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Clinical Features of Patients With Cervical Artery Dissection and Fibromuscular Dysplasia

Sonia Bonacina, MD; Mario Grassi, PhD; Marialuisa Zedde¹, MD; Andrea Zini¹, MD; Anna Bersano¹, MD; Carlo Gandolfo¹, MD; Giorgio Silvestrelli, MD; Claudio Baracchini, MD; Paolo Cerrato, MD; Corrado Lodigiani, MD, PhD; Simona Marcheselli¹, MD; Maurizio Paciaroni¹, MD; Maurizia Rasura, MD; Manuel Cappellari¹, MD; Massimo Del Sette, MD; Anna Cavallini¹, MD; Andrea Morotti¹, MD; Giuseppe Micieli¹, MD; Enrico Maria Lotti, MD; Maria Luisa DeLodovici, MD; Mauro Gentile, MD; Mauro Magoni, MD; Cristiano Azzini, MD; Maria Vittoria Calloni, MD; Elisa Giorli, MD; Massimiliano Braga, MD; Paolo La Spina, MD; Fabio Melis, MD; Rossana Tassi¹, MD; Valeria Terruso, MD; Rocco Salvatore Calabrò, MD; Valeria Piras, MD; Alessia Giossi, MD; Martina Locatelli, MD; Valentina Mazzoleni, MD; Debora Pezzini, MD; Sandro Sanguigni, MD; Carla Zanferrari, MD; Marina Mannino, MD; Irene Colombo, MD; Carlo Dallochio, MD; Patrizia Nencini, MD; Valeria Bignamini, MD; Alessandro Adami, MD; Eugenio Magni¹, MD; Rita Bella¹, MD; Alessandro Padovani, MD, PhD; Alessandro Pezzini¹, MD; on behalf of the IPSYS CeAD Research Group*

BACKGROUND AND PURPOSE: Observational studies have suggested a link between fibromuscular dysplasia and spontaneous cervical artery dissection (sCeAD). However, whether patients with coexistence of the two conditions have distinctive clinical characteristics has not been extensively investigated.

METHODS: In a cohort of consecutive patients with first-ever sCeAD, enrolled in the setting of the multicenter IPSYS CeAD study (Italian Project on Stroke in Young Adults Cervical Artery Dissection) between January 2000 and June 2019, we compared demographic and clinical characteristics, risk factor profile, vascular pathology, and midterm outcome of patients with coexistent cerebrovascular fibromuscular dysplasia (cFMD; cFMD+) with those of patients without cFMD (cFMD-).

RESULTS: A total of 1283 sCeAD patients (mean age, 47.8±11.4 years; women, 545 [42.5%]) qualified for the analysis, of whom 103 (8.0%) were diagnosed with cFMD+. In multivariable analysis, history of migraine (odds ratio, 1.78 [95% CI, 1.13–2.79]), the presence of intracranial aneurysms (odds ratio, 8.71 [95% CI, 4.06–18.68]), and the occurrence of minor traumas before the event (odds ratio, 0.48 [95% CI, 0.26–0.89]) were associated with cFMD. After a median follow-up of 34.0 months (25th to 75th percentile, 60.0), 39 (3.3%) patients had recurrent sCeAD events. cFMD+ and history of migraine predicted independently the risk of recurrent sCeAD (hazard ratio, 3.40 [95% CI, 1.58–7.31] and 2.07 [95% CI, 1.06–4.03], respectively) in multivariable Cox proportional hazards analysis.

CONCLUSIONS: Risk factor profile of sCeAD patients with cFMD differs from that of patients without cFMD. cFMD and migraine are independent predictors of midterm risk of sCeAD recurrence.

Key Words: cohort studies ■ demography ■ dissection ■ follow-up studies ■ risk factors

Fibromuscular dysplasia (FMD) is an idiopathic, segmental, nonatherosclerotic, and noninflammatory disease of small- to medium-sized arteries, characterized by disrupted architecture of the vessel wall.^{1,2}

Although FMD is a systemic disease affecting >1 vascular district in a single patient, the involvement of the renal arteries and cervical (carotid and vertebral) arteries is far more frequent than that of other vessels. In

Correspondence to: Alessandro Pezzini, MD, Dipartimento di Scienze Cliniche e Sperimentali, Clinica Neurologica, Università degli Studi di Brescia, P.le Spedali Civili 1, 25123 Brescia, Italia, Email ale_pezzini@hotmail.com

*A list of all IPSYS CeAD Research Group collaborators is given in the Data Supplement.

