetic medication(s). We used a standardized questionnaire to diagnose migraine, with or without aura, in accordance with the international classification of headaches.¹³

After inclusion, all patients diagnosed with FMD underwent head-to-pelvis vascular imaging; patients with renal artery FMD underwent computed tomography angiography or magnetic resonance angiography from the aortic arch to the intracranial arteries, and those with cervical/intracranial FMD underwent computed tomography angiography or magnetic resonance angiography from the diaphragm to the pelvis. Computed tomography angiography was the preferred imaging test because of its higher resolution when compared with magnetic resonance angiography. Images were reviewed by at least 2 readers in each participating center, and type of FMD was classified as focal FMD in case of a single stenosis on a given vessel, regardless of its length, or multifocal FMD (the string-of-beads pattern) in the presence of ≥ 2 stenoses on a given vessel segment, as previously reported.¹² Patients with focal or multifocal lesions affecting at least 2 of the 4 predefined vascular sites (renal, cervical or intracranial, mesenteric/splenic, and iliac arteries) were classified as having multisite FMD, and the others, irrespective of the presence of unilateral or bilateral FMD lesions of the renal or cervical/intracranial arteries, were classified as single-site FMD. The radiological diagnosis of multifocal FMD could be asserted by local investigators/radiologists, whereas focal FMD had to be confirmed centrally by 2 independent investigators before inclusion. All imaging studies from patients diagnosed locally with multisite FMD were centrally reviewed by a core imaging committee to confirm multisite status. The protocol was approved by the local ethics committee, and all participants provided written informed consent. The study is registered at ClinicalTrials.gov (URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT02884141).

The diagnosis of CeAD was established by stroke specialists in each participating center, according to standard diagnostic criteria, and at least 1 of the

following imaging parameters was mandatory: presence of a mural hematoma, aneurysmal dilation, long tapering stenosis, intimal flap, double lumen, or occlusion >2 cm above the carotid bifurcation revealing a flame-shaped occlusion, an aneurysm, or a long tapering stenosis after recanalization.¹⁴ For the present study, patients with an acute symptomatic CeAD and those with a past history of CeAD or a typical sequela of CeAD (extracranial dissecting aneurysm) on imaging, whether symptomatic or not, were all considered as having a CeAD. Patients with intracranial extension of their CeAD ($n=3$) were not excluded, and no patient with isolated intracranial artery dissection was included.

In view of our findings on the association between CeAD and sex observed in the ARCADIA registry, we undertook a systematic review of studies of patients with FMD reporting data on CeAD and sex. We report our study according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.¹⁵ We used a search strategy using the keyword “fibromuscular dysplasia” in PubMed from inception to January 31, 2020. Two reviewers (C.A. and M.B.) independently screened all titles and the abstracts, and then the full texts of potentially eligible studies to extract data on sex and CeAD in patients with FMD. If there were multiple publications from a study cohort, we included only the publication with the largest amount of data relevant to this review. We did not restrict inclusion by language of publication or sample size. We also added unpublished data from the European/International FMD Registry (A. Persu, PhD, unpublished data, 2019) and US FMD registry (J.W. Olin, PhD, unpublished data, 2019). Although there was no peer review on the latest data from these 2 registries, FMD diagnosis and patients’ clinical and imaging characteristics were assessed by experienced physicians in both registries.

Two reviewers (C.A. and M.B.) assessed risk of bias at the study level on the basis of whether the inclusion was prospective or retrospective, the characteristics of the population (setting, mean age, race, proportion of history of hypertension), and FMD type. We relied on the authors’ definition of CeAD. Risk of bias across studies was not assessed.

Statistical Analysis

Categorical variables were compared with the Pearson χ^2 test and continuous variables with 2-tailed t tests. Associations between CeAD and potential determinants were assessed by univariate regression analysis, and odds ratio and corresponding 95% CI were reported. Relevant variables that were associated with CeAD at a level of $P \leq 0.10$ were entered into the logistic regression model, and adjusted odds ratio

and 95% CI were reported. Accurate information on the start of FMD can be challenging to record because the disease can remain asymptomatic or diagnosed years after the first symptom, and FMD diagnosis is often made when patients suffer from complications (eg, stroke, acute renal infarction). Therefore, the age at FMD diagnosis might not be reliable, and we thought that the age at inclusion would be more relevant. To further minimize the risk of bias, we estimated the dichotomized variable of age ≥ 50 years at inclusion to be the most reliable data.

We used meta-analysis to pool studies' unadjusted summary measures of association between male sex and CeAD using the Mantel-Haenszel random-effects method, and we reported odds ratios and 95% CIs. We quantified statistical heterogeneity between studies with the χ^2 test and inconsistency across studies using the I^2 statistic that describes the percentage of the variability in effect estimates that is caused by heterogeneity rather than sampling error.¹⁶

All analyses were done using Stata SE 15.0 software (StataCorp, College Station, TX).

RESULTS

As previously reported, among the 499 patients recruited in the ARCADIA study, FMD was confirmed in 469 patients, of whom 75 (16%) were men and 415 (89%) were Caucasian (Table 1).⁶ Circumstances leading to the diagnosis of FMD were renal presentations in 304 (65%) patients, including 268 with hypertension and 11 with acute renal infarction. Neurological presentations occurred in 165 (35%) patients, including 100 patients with acute cerebrovascular events (21 with ischemic stroke, 13 with transient ischemic attack, 21 with SAH, 25 with acute isolated CeAD, 10 with acute CeAD with ischemic stroke, 9 with acute CeAD with transient ischemic attack, 1 with acute CeAD and subarachnoid hemorrhage).

