RESEARCH ARTICLE

Risk Profile of Patients with Spontaneous Cervical Artery Dissection

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Objective: Epidemiological data to characterize the individual risk profile of patients with spontaneous cervical artery dissection (sCeAD) are rather inconsistent.
Methods and Results: In the setting of the Italian Project on Stroke in Young Adults Cervical Artery Dissection (IPSYS CeAD), we compared the characteristics of 1,468 patients with sCeAD (mean age = 47.3 ± 11.3 years, men = 56.7%) prospectively recruited at 39 Italian centers with those of 2 control groups, composed of (1) patients whose ischemic stroke was caused by mechanisms other than dissection (non-CeAD IS) selected from the prospective IPSYS registry and Brescia Stroke Registry and (2) stroke-free individuals selected from the staff members of participating hospitals, matched 1:1:1 by sex, age, and race. Compared to stroke-free subjects, patients with sCeAD were more likely to be hypertensive (odds ratio [OR] = 1.65, 95% confidence interval [CI] = 1.37–1.98), to have personal history of migraine with aura (OR = 2.45, 95% CI = 1.74–3.34), without aura (OR = 2.67, 95% CI = 2.15–3.32), and family history of vascular disease in first-degree relatives (OR = 1.69, 95% CI = 1.39–2.05), and less likely to be diabetic (OR = 0.65, 95% CI = 0.47–0.91), hypercholesterolemic (OR = 0.75, 95% CI = 0.62–0.91), and obese (OR = 0.41, 95% CI = 0.31–0.54). Migraine without aura was also associated with sCeAD (OR = 1.81, 95% CI = 1.47–2.22) in comparison with patients with non-CeAD IS. In the subgroup of patients with migraine, patients with sCeAD had higher frequency of migraine attacks and were less likely to take anti-migraine preventive medications, especially beta-blockers, compared with the other groups.
Interpretation: The risk of sCeAD is influenced by migraine, especially migraine without aura, more than by other factors, increases with increasing frequency of attacks, and seems to be reduced by migraine preventive medications, namely beta-blockers.

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Introduction

Despite recent improvements in diagnosis and recognition of the importance of the disease, cervical artery dissection (CeAD), a major cause of brain ischemia in young and middle-aged adults, remains poorly studied and understood.[1] The little we currently know comes mainly from a few observational studies, including large cohorts of patients and a small amount of randomized trial data, and it is reflected by the limited strength of the recommendations for management provided by the scientific guidelines recently published by the European Stroke Organization working group.[2] Advances in our understanding of the genetic basis of the disease have strengthened the prevailing idea that spontaneous cases (sCeAD) may be facilitated by an underlying, constitutional disorder of the vessel