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Nonstandard Abbreviations and Acronyms

cFMD	cerebrovascular fibromuscular dysplasia
ET-1	endothelin 1
FMD	fibromuscular dysplasia
IPSYS CeAD	Italian Project on Stroke at Young Age Cervical Artery Dissection
PHACTR1	phosphatase and actin regulator 1
sCeAD	spontaneous cervical artery dissection

particular, cervical and intracranial arteries appear to develop FMD more often than previously thought and, at least, as commonly as renal arteries, according to recent data from the Assessment of Renal and Cervical Artery Dysplasia international registry.³ In addition to being a direct cause of potentially devastating neurological complications, including ischemic and hemorrhagic stroke, FMD has been consistently associated to a number of nonatherosclerotic vasculopathies and vascular anomalies over the last decade, lending support to the hypothesis that apparently distinct disease entities might share several biologic mechanisms and represent different phenotypes of a common generalized arteriopathy. This seems especially true for spontaneous cervical artery dissection (sCeAD), the most frequent cause of ischemic stroke in young and middle-aged adults, whose coexistence with FMD, especially when involving the cerebrovascular district (cerebrovascular FMD [cFMD]), has been repeatedly reported. Notwithstanding, the available evidence is still too limited to allow any definitive conclusions on such a relationship.⁴ Studies reported to date provide, at best, information on the prevalence of FMD in sCeAD patients,^{5–7} and only 1 study, conducted on a relatively small cohort, was specifically designed to assess whether the clinical phenotype of patients with sCeAD differs according to FMD status.⁸

In the present study, we, therefore, aimed at filling this gap by investigating cFMD characteristics in the setting of a multicenter project comprising one of the largest series of sCeAD patients reported to date. In particular, our specific purpose was to investigate whether (1) sCeAD with and without FMD represents disease entities with distinctive predisposing factors and clinical features and (2) the midterm outcome of sCeAD patients might vary depending on the coexistence of FMD.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Patient Selection

IPSYS CeAD (Italian Project on Stroke at Young Age Cervical Artery Dissection) is a substudy of the Italian Project on Stroke in Young Adults project—a countrywide network of neurological centers with special interest in cerebral ischemia at young age across Italy.^{9,10} For the purpose of the present analysis, we screened data sets from patients consecutively admitted to 39 hospitals to select cases with first-ever CeAD, regardless of whether they had a stroke or not. The recruitment process of eligible cases took place prospectively from January 2000 through June 2019. The Institutional Ethical Standards Committee on human experimentation at the Brescia University Hospital provided approval for the study. Written informed consent was obtained for all participants (or next of kin).¹⁰

Risk Factor Definition

The following risk factors for premature cerebral ischemia were retained: hypertension, diabetes, cigarette smoking, hypercholesterolemia, and migraine. We also collected information on alcohol consumption, use of contraceptives and hormone replacement therapy, family history of thrombosis, and family history of arterial dissection¹⁰ (Table I in the [Data Supplement](#)).

Diagnosis of Cervical Artery Dissection

Diagnosis of CeAD was based on established radiological criteria. Performance of the specific imaging modality was left to the discretion of the investigator in charge of the patient in each center, with no central adjudication of radiological findings.¹⁰

Definition of Traumatic CeAD

We considered mechanisms of trauma associated with CeAD: (1) any direct mechanical impact to the neck region or (2) any impact to the head with indirect involvement of the neck region or (3) any mechanical activity causing extraordinarily increased intrathoracic pressure (eg, heavy lifting), which had occurred within 1 month before first symptoms of dissection. Traumatic events leading to medical examination or hospitalization were considered major, and all others were minor.¹¹ Patients whose dissection was related to a major trauma were excluded from the present analysis.

Diagnosis of cFMD

The diagnosis of cFMD was made according to the diagnostic criteria expressed in the most recent expert consensus document,¹² based on acute and postacute (3–6 months after the index event) vascular imaging, at each participating center, with no central reading of the images except in a subset of 65 patients. For the purpose of the present analysis, patients included in the registry were dichotomized into 2 groups: patients with CeAD and cFMD (FMD+) and patients with CeAD and no evidence of cFMD (FMD–).

Outcomes

Follow-up evaluations were conducted between 3 and 6 months after the initial event and then annually.¹⁰ Death was considered due to the index stroke if it occurred within 30 days of the onset of symptoms. The primary outcome measure was

recurrent sCeAD, which was defined by using the same criteria applied for the definition of the index event. If >1 recurrent event occurred, the first was used for calculation of the disease-free survival time. Long-term antithrombotic therapy for secondary prevention was administered in accordance with the published guidelines.¹³ Patients were considered persistent medication users if they were still using treatments prescribed at hospital discharge or at subsequent clinical evaluations at the end of follow-up and nonpersistent medication users if they discontinued a medication regardless of the reason. Medication discontinuation was considered to influence recurrence and, thus, was entered into the analysis when it was detected before the occurrence of the recurrent event.