Demographics and prior comorbidities were similar in patients with renal and neurological presentations except for the prevalence of hypertension, which was higher in those with renal presentation (Table 1). Presence of intracranial aneurysm was more frequent in patients with neurological presentation than in those with renal presentation (Table 1).

Table 1. Baseline Characteristics of Patients With FMD in the ARCADIA Registry, Based on Renal or Neurological Presentation

	All Patients, N=469	Type of FMD Presentation		P Value
		Renal, n=304	Neurological, n=165	
Demographics				
Male sex	75 (16)	47 (15)	28 (17)	0.67
Caucasian	415 (88)	269 (88)	146 (88)	1.00
Mean (SD) age at FMD diagnosis, y	53.1 (13.4)	52.7 (14.0)	53.9 (12.2)	0.36
Mean (SD) age at inclusion, y	53.9 (13.3)	53.5 (13.9)	54.7 (12.0)	0.33
Age ≥50 y at inclusion	293 (62)	183 (60)	110 (67)	0.17
Prior comorbidities				
Hypertension	363 (77)	268 (88)	95 (58)	<0.001
Diabetes mellitus	19 (4)	15 (5)	4 (2)	0.20
BMI ≥25 kg/m ²	161 (34)	110 (36)	51 (31)	0.25
Smoking	199 (42)	126 (41)	33 (20)	0.56
Menopause, in women*	217 (46)	140 (54)	77 (56)	0.90
Migraine [†]	133 (28)	77 (25)	56 (34)	0.07
Imaging				
Multifocal FMD	429 (91)	275 (90)	154 (93)	0.29
Intracranial arterial aneurysm	53 (11)	16 (25)	288 (71)	<0.001
Multisite involvement, no. of predefined sites involved				0.036 [‡]
1	244 (52)	168 (55)	76 (43)	...
2	154 (33)	98 (32)	56 (34)	...
≥3	71 (15)	38 (13)	33 (20)	...
Presence of multisite involvement (yes vs no)	225 (48)	136 (45)	89 (54)	0.06

Data are presented as number (%) unless otherwise specified. ARCADIA indicates Assessment of Renal and Cervical Artery Dysplasia; BMI, body mass index; and FMD, fibromuscular dysplasia.

*Data missing for 3 patients.

†Data missing 1 patient.

‡ANOVA test. Multisite involvement is defined by the presence of FMD lesions in at least 2 of the 4 predefined sites: renal, cervico-encephalic, mesenteric/splenic, or iliac arteries.

Men and women were comparable in terms of age, race, and presence of main vascular risk factors except for smoking and high body mass index, which were higher in men (Table 2). Men were less likely to have migraine. The prevalence of multifocal FMD type, multisite involvement, and intracranial aneurysm did not significantly differ between men and women (Table 2).

A total of 65 patients (14%) had at least 1 CeAD, with 87 arteries (67 carotid and 20 vertebral) being involved. Among the 65 patients with a CeAD, 49 (75%) had a neurological symptom leading to the diagnosis of FMD, and 16 (25%) had a renal presentation of FMD (Table 3). Of the 65 patients with CeAD, 46 (71%) had acute symptomatic CeAD, 4 (5%) had a past history of symptomatic CeAD, and 15 (23%) had a typical arterial sequela of CeAD on imaging only. Among the 46 patients with an acute CeAD, 9 (20%) had multiple CeADs, 3 (6%) had intracranial artery extension, and 5 (11%) had a past history of CeAD.

Compared with patients with FMD and no CeAD, those with CeAD were younger, more likely to be men and to have a history of migraine, and less likely to have a history of hypertension (Table 3). In women, those with CeAD were less likely to have gone through menopause than those without CeAD (Table 3). There

was a nonsignificant increased prevalence of multisite involvement in patients with CeAD than in those without CeAD (Table 3). There were no statistically significant differences between FMD type or presence of intracranial aneurysm and CeAD (Table 3).

After multivariable adjustment, male sex, history of migraine, age ≥ 50 years at inclusion, absence of history of hypertension, and increasing number of FMD sites involved (ie, the variable multisite involvement used as a continuous variable) remained significantly associated with CeAD (Table 4). In contrast, there was no statistically significant association between Caucasian ethnicity or menopause and CeAD, after multivariable adjustment (Table 4).

To further investigate the association between sex and CeAD in FMD, which has rarely been investigated in patients with FMD, we undertook a systematic review. We did not further investigate the association between other significant factors such as age and history of migraine and CeAD, because information on these topics has been previously reported and because of the risk of selection bias for the diagnosis of migraine and the uncertainties with age as previously mentioned.^{7,10,17} Also, we did not assess the association between ethnicity and CeAD because the vast majority

Table 2. Baseline Characteristics of Patients With FMD in the ARCADIA Registry, Stratified by Sex

	All Patients, n=469	Sex		P Value
		Men, n=75	Women, n=394	
Demographics				
Caucasian	415 (88)	69 (92)	346 (88)	0.30
Mean (SD) age at FMD diagnosis, y	53.1 (13.4)	55.2 (1.6)	52.7 (0.7)	0.13
Mean (SD) age at inclusion, y	53.9 (13.3)	56.0 (1.6)	53.5 (0.7)	0.12
Age ≥50 y at inclusion	293 (62)	53 (71)	240 (61)	0.11
Prior comorbidities				
Hypertension	363 (77)	62 (83)	301 (76)	0.23
Diabetes mellitus	19 (4)	5 (7)	14 (4)	0.21
BMI ≥25 kg/m ²	161 (34)	42 (56)	119 (30)	0.005
Smoking	199 (42)	43 (57)	156 (40)	0.004
Migraine*	133 (28)	13 (17)	120 (30)	0.020
Imaging				
Multifocal FMD	429 (91)	65 (87)	364 (92)	0.10
Intracranial arterial aneurysm	53 (11)	4 (5)	49 (12)	0.07
Multisite involvement, no. of predefined sites involved				0.42†
1	244 (52)	39 (52)	205 (52)	...
2	154 (33)	28 (37)	126 (32)	...
≥3	71 (15)	8 (11)	63 (16)	...
Presence of multisite involvement (yes vs no)	225 (48)	36 (48)	189 (48)	0.99

Data are presented as number (%) unless otherwise specified. ARCADIA indicates Assessment of Renal and Cervical Artery Dysplasia; BMI, body mass index; and FMD, fibromuscular dysplasia.

*Data missing for 1 patient.

†ANOVA test. Multisite involvement is defined by the presence of FMD lesions in at least 2 of the 4 predefined sites: renal, cervico-encephalic, mesenteric/splenic, or iliac arteries.

Table 3. Baseline Characteristics of Patients With FMD in the ARCADIA Registry, Based on the Presence of Cervical Artery Dissection

	All Patients, N=469	Cervical Artery Dissection		P Value	Unadjusted OR (95% CI)
		Yes, n=65	No, n=404		
Demographics					
Male sex	75 (16)	16 (25)	59 (15)	0.04	1.91 (1.02–3.58)
Caucasian	415 (88)	62 (95)	353 (87)	0.07	2.98 (0.90–9.70)
Mean (SD) age at FMD diagnosis, y	53.1 (13.4)	49.8 (9.9)	53.6 (13.8)	0.03	...
Mean (SD) age at inclusion, y	53.9 (13.3)	50.7 (9.9)	54.4 (13.7)	0.04	...
Age ≥50 y at inclusion	293 (62)	32 (49)	261 (65)	0.02	0.53 (0.31–0.90)
Type of FMD presentation					
Neurological presentation	165 (35)	49 (75)	116 (29)	<0.001	7.66 (4.16–13.90)
Renal presentation	304 (65)	16 (25)	288 (71)		...
Prior comorbidities					
Hypertension	363 (77)	38 (58)	325 (80)	<0.001	0.34 (0.20–0.59)
Diabetes mellitus	19 (4)	0 (0)	19 (5)	0.07	...
BMI ≥25 (kg/m²)	161 (34)	22 (34)	139 (34)	0.93	0.97 (0.56–1.70)
Smoking	199 (42)	26 (40)	173 (43)	0.67	0.89 (0.52–1.52)
Menopause, in women*	217 (46)	18 (28)	199 (49)	<0.001	0.39 (0.22–0.69)
Migraine†	133 (28)	28 (43)	105 (26)	0.005	2.15 (1.25–3.68)
Imaging					
Multifocal FMD	429 (91)	60 (92)	369 (91)	0.80	1.14 (0.43–3.02)
Intracranial arterial aneurysm	53 (11)	6 (9)	47 (12)	0.57	0.77 (0.32–1.89)
Multisite involvement, no. of predefined sites involved				0.0216‡	
1	244 (52)	27 (42)	217 (54)	...	1.0
2	154 (33)	23 (35)	131 (79)		1.41 (0.78–2.56)
≥3	71 (15)	15 (23)	56 (14)		2.15 (1.08–4.32)
Presence of multisite involvement (yes vs no)	225 (48)	38 (58)	187 (46)	0.06	1.63 (0.96–2.78)

Data are presented as number (%) unless otherwise specified. ARCADIA indicates Assessment of Renal and Cervical Artery Dysplasia; BMI, body mass index; FMD, fibromuscular dysplasia; and OR, odds ratio.

*Data missing for 3 patients.

†Data missing for 1 patient. Multisite involvement is defined by the presence of FMD lesions in at least 2 of the 4 predefined sites: renal, cervico-encephalic, mesenteric/splenic, or iliac arteries.

‡P for trend.

of patients in the 2 largest prospective FMD registries (US FMD Registry and European/International FMD Registry) are of Caucasian ethnicity, and therefore, the expected number of patients of other ethnicity was small. Additionally, we estimated the risk of selection bias for the association between multisite involvement and CeAD in FMD to be high in the literature, because the prevalence of multisite involvement is highly dependent of the use of systematic imaging from the brain to the pelvis. No valid study has reported reliable data on multisite involvement in patients with FMD, stratified by presence of CeAD. Our search in PubMed identified 2707 titles, of which 177 abstracts were screened, leading to the assessment of 173 full texts. In addition, we added unpublished data on sex and CeAD from the US FMD Registry and the European/International FMD

Registry (2 independent populations) and those from ARCADIA. A total of 171 studies were finally excluded, leaving 5 independent studies^{18,19} for inclusion in the meta-analysis (Figure 1 and Table 5). Patients were predominantly Caucasian in 4 out of the 5 included studies^{6,19} (A. Persu, PhD, unpublished data, 2019; J.W. Olin, PhD, unpublished data, 2019), whereas patients were predominantly Asian in the other study.¹⁸ Recruitment of patients was prospective in 1 study,⁶ retrospective in 1 study,¹⁸ and both in 3 studies¹⁹ (A. Persu, PhD, unpublished data, 2019; J.W. Olin, PhD, unpublished data, 2019). In the 5 included studies, the majority of patients had a multifocal form (Table 5). Male sex was significantly associated with CeAD, with no heterogeneity across studies (odds ratio, 2.04; 95% CI, 1.41–2.95; $P<0.0001$; I^2 , 0%; Figure 2).