Statistical Analyses

Differences between the two subgroups (cFMD+ and cFMD-) were examined with the χ^2 test, the Student *t* test, and the Mann-Whitney *U* test, when appropriate. Multivariate logistic regression model was planned to examine the conditional effect of variables potentially related to cFMD status, in the prediction of each subgroup, and adjusted for age and sex. Results are given as odds ratios with 95% CIs. Duration of follow-up was calculated by using the follow-up of each participant from baseline examination until death, recurrent event, or most recent censored follow-up assessment. Kaplan-Meier survival analysis was used to estimate the cumulative survival curve of recurrent events by follow-up time.¹⁴ Hazard ratios and 95% CIs were assessed by multivariable Cox proportional hazards models adjusted for age, sex, and any other relevant baseline characteristics significantly associated with the outcome measure, to detect the independent predictors of sCeAD recurrence. $P \leq 0.05$ on 2-sided test was considered significant. Data were analyzed using the SPSS (version 21.0) package (www.spss.com).

RESULTS

Of the 1530 CeAD patients included in the IPSYS CeAD registry, 185 (11.8%) were excluded from the present analysis because vessel images were not suitable for adequate FMD assessment and 62 (4.0%) because vessel dissection occurred as an immediate consequence of a major trauma. Therefore, the study group was composed of 1283 patients with spontaneous events. The mean age of the study population was 47.8 ± 11.4 years, and 545 (42.5%) were women. At the time of diagnosis, 1099 patients (85.6%) had an ischemic cerebral event (ischemic stroke/TIA, 937/162) and 18 patients (1.5%) had a subarachnoid hemorrhage. CeAD affected predominantly the carotid artery (771 patients [60.0%] had a single carotid involved), whereas 189 patients (14.7%) had >1 cervical artery involved. Of the 1283 sCeAD patients, 103 (8.0%) were cFMD+ and 1180 (92.0%) were cFMD-. Interrater agreement for the diagnosis of cFMD was high with all the 65 patients whose images underwent central adjudication rated identically by independent raters. Demographic characteristics of the study population

grouped according to cFMD status and the prevalence of selected risk factors are summarized in Table 1.

Among cFMD+ patients, 82 (79.6%) had carotid artery FMD (bilateral in half of the cases), 17 (20.7%) of whom with additional abnormalities in the vertebral arteries consistent with cFMD. Dissection occurred in the same vessel affected by cFMD in 14 (13.6%) patients. None of the patients had received the diagnosis of cFMD before sCeAD occurrence.

As expected, cFMD+ patients were more frequently women and had a higher prevalence of intracranial aneurysms and of arterial dissection in first-degree relatives than cFMD- patients. Furthermore, they were more likely to experience migraine, though there were no disparities by migraine subtype and no substantial differences in migraine features, except for a lower frequency of active migraine, in comparison with cFMD- patients (Table II in the [Data Supplement](#)).

Clinical manifestations of the index event, site of the dissected vessels, and acute-phase treatment did not differ substantially between the two subgroups. Compared with cFMD- patients, cFMD+ patients tended to develop pseudoaneurysms more frequently but less often had vessel occlusion (Table 2).

In multivariable analysis, personal history of migraine and the presence of intracranial aneurysms were associated to cFMD, while the occurrence of minor traumas before the index event was inversely associated (Table 3).

Of the 1283 patients included in the analysis, 5 died during the acute phase while 84 were lost to follow-up. Longitudinal data were, therefore, available in 1194 patients who were followed up for a total of 63 293 patient-months. The median follow-up time in patients who did not experience recurrent CeAD events was 34.0 months (25th to 75th percentile, 60.0). Nonincluded cases were not significantly different from those who entered into the final analysis with regard to baseline characteristics (not shown). One hundred fifty-eight (13.2%) patients stopped antithrombotic medications for secondary prevention prescribed at hospital discharge. Recurrent CeAD events were recorded in 39 (3.3%) patients (average rate, 7.39 per 1000 person-years at risk). The median interval between the index event and the recurrent outcome event was 3.0 months (25th to 75th percentile, 10.0; Figure [A]).

Clinical characteristics, dissection site, and vascular pathology of recurrent sCeAD events were not substantially different in the two subgroups stratified by cFMD status, except for a higher frequency of multivessel involvement in the cFMD+ subgroups (40.0% versus 3.4%; $P=0.011$; Table III in the [Data Supplement](#)). Most of the new asymptomatic dissections (12/14, 85.7%) occurred within the first 6 months since the index event. The status of cFMD carrier was predictor of sCeAD recurrence ($P \leq 0.001$ by the log-rank test in Kaplan-Meier analysis; Figure [A]) and was significantly

Table 1. Demographic and Baseline Characteristics of the Study Group Stratified by cFMD Status