Table 4. Association Between Risk Factors and Presence of Cervical Artery Dissection in Patients With Fibromuscular Dysplasia

	Adjusted OR (95% CI)*	P Value
Male sex	2.66 (1.34–5.25)	0.005
History of migraine	1.90 (1.06–3.39)	0.031
Caucasian	2.11 (0.62–7.15)	0.23
Age ≥50 y at inclusion	0.41 (0.23–0.73)	0.003
History of hypertension	0.35 (0.20–0.64)	0.001
Multisite involvement, no. of predefined sites involved		0.020†
≥3	2.49 (1.15–5.40)	0.021
2	1.48 (0.79–2.81)	0.23
1	1.0	...

OR indicates odds ratio.

*Adjusted OR for sex, age ≥50 y at inclusion, Caucasian, history of migraine, hypertension, and presence of multisite involvement.

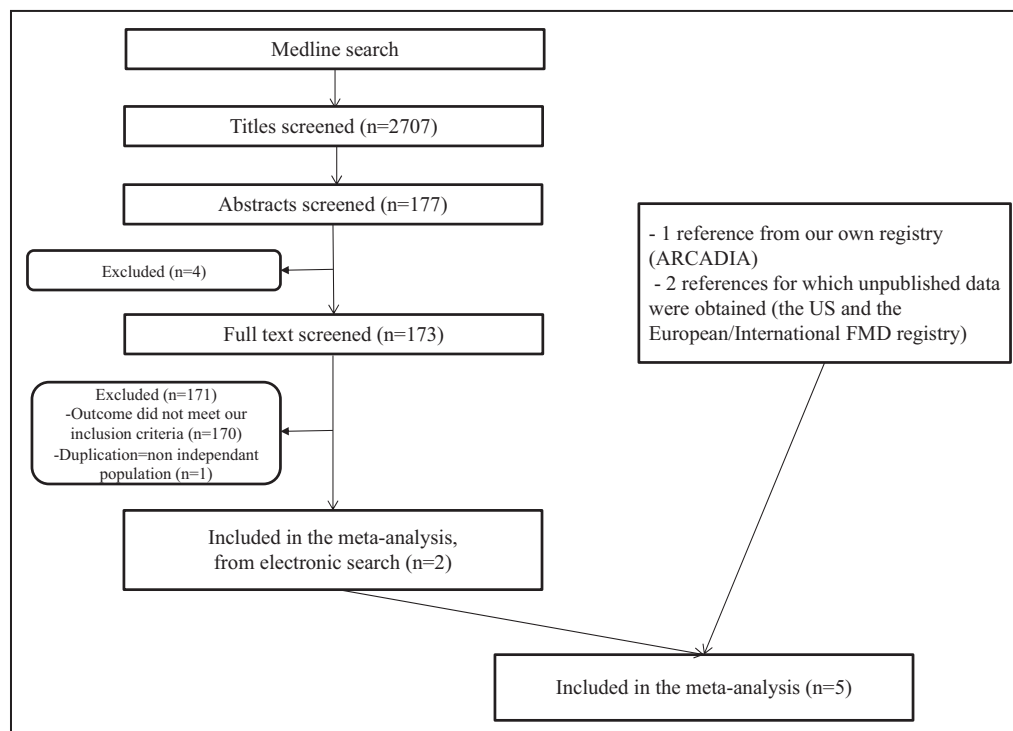
†P for trend analysis. Multisite involvement is defined by the presence of fibromuscular dysplasia lesions in at least 2 of the 4 predefined sites: renal, cervico-encephalic, mesenteric/splenic, or iliac arteries.

DISCUSSION

In this large prospective French–Belgian multicenter study on FMD, we found that 13.8% of the patients had a CeAD either at the time of the diagnosis of FMD or

in their past medical history. This finding is consistent with those of other studies of patients with FMD, which reported a prevalence of CeAD ranging from 12.1% to 25%.^{4,7,19,20} The association between CeAD and FMD has never been formally demonstrated in case–control or cohort studies. However, the high prevalence of CeAD in patients with FMD, the high prevalence of cervical FMD in patients with CeAD,³ the association between FMD and multiple CeAD,⁸ and the increased risk of recurrent CeAD in the presence of FMD,⁹ altogether strongly support that FMD is a risk factor for CeAD, as reported for spontaneous coronary dissection.²¹ In our cohort of patients with FMD, we also found that male sex, young age, history of migraine, and the extent of FMD (number of vascular beds involved) were associated with an increased risk of CeAD, whereas a history of hypertension was associated with a lower risk.

In this study, we found an independent association between male sex and CeAD in patients with FMD, which was subsequently confirmed in the meta-analysis we undertook. Our results are unlikely to be explained by a diagnosis or referral bias, because FMD is rare in men compared with women, as reported in both the European/International FMD Registry and the US FMD Registry.^{1,4} Confounding is also unlikely because we adjusted our analyses for several known risk factors for CeAD. We did not collect information

**Figure 1. Flowchart of the systematic review on male sex and cervical artery dissection in patients with FMD.**

ARCADIA indicates Assessment of Renal and Cervical Artery Dysplasia; and FMD, fibromuscular dysplasia.