Variable	cFMD+ (n=103)	cFMD- (n=1180)	P value
Demographic characteristics			
Age, y; mean±SD	46.3±12.1	47.9±11.2	0.165
Sex, female	59 (57.3)	486 (41.2)	0.002
Race, White	101 (98.3)	1148 (97.3)	1.000
Putative risk factors			
Height, cm	170.0±9.0	171.3±10.0	0.258
Weight, kg	68.1±11.9	72.8±20.9	0.109
Body mass index, kg/m ²	23.8±3.2	24.6±7.0	0.281
Hypertension			0.452
Nohypertensive	79 (76.7)	839 (71.1)	
Hypertensive under treatment	18 (17.5)	243 (20.6)	
Hypertensive not under treatment	6 (5.8)	98 (8.3)	
Diabetes			0.329
Nondiabetic	101 (98.1)	1121 (95.0)	
Diabetic under treatment	2 (1.9)	45 (3.8)	
Diabetic not under treatment	0 (0.0)	14 (1.2)	
Hypercholesterolemia			0.647
Nonhypercholesterolemic	88 (85.4)	968 (82.0)	
Hypercholesterolemic under treatment with statins	5 (4.9)	81 (6.9)	
Hypercholesterolemic not under treatment	10 (9.7)	131 (11.1)	
Smoking habit			0.452
Never smoker	48 (46.6)	528 (44.7)	
Former smoker	25 (24.3)	242 (20.5)	
Current smoker	30 (29.1)	410 (34.7)	
Alcohol			0.433
Never drinker	54 (52.4)	554 (46.9)	
Former drinker	11 (10.7)	113 (9.6)	
Current drinker	38 (36.9)	513 (43.5)	
Migraine			
Any migraine	48 (46.6)	343 (29.1)	≤0.001
Migraine subtype			0.893
Migraine without aura	37 (77.1)	258 (75.2)	
Migraine without aura+migraine with aura	6 (12.5)	44 (12.8)	
Migraine with aura	5 (10.4)	44 (12.8)	
Oral contraceptives*	13 (22.2)	113 (23.6)	1.000
Hormonal replacement therapy*	5 (10.0)	15 (3.7)	0.058
Intracranial aneurysms	14 (13.6)	17 (1.4)	≤0.001
Familial history of thrombosis	24 (23.3)	268 (22.8)	0.898
Familial history of arterial dissection	4 (3.9)	12 (1.0)	0.034

cFMD indicates cerebrovascular fibromuscular dysplasia.

*In women.

associated with an increased hazard of recurrent dissection in the univariate analysis (hazard ratio, 3.99 [95% CI, 1.94–8.19]). In the multivariable Cox proportional regression model, both personal history of migraine and cFMD turned out to predict independently the risk of recurrence at any follow-up time. Conversely, although discontinuation of antithrombotic medications for long-term secondary prevention was recorded more frequently

among patients who eventually had recurrent events (23.1% versus 13.1% in the subgroup of those who did not experience recurrence), this turned out to have no independent effect on the midterm risk of new dissection (Table 4; Figure [B]).

Since the study protocol did not include serial magnetic resonance imaging at well-established time points in all patients beyond the first 6 months after the index

Table 2. Clinical Features, Triggering Factors, and Vascular Pathology of Index Cervical Artery Dissection by cFMD Status

Variable	cFMD+ (n=103)	cFMD- (n=1180)	P value
Clinical features			
Cervical pain	41 (39.8)	493 (41.8)	0.755
Headache	50 (48.5)	587 (49.7)	0.815
Tinnitus	6 (5.8)	57 (4.8)	0.633
Cranial nerve involvement	8 (7.8)	134 (11.4)	0.327
Horner syndrome	26 (25.2)	229 (19.4)	0.155
TIA	15 (14.6)	147 (12.5)	0.536
Cerebral infarct	73 (70.9)	864 (73.2)	0.607
Subarachnoid hemorrhage	0 (0.0)	18 (1.5)	0.390
Dissection site			0.547
Carotid	63 (61.2)	708 (60.0)	
Vertebral	19 (18.4)	277 (23.5)	
Intracranial arteries	2 (1.9)	25 (2.1)	
Multiple vessel	19 (18.4)	170 (14.4)	
Vascular pathology			≤0.001
Occlusion	33 (32.0)	520 (44.1)	
Stenosis	40 (38.8)	444 (37.6)	
Intimal flap	3 (2.9)	47 (4.0)	
Pseudoaneurysm	9 (8.7)	47 (4.0)	
Other	18 (17.5)	104 (9.0)	
Triggering factors			
Infections, past 30 d*	13 (12.6)	133 (11.3)	0.630
Antibiotics use	8 (61.5)	72 (54.1)	0.773
Trauma, minor	8 (7.8)	176 (14.9)	0.055
Strenuous physical activity	38 (36.9)	544 (46.1)	0.079
Acute-phase treatment			0.517
Antiplatelet therapy	51 (49.5)	538 (45.6)	
Anticoagulant treatment	40 (38.8)	457 (38.7)	
Any recanalization therapy	12 (11.7)	185 (15.7)	

cFMD indicates cerebrovascular fibromuscular dysplasia.