Table 5. Characteristics of the Included Studies in the Systematic Review on Male Sex and Cervical Artery Dissection in Patients With FMD

First Author/ Study Name	Setting	Study Period	Inclusion	Male Sex, %	Mean Age at Inclusion, y	Mean Age at FMD Diagnosis, y	History of HTN, %	Race/Ethnicity, %	FMD Type, %
Liu ¹⁸	Taiwan	2000–2011	R	5	NA	46	26	Asian: >99	M: 74, F: 26
Pasquini ¹⁹	France	2000–2008	R, P	11	NA	57	39	White: >99	M: 97, F: 3
ARCADIA	France, Belgium	2009–2014	P	16	54	53	77	White: >99	M: 91, F: 9
US FMD Registry	United States	2009–2019	R, P	5	56	53	67	White: 91 Other: • African descent: 5 • Maghreb–Middle Eastern: <1 • Asian: 0.3 • Hispanic: 3	M: 76, F: 2
European/ International FMD Registry	17 European countries+Argentina, Japan, and Tunisia	2015–2019	R, P	17	51	46	74	White: 82 Other: • African descent: 1 • Maghreb–Middle Eastern: 3 • Asian: 7 • Hispanic: 7	M: 72, F: 28

ARCADIA indicates Assessment of Renal and Cervical Artery Dysplasia; F, focal; FMD, fibromuscular dysplasia; HTN, hypertension; M, multifocal; NA, not appropriate; P, prospective; R, retrospective; and US FMD Registry, US Registry for Fibromuscular Dysplasia.

on trauma and infection within the few weeks before diagnosis of CeAD; however, there are no data in the literature supporting evidence for a difference in the prevalence of infection and trauma between men and women before CeAD. Although we consider our finding to be valid, biological plausibility remains to be found. A male predominance has also been reported in several studies of patients with CeAD, including those of unselected patients with CeAD.²² In the CADISP (Cervical Artery Dissections and Ischemic Stroke Patients) genome-wide association study performed in 1393 unselected CeAD cases and 14 416 controls, male sex was predominant (~68%).²² This is in contrast with spontaneous coronary dissection, where cases are reported almost exclusively in middle-aged women,²³ especially in the peripartum period.²⁴

Another important finding from our study is the association between CeAD and the number of vascular beds involved with FMD, with a significant dose-dependent relationship, as also reported in patients with spontaneous coronary dissection.²⁵ This result supports the hypothesis that the risk of CeAD increases with the vascular extension of FMD, and thus the systemic nature of FMD.

In our study of patients with FMD, we identified an independent association between absence of history of hypertension and CeAD. However, we cannot exclude the possibility of selection bias, because hypertension was the most frequent manifestation of patients with FMD and renal presentations (88%), whereas CeAD occurred more frequently in patients with FMD and neurological presentations, in whom the prevalence of hypertension was lower (58%).⁶ One small study of patients with FMD also found a lower prevalence of hypertension in the subgroup with CeAD.¹⁹ The relation between hypertension and CeAD is controversial. Several case-control studies have shown an increased prevalence of hypertension in patients with CeAD as compared with patients with stroke without CeAD or healthy controls,^{26–28} whereas other smaller studies did not.^{29,30} However, hypertension was not found to be associated with CeAD in a systematic review of the risk factors for CeAD.¹¹

We also found an independent association between history of migraine and CeAD in patients with FMD. This is consistent with the results of a recent meta-analysis of patients with CeAD that reported a 2-fold increased risk of CeAD with history of migraine, with no difference in risk between migraine with and without aura.¹⁷

Our study has potential limitations. First, despite the large number of patients included in the ARCADIA study, our analysis was based on a relatively small number of patients with CeAD. Also, the number of male patients with FMD (with and without CeAD) was small, but this corresponds to the epidemiology of

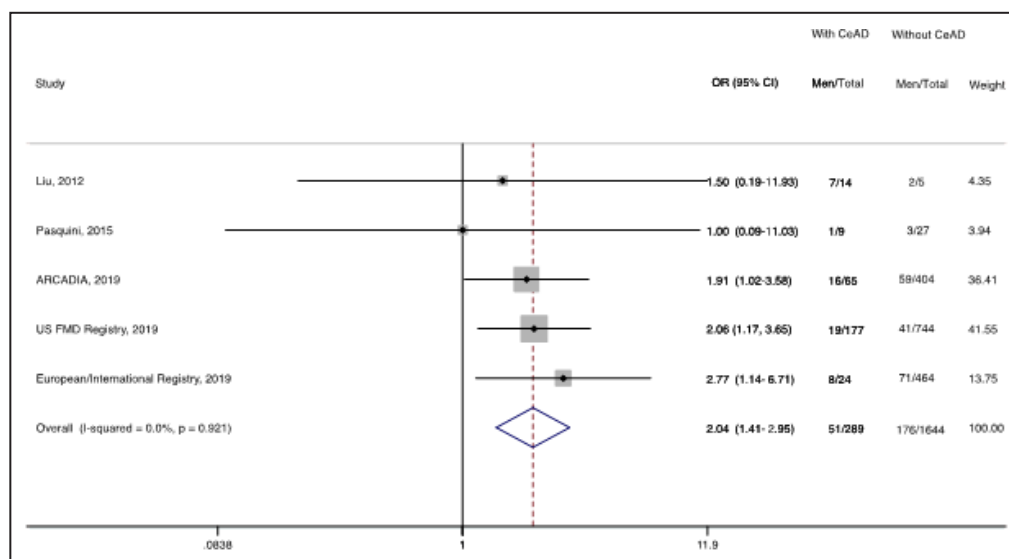


Figure 2. Pooled analysis of published and unpublished data on the association between male sex and cervical artery dissection (CeAD) in patients with fibromuscular dysplasia.

ARCADIA indicates Assessment of Renal and Cervical Artery Dysplasia; European/International Registry, European/International FMD Registry; OR, odds ratio; and US FMD Registry, US Registry for Fibromuscular Dysplasia.

FMD; thus, other registries and observational studies have reported that FMD is much more common in women than in men, with estimates being up to 95% in women in the US FMD Registry.^{1,4} In addition, our population consisted of a predominantly Caucasian population, which will limit the generalizability of the findings. However, we found a strong association between male sex and CeAD in FMD, which was confirmed in the meta-analysis and in studies with a higher prevalence of non-Caucasian ethnicity than in our study population. Second, we recruited 2 different FMD populations (renal presentation and neurological presentation), and because CeAD was mostly observed in patients with neurological presentation, we cannot exclude that some differences in patients' characteristics between patients with CeAD and without CeAD were because of selection biases. However, as discussed above, we consider this potential bias as unlikely for sex. Although the independent association between male sex and CeAD, which has been found in various populations including patients without FMD, suggest a genetic predisposition, and replication in larger studies is required to confirm our results. Future studies should also take into account genetic factors such as the PHACTR1 variant,^{3,22,31,32} or the potential precipitating stressors such as medication/drug use that might differ by sex.¹⁰ Finally, we undertook a systematic review on the association between sex and CeAD in patients with FMD based on our findings in the ARCADIA study, and did not explore the association with the other significant risk factors we identified, because

these factors are either already well documented in patients with CeAD or likely to be subjected to biases. Finally, we did not screen patients for spontaneous coronary artery dissection.

In practice, our findings can help to stratify the risk of CeAD in patients with FMD. Although the association with multisite involvement can be explained by disease severity, the association with male sex and CeAD needs further investigation.

APPENDIX

Co-Investigators in the ARCADIA (Assessment of Renal and Cervical Artery Dysplasia) Study

The following investigators (with the number of patients enrolled given in parentheses) and committee participated in the ARCADIA study: Hôpital Européen Georges Pompidou, Paris (156): Arshid Azarine, Michel Azizi, Gilles Chatellier, Antoine Chedid, Béatrice Fiquet, Xavier Jeunemaitre, Elie Mousseaux, Pierre-François Plouin; Centre hospitalo-universitaire (CHU) Grenoble (140): Jean-Philippe Baguet, Olivier Ormezzano, Frédéric Thony; CHU Timone, Marseille (37): François Silhol; Centre hospitalier Sainte-Anne (28): Eric Bodiguel, Valérie Domigo, Catherine Oppenheim, Marta Pasquini, Emmanuel Touzé, Denis Trystram; CHU Clermont-Ferrand (28): Louis Boyer, Pierre Clavelou; CHU Rangueil, Toulouse (25): Bernard Chamontin, Béatrice Duly-Bouhanick; Hôpital Cardiologique, Lille (21): Hilde Hénon, Claire Mounier-Vehier; Cliniques

Universitaires Saint-Luc, Bruxelles (19): Parla Astarci, Pierre Goffette, Frank Hammer, Jean-Philippe Lengelé, Alexandre Persu, Francesca Severino, Robert Verhelst; CHU de Caen (10): Claire Le Hello; Hôpital Saint André, Bordeaux (10): Philippe Gosse; CHU Lariboisière, Paris (6): Dominique Hervé; Centre hospitalier de Versailles (3): Fernando Pico; CHU de Nancy (2): Michèle Kessler, Patrick Rossignol; CHU Pitié Salpêtrière, Paris (2): Yves Sanson; Hôpital Saint Joseph, Paris (2): Mathieu Zuber; Hôpital Bichat, Paris (2): Mikael Mazighi; Hôpital Tenon, Paris (1): Sonia Alamowitch.

Imaging Committee: Arshid Azarine, Elie Mousseaux [chair], Catherine Oppenheim, Pierre-François Plouin, Emmanuel Touzé, Frédéric Thony.

ARTICLE INFORMATION

Received November 17, 2020; accepted March 9, 2021.

Affiliations

Department of Neurology, Inserm U1237, Normandie Université, Université Caen Normandie, CHU Caen Normandie, Caen, France (C.A., M.B., E.T.); Hypertension Unit, Assistance Publique-Hôpitaux de Paris (A.L., L.A., A.A., G.C., X.J., M.A.); and Department of Radiology, Assistance Publique-Hôpitaux de Paris (A.A., E.M.), Hôpital Européen Georges Pompidou, France; Department of Radiology, CHU Clermont-Ferrand, Hôpital Gabriel Montpied, Clermont Ferrand, France (L.B.); Clinical Research Unit, Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Paris, France (G.C.); ; Division of Internal Medicine and Hypertension Unit, Department of Medical Sciences, University of Turin, Italy (S.D.M.); Pole of Cardiovascular Research, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels, Belgium (S.D.M., A.P.); Division of Cardiology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium (S.D.M., A.P.); Department of Genetics, Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Université de Paris, France (X.J.); Department of Radiology, CHU de Grenoble, France (A.K., F.T.); Department of Radiology and INSERM U1266, GHU Paris Psychiatry and Neurosciences, Université de Paris, France (C.O.); Zena and Michael A. Wiener Cardiovascular Institute and Marie-Josée and Henry R. Kravis Center for Cardiovascular Health, Icahn School of Medicine at Mount Sinai, New York, NY (J.W.O.); and INSERM CIC1418, Paris, France (M.A.).

Acknowledgments

Drs Arnaud and Boulanger: statistical analysis, interpretation of results, drafting of the manuscript. Dr Lorthioir: statistical analysis, interpretation of results, revision of the manuscript. Dr Amar: data collection, revision of the manuscript. Drs Azarine, Boyer, Di Monaco, Kastler, Oppenheim, and Thony: data collection. Dr Chatellier: concept and design of the study. Dr Jeunemaitre: concept and design of the study, revision of the manuscript. Dr Mousseaux: concept and design of the study, data collection, revision of the manuscript. Drs Persu and Olin: data collection, interpretation of results, revision of the manuscript. Dr Azizi: concept and design of the study, interpretation of results, revision of the manuscript. Dr Touzé: concept and design of the study, data collection, interpretation of results, drafting of the manuscript.