*Diagnosis of infection required at least 1 typical symptom in combination with fever (temperature, ≥38°C), subfebrile temperature (37.5–37.9°C), or corresponding serological, cultural, or radiological findings indicating an acute infection. In addition, at least 2 typical corresponding symptoms were accepted [29]; multiple-vessel cervical artery dissection was defined as the simultaneous presence of >1 dissected vessels at the initial diagnosis.

event, a bias due to the misdiagnosis of asymptomatic cases could not be excluded a priori. We, therefore, performed the same survival analysis by restricting the follow-up to the first 6 months, during which all patients were systematically investigated by serial magnetic resonance imaging (usually, at 3 and 6 months). The results confirmed both personal history of migraine and cFMD as independent predictors of sCeAD recurrence (hazard ratio, 2.36 [95% CI, 1.13–4.90] and 2.86 [95% CI, 1.24–6.62], respectively).

cFMD+ patients underwent a further follow-up assessment in August 2020 either in an outpatient

Table 3. Multivariate Analyses (Logistic Regression) of the Association of Putative Risk Factors With Cerebrovascular Fibromuscular Dysplasia

	OR	95% CI	P value
Sex, women	1.50	0.96–2.35	0.074
Age, y	0.99	0.97–1.01	0.547
Any migraine	1.78	1.13–2.79	0.010
Intracranial aneurysms	8.71	4.06–18.68	≤0.001
Familial history of arterial dissection	3.33	0.94–11.79	0.062
Trauma, minor	0.48	0.26–0.89	0.010
Strenuous physical activity	0.65	0.42–1.01	0.062

OR indicates odds ratio.

setting or by telephone interview. After a median follow-up time of 38.5 months (25th to 75th percentile, 77.5), there were 2 deaths (one of unclear etiology and one due to spontaneous intracerebral hemorrhage), and 1 acute myocardial infarction. The majority of cFMD+ patients had a stable disease with no additional clinical manifestations, including signs of renal impairment.

DISCUSSION

In a large multicenter sample of patients with sCeAD, we found differences in demographic characteristics and risk factor profile but no substantial differences in clinical presentation, between patients with and without cFMD. In agreement with previous reports, we observed that sCeAD patients who were cFMD+ more frequently had intracranial aneurysms.⁴ As novel findings, they were more often diagnosed as migraineurs, though with no disparities in migraine characteristics compared with cFMD- patients, and more frequently, they had a first-degree relative with history of arterial dissection. Another notable result of the present analysis is that the coexistence of cFMD with sCeAD, as well as a personal history of migraine in sCeAD patients, strongly and independently predicts the midterm risk of recurrent sCeAD.

Most of the studies conducted to date on patients' prognosis after first-ever sCeAD were clearly underpowered for multivariable analysis because of the rather modest number of patients involved¹⁵ or because of the relatively short follow-up, limited to the first 3 to 6 months after the index event.⁷ To our knowledge, this is the largest study population of sCeAD patients with extensive data available on midterm follow-up and the first to include cFMD in the recurrence prediction models.^{16–19} Our study provides, therefore, essential new information on the outcome of sCeAD patients.

Potential Biologic Mechanisms

In spite of the strong epidemiological evidence of association between sCeAD and FMD and the results of the present study linking cFMD to recurrent CeAD events,

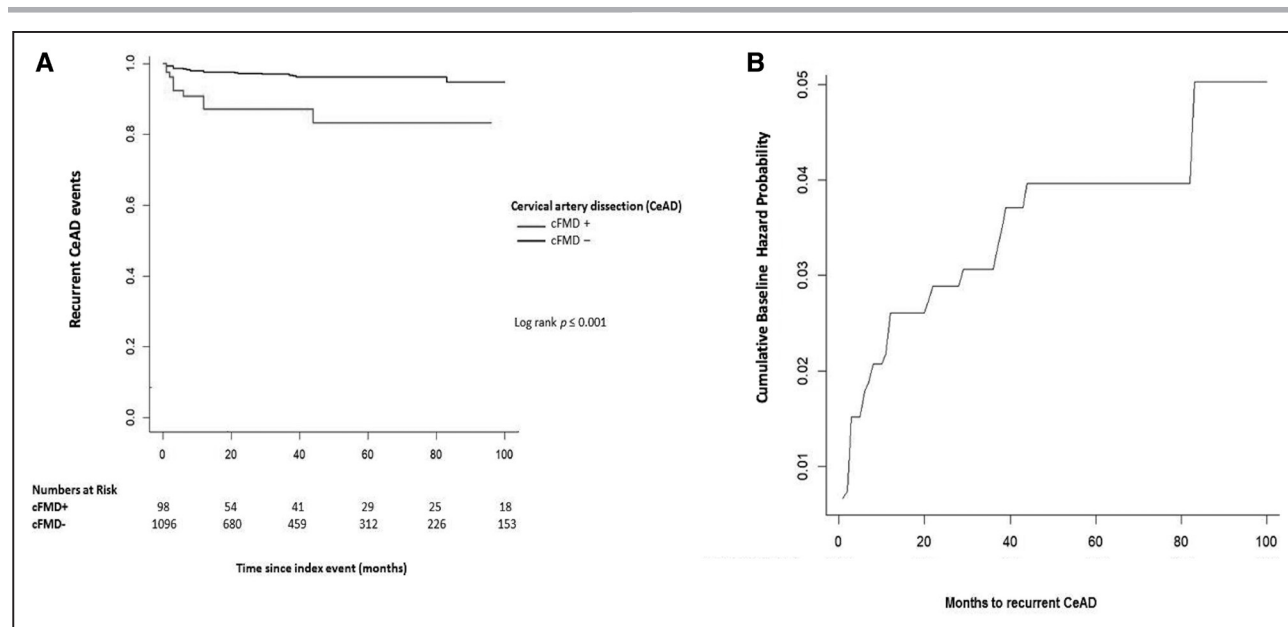


Figure. Outcome of the study group stratified by cerebrovascular fibromuscular dysplasia (cFMD) status.

Kaplan-Meier curve for the risk of recurrent spontaneous cervical artery dissection (sCeAD) during follow-up (**A**) and baseline cumulative hazard rate of the fitted Cox model fixing all covariates=0 (**B**). *P* for difference in recurrent sCeAD between cFMD+ patients vs cFMD- patients with the log-rank test.

the underlying biologic mechanisms remain a matter of speculation. The most intriguing findings in this regard come from genome-wide association studies and support the hypothesis of a common genetic susceptibility. In particular, the noncoding single-nucleotide polymorphism rs9349379 of the *PHACTR1* (phosphatase and actin regulator 1) gene (locus 6p24)—an established risk variant for coronary artery dissection²⁰ and for CeAD²¹—has been reported to be also a risk allele for FMD.²² Even more interesting, rs9349379 also links these two nonatherosclerotic diseases to migraine²³—a condition whose prevalence among FMD patients and sCeAD patients appears higher than in the general population.^{4,24,25} This indirectly supports our findings and strengthens the hypothesis of a plausible triangular relation between migraine, FMD, and sCeAD. Though further investigation is needed to elucidate the exact biology of

the rs9349349 variant, Gupta et al²⁶ recently showed that the G allele correlates with increased expression of the *EDN1* gene, but not *PHACTR1*, during the differentiation to endothelial and smooth muscle lineages. This study suggests that *EDN1* may act as a mediator of several important biological mechanisms for vascular diseases genetically linked to rs9349379 (eg, vasoconstriction, proliferation, and vasodilation). In addition, the rs9349379-A allele was reported to associate with lower levels of circulating ET-1 (endothelin 1) in healthy volunteers,^{22,26} as well as in patients with spontaneous coronary artery dissection.²¹ The hemodynamic effects of ET-1 provide, therefore, an attractive potential contributing mechanism for many of the vascular diseases, including migraine, FMD, and sCeAD, where rs9349379 is genetically involved. Obviously, the possible contribution of other factors to the relation between FMD and sCeAD cannot be ruled out. This might be the case, for example, of environmental triggers. Vessel lesions in cases of sCeAD or cFMD are more frequently located in the middle-distal segment of the cervical arteries—the maximum point of traction when the head is vertically or rotationally moved. Similarly, lesions in other vessels affected by FMD are located in arterial segments exposed to repeated mechanical stretching, such as the right more than the left renal artery or the external iliac arteries.⁴ Finally, because FMD is far more prevalent in women than in men, a role of female hormones in cases of sCeAD with coexistent FMD can be hypothesized.^{5,27}

With regard to migraine, as hypothesized before,²⁴ patients experiencing this condition might be at increased risk of extracellular matrix degradation. Furthermore,

Table 4. Multivariate Analyses (Cox Model) of Predictors of Recurrent Spontaneous Cervical Artery Dissection During Follow-Up