Sources of Funding

The ARCADIA study was sponsored by the Assistance Publique-Hôpitaux de Paris and funded by grants from the French Ministry of Health (Programme Hospitalier de Recherche Clinique 2009, AOM 08192) and the Fondation de Recherche sur l'Hypertension Artérielle (FRHA1).

Disclosures

Dr Olin is on the Medical Advisory Board of the Fibromuscular Dysplasia Society of America (no compensation); chair, steering committee, and principal investigator at the United States Registry for Fibromuscular Dysplasia. Dr Touzé is an assistant editor for the *Stroke* journal, American Heart Association, no compensation. The remaining authors have no disclosures to report.

REFERENCES

- Gornik HL, Persu A, Adlam D, Aparicio LS, Azizi M, Boulanger M, Bruno RM, De Leeuw P, Fendrikova-Mahlay N, Froehlich J, et al. First international consensus on the diagnosis and management of fibromuscular dysplasia. *J Hypertens*. 2019;37:229–252. DOI: 10.1097/HJH.0000000000002019.
- Olin JW, Gornik HL, Bacharach JM, Biller J, Fine LJ, Gray BH, Gray WA, Gupta R, Hamburg NM, Katzen BT, et al. Fibromuscular dysplasia: state of the science and critical unanswered questions: a scientific statement from the American Heart Association. *Circulation*. 2014;129:1048–1078. DOI: 10.1161/01.cir.0000442577.96802.8c.
- Touzé E, Southerland AM, Boulanger M, Labeyrie P-E, Azizi M, Bouatia-Naji N, Debette S, Gornik HL, Hussain SM, Jeunemaitre X, et al. Fibromuscular dysplasia and its neurologic manifestations: a systematic review. *JAMA Neurol*. 2019;76:217–226. DOI: 10.1001/jamaneurol.2018.2848.
- Olin JW, Froehlich J, Gu X, Bacharach JM, Eagle K, Gray BH, Jaff MR, Kim ESH, Mace P, Matsumoto AH, et al. The United States registry for fibromuscular dysplasia: results in the first 447 patients. *Circulation*. 2012;125:3182–3190. DOI: 10.1161/CIRCULATIONAHA.112.091223.
- Touzé E, Oppenheim C, Trystram D, Nokam G, Pasquini M, Alamowitch S, Herve D, Garnier P, Mousseaux E, Plouin PF. Fibromuscular dysplasia of cervical and intracranial arteries. *Int J Stroke*. 2010;5:296–305. DOI: 10.1111/j.1747-4949.2010.00445.x.
- Plouin P-F, Baguet J-P, Thony F, Ormezzano O, Azarine A, Silhol F, Oppenheim C, Bouhanick B, Boyer L, Persu A, et al. High prevalence of multiple arterial bed lesions in patients with fibromuscular dysplasia: the ARCADIA registry (assessment of renal and cervical artery dysplasia). *Hypertension*. 2017;70:652–658. DOI: 10.1161/HYPERTENSIONAHA.117.09539.
- Kadian-Dodov D, Gornik HL, Gu X, Froehlich J, Bacharach JM, Chi YW, Gray BH, Jaff MR, Kim ES, Mace P, et al. Dissection and aneurysm in patients with fibromuscular dysplasia: findings from the U.S. Registry for FMD. *J Am Coll Cardiol*. 2016;68:176–185. DOI: 10.1016/j.jacc.2016.04.044.
- Béjot Y, Aboa-Eboulé C, Debette S, Pezzini A, Tatlisumak T, Engelter S, Grond-Ginsbach C, Touzé E, Sessa M, Metso T, et al. Characteristics and outcomes of patients with multiple cervical artery dissection. *Stroke*. 2014;45:37–41. DOI: 10.1161/STROKEAHA.113.001654.
- de Bray JM, Marc G, Pautot V, Vielle B, Pasco A, Lhoste P, Dubas F. Fibromuscular dysplasia may herald symptomatic recurrence of cervical artery dissection. *Cerebrovasc Dis*. 2007;23:448–452. DOI: 10.1159/000101470.
- Debette S. Pathophysiology and risk factors of cervical artery dissection: what have we learnt from large hospital-based cohorts? *Curr Opin Neurol*. 2014;27:20–28. DOI: 10.1097/WCO.0000000000000056.
- Rubinstein SM, Peerdeman SM, van Tulder MW, Riphagen I, Haldeman S. A systematic review of the risk factors for cervical artery dissection. *Stroke*. 2005;36:1575–1580. DOI: 10.1161/01.STR.0000169919.73219.30.
- Savard S, Steichen O, Azarine A, Azizi M, Jeunemaitre X, Plouin PF. Association between 2 angiographic subtypes of renal artery fibromuscular dysplasia and clinical characteristics. *Circulation*. 2012;126:3062–3069. DOI: 10.1161/CIRCULATIONAHA.112.117499.
- Headache Classification Committee of the International Headache S. The international classification of headache disorders, 3rd edition (beta version). *Cephalalgia*. 2013;33:629–808. DOI: 10.1177/0333102413485658.
- Debette S, Leys D. Cervical-artery dissections: predisposing factors, diagnosis, and outcome. *Lancet Neurol*. 2009;8:668–678. DOI: 10.1016/S1474-4422(09)70084-5.
- Moher D, Liberati A, Tetzlaff J, Altman DG; Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535. DOI: 10.1136/bmj.b2535.
- Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539–1558. DOI: 10.1002/sim.1186.
- Rist PM, Diener HC, Kurth T, Schürks M. Migraine, migraine aura, and cervical artery dissection: a systematic review and meta-analysis. *Cephalalgia*. 2011;31:886–896. DOI: 10.1177/0333102411401634.
- Liu CH, Wu D, Chin SC, Fu SC, Wu TC, Chang CH, Peng TI, Chang YJ, Lee TH. Cervicocranial fibromuscular dysplasia in Taiwanese ischemic stroke patients. *Eur Neurol*. 2012;67:129–135. DOI: 10.1159/000331623.