	HR	95% CI	<i>P</i> value
Age, y	0.98	0.95–1.01	0.456
Sex, women	0.59	0.29–1.19	0.145
Migraine	2.07	1.06–4.03	0.033
Fibromuscular dysplasia	3.40	1.58–7.31	0.002
Antithrombotics at follow-up	0.65	0.30–1.41	0.270
Intracranial aneurysms	1.26	0.27–5.73	0.761
Trauma, minor	0.27	0.06–1.16	0.080
Strenuous physical activity	1.61	0.84–3.09	0.151

HR indicates hazard ratio.

endothelium-dependent vasodilatation is impaired in migraine patients. These observations suggest that there could be an underlying generalized vasculopathy, whose origin is likely multifactorial resulting from a combination of genetic and environmental factors, which might predispose migraine patients to an increased risk of both sCeAD and cFMD. Whether such an underlying arteriopathy is more severe in patients with sCeAD and concomitant cFMD and it is, therefore, responsible for some vascular anomalies, including dissecting pseudoaneurysms whose prevalence was increased in these subjects, is an attractive, though untestable, hypothesis in the setting of the present study.

Strengths and Limitations

The main strengths of this study are the large sample size, the racial homogeneity, and the midterm follow-up of the patients included. Despite being the most frequent cause of brain ischemia in young adults, CeAD is rare in the general population (incidence, 2.6/100 000 per year²⁸). Thus, only a multicenter effort could achieve a sufficiently large sample size for longitudinal analyses. Several shortcomings are also noteworthy. First, our study sample is not perfectly representative of all cases of CeAD in an unselected population. Patients were recruited through neurology departments, mostly in tertiary centers, which are theoretically biased toward more complicated cases and rare causes. CeAD cases causing only local signs or minor strokes, which may be underdiagnosed, and CeAD patients with severe strokes requiring intensive care were less likely to be included. However, the characteristics of our cohort are comparable to those of other large series reported in the literature, which makes this potential drawback very unlikely. Second, since our protocol did not include a systematic and standardized examination of the cervical arteries at regular intervals during follow-up in all patients, we cannot exclude that some cases of asymptomatic recurrent sCeAD went undiagnosed. Though noteworthy, we believe this potential limitation does not reduce the relevance of our results. Actually, since all the IPSYS CeAD centers carried out specific diagnostic investigations aimed at identifying recurrent events in case of clinical suspicion, it is extremely unlikely that new dissections with a potential clinical impact were missed. Furthermore, the analysis of data obtained within the first 6 months since the index event, during which all patients underwent systematic follow-up imaging, substantially confirmed our findings over a longer period. Third, the study design did not include a systematic central reading of angiographic imaging, which might have improved the accuracy of diagnoses. However, since CeAD and cFMD were centrally confirmed in a small subset of patients recruited at peripheral centers, we assume that the inter-rater reliability of radiological diagnoses was high and, hence, believe it unlikely that diagnostic inaccuracy is a

real limitation of our analysis. Furthermore, the diagnosis of FMD can be challenging in case of acute CeAD, as angiographic features of both entities can be similar. However, this is only a theoretical concern. As it is now common practice in patients with CeAD, all patients included in the IPSYS CeAD registry underwent at least 1 follow-up angiography out of the acute phase. This allowed us to confirm the diagnosis of FMD, making unlikely that any acute, dissection-related anomalies of the arterial wall could lead to a misdiagnosis. Fourth, we cannot formally exclude nonrandom misclassification of family history if the number of individuals with less prior access to care and, therefore, less opportunity for formal diagnoses differed between groups. Fifth, for some variables (ie, alcohol consumption), we used reported values that tend to be an underestimation of the true measure. Finally, we did not systematically analyze the frequency of FMD in vascular beds other than cervical, which partially limits the generalizability of our results.

Conclusions

Our findings, if confirmed in independent data sets, could improve the understanding of the mechanisms underlying sCeAD—a major cause of ischemic stroke in young adults—and its relationship with FMD. Migraine was associated with cFMD in sCeAD patients, which implicates the possibility to identify those cFMD carriers at increased risk of sCeAD and, accordingly, the opportunity to implement primary prevention strategies in these subjects. Similarly, the observation that cFMD is a marker of increased risk of sCeAD recurrence in the medium run might have implications in terms of secondary prevention. In addition to validating these associations, future studies should include a simultaneous assessment of the arterial wall structure, as well as genetic and biochemical susceptibility factors, to explore the underlying mechanisms.

ARTICLE INFORMATION

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Affiliations

Dipartimento di Scienze Cliniche e Sperimentali, Clinica Neurologica, Università degli Studi di Brescia, Italy (S.B., M.L., V.M., D.P., A. Padovani, A. Pezzini). Dipartimento di Scienze del Sistema Nervoso e del Comportamento, Unità di Statistica Medica e Genomica, Università di Pavia, Italy (M. Grassi). S.C. Neurologia, Stroke Unit, Azienda Unità Sanitaria Locale—IRCCS di Reggio Emilia, Italy (M.Z.). IRCCS Istituto di Scienze Neurologiche di Bologna, UOC Neurologia e Rete Stroke Metropolitana, Ospedale Maggiore, Bologna, Italy (A.Z., M. Gentile). U.O. Malattie Cerebrovascolari, Fondazione IRCCS Istituto Neurologico “Carlo Besta,” Milano, Italy (A.B.). Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili, Università di Bologna, Italy (C.G.). Dipartimento di Neuroscienze, Stroke Unit, Ospedale Carlo Poma, Mantova, Italy (G.S.). UOSD Stroke Unit e Laboratorio di Neurosonologia, Azienda Ospedale—Università di Padova, Italy (C.B.). Dipartimento di Neuroscienze, Stroke Unit, Università di Torino, Italy (P.C.). Centro Trombosi, IRCCS Humanitas Research Hospital, Rozzano-Milano, Italy (C.L.). Neurologia d'Urgenza e Stroke Unit, IRCCS Humanitas Research Hospital, Rozzano-Milano, Italy (S.M.). Stroke Unit and Divisione di Medicina Cardiovascolare, Università di Perugia, Italy (M.P.). Stroke Unit, Azienda Ospedaliera

Sant'Andrea, Università "La Sapienza," Roma, Italy (M.R.). Stroke Unit, Azienda Ospedaliera Universitaria Integrata Borgo Trento, Verona, Italy (M.C.). U.O. di Neurologia, Ospedale Galliera, Genova, Italy (M.D.S.). UC Malattie Cerebrovascolari e Stroke Unit (A.C.) and Neurologia d'Urgenza (G.M.), IRCCS Fondazione Istituto "C. Mondino," Pavia, Italy. UO Neurologia, ASST della Valle Camonica, Esine, Italy (A.M.). UOC Neurologia, AUSL Romagna, Ravenna, Italy (E.M.L.). UO Neurologia, Ospedale di Circolo, Università dell'Insubria, Varese, Italy (M.L.D.). Stroke Unit, Neurologia Vascolare, ASST Spedali Civili di Brescia, Italy (M. Magoni). U.O. di Neurologia, Dipartimento di Neuroscienze e Riabilitazione, Azienda Ospedaliero-Universitaria di Ferrara (C.A.). U.O. di Neurologia-Stroke Unit, Ospedale di Legnano, ASST-Ovest Milanese, Milano, Italy (M.V.C.). Unità di Neurologia, Ospedale S. Andrea, La Spezia, Italy (E.G.). UOC Neurologia, ASST Vimercate, Italy (M.B.). UOSD Stroke Unit, Dipartimento di Medicina Clinica e Sperimentale, Università di Messina, Italy (P.L.S.). SS NeuroVascolare Ospedale Maria Vittoria, ASL Città di Torino, Italy (F.M.). UOC Stroke Unit, Azienda Ospedaliera Universitaria Senese, Siena, Italy (R.T.). UO Neurologia, Ospedale Villa Sofia, Palermo, Italy (V.T.). Istituto di Ricovero e Cura a Carattere Scientifico, Centro Neurolesi Bonino-Pulejo, Messina, Italy (R.S.C.). SC Neurologia e Stroke Unit, Dipartimento Neuroscienze e Riabilitazione, Azienda Ospedaliera "G. Brotzu," Cagliari, Italy (V.P.). UO Neurologia, Istituti Ospitalieri, ASST Cremona, Italy (A.G.). Dipartimento di Neurologia, Ospedale "Madonna del Soccorso," San Benedetto del Tronto, Italy (S.S.). UOC Neurologia-Stroke Unit, ASST Melegnano-Martesana, PO Vizzolo Predabissi, Italy (C.Z.). Stroke Unit, Ospedale Civico, Palermo, Italy (M. Mannino). S.C. Neurologia e Unità Neurovascolare, Ospedale di Desio-ASST Monza, Italy (I.C.). Dipartimento di Area Medica, UOC Neurologia, ASST Pavia, Voghera, Italy (C.D.). Stroke Unit, Università degli Studi di Firenze, Azienda Ospedaliero-Universitaria Careggi, Firenze, Italy (P.N.). Stroke Unit, UO Neurologia, Ospedale "S. Chiara," Trento, Italy (V.B.). Stroke Center, Dipartimento di Neurologia, IRCCS Sacro Cuore Negrar, Verona, Italy (A.A.). UO Neurologia, Istituto Ospedaliero Poliambulanza, Brescia, Italy (E.M.). Dipartimento Di Scienze Mediche e Chirurgiche e Tecnologie Avanzate, Sezione di Neuroscienze, Università di Catania, Italy (R.B.).

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Supplemental Materials

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Tables I–III
List of Collaborators

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