19. Pasquini M, Trystram D, Nokam G, Gobin-Metteil MP, Oppenheim C, Touzé E. Fibromuscular dysplasia of cervicocephalic arteries: prevalence of multisite involvement and prognosis. *Rev Neurol (Paris)*. 2015;171:616–623. DOI: 10.1016/j.neurol.2015.02.011.
20. Harriott AM, Zimmerman E, Singhal AB, Jaff MR, Lindsay ME, Rordorf GA. Cerebrovascular fibromuscular dysplasia: the MGH cohort and literature review. *Neurol Clin Pract*. 2017;7:225–236. DOI: 10.1212/CPJ.0000000000000339.
21. Adlam D, Alfonso F, Maas A, Vrints C, al-Hussaini A, Bueno H, Capranzano P, Gevaert S, Hoole SP, Johnson T, et al. European Society of Cardiology, acute cardiovascular care association, SCAD study group: a position paper on spontaneous coronary artery dissection. *Eur Heart J*. 2018;39:3353–3368. DOI: 10.1093/eurheartj/ehy080.
22. Debette S, Kamatani Y, Metso TM, Kloss M, Chauhan G, Engelter ST, Pezzini A, Thijs V, Markus HS, Dichgans M, et al. Common variation in PHACTR1 is associated with susceptibility to cervical artery dissection. *Nat Genet*. 2015;47:78–83. DOI: 10.1038/ng.3154.
23. Saw J, Starovoytov A, Humphries K, Sheth T, So D, Minhas K, Brass N, Lavoie A, Bishop H, Lavi S, et al. Canadian spontaneous coronary artery dissection cohort study: in-hospital and 30-day outcomes. *Eur Heart J*. 2019;40:1188–1197. DOI: 10.1093/eurheartj/ehz007.
24. Tweet MS, Hayes SN, Codsí E, Gulati R, Rose CH, Best PJM. Spontaneous coronary artery dissection associated with pregnancy. *J Am Coll Cardiol*. 2017;70:426–435. DOI: 10.1016/j.jacc.2017.05.055.
25. Saw J, Ricci D, Starovoytov A, Fox R, Buller CE. Spontaneous coronary artery dissection: prevalence of predisposing conditions including fibromuscular dysplasia in a tertiary center cohort. *JACC Cardiovasc Interv*. 2013;6:44–52. DOI: 10.1016/j.jcin.2012.08.017.
26. Debette S, Metso T, Pezzini A, Abboud S, Metso A, Leys D, Bersano A, Louillet F, Caso V, Lamy C, et al. Association of vascular risk factors with cervical artery dissection and ischemic stroke in young adults. *Circulation*. 2011;123:1537–1544. DOI: 10.1161/CIRCULATIONAHA.110.000125.
27. Longoni M, Grond-Ginsbach C, Grau AJ, Genius J, Debette S, Schwanninger M, Ferrarese C, Lichy C. The ICAM-1 E469K gene polymorphism is a risk factor for spontaneous cervical artery dissection. *Neurology*. 2006;66:1273–1275. DOI: 10.1212/01.wnl.0000208411.01172.0b.
28. Pezzini A, Caso V, Zanferrari C, Del Zotto E, Paciaroni M, Bertolino C, Grassi M, Agnelli G, Padovani A. Arterial hypertension as risk factor for spontaneous cervical artery dissection. A case-control study. *J Neurol Neurosurg Psychiatry*. 2006;77:95–97. DOI: 10.1136/jnnp.2005.063107.
29. Konrad C, Langer C, Muller GA, Berger K, Dziewas R, Stogbauer F, Nabavi DG, Junker R, Ringelstein EB, Kühlenbaumer G. Protease inhibitors in spontaneous cervical artery dissections. *Stroke*. 2005;36:9–13. DOI: 10.1161/01.STR.0000149631.52985.27.
30. Arnold M, Pannier B, Chabrier H, Nedeltchev K, Stapf C, Buffon F, Crassard I, Thomas F, Guize L, Baumgartner RW, et al. Vascular risk factors and morphometric data in cervical artery dissection: a case-control study. *J Neurol Neurosurg Psychiatry*. 2009;80:232–234. DOI: 10.1136/jnnp.2008.151324.
31. Kiando SR, Tucker NR, Castro-Vega L-J, Katz A, D'Escamard V, Tréard C, Fraher D, Albuisson J, Kadian-Dodov D, Ye ZI, et al. PHACTR1 is a genetic susceptibility locus for fibromuscular dysplasia supporting its complex genetic pattern of inheritance. *PLoS Genet*. 2016;12:e1006367. DOI: 10.1371/journal.pgen.1006367.
32. Adlam D, Olson TM, Combaret N, Kovacic JC, Iismaa SE, Al-Hussaini A, O'Byrne MM, Bouajila S, Georges A, Mishra K, et al. Association of the PHACTR1/EDN1 genetic locus with spontaneous coronary artery dissection. *J Am Coll Cardiol*. 2019;73:58–66. DOI: 10.1016/j.jacc.2018.09.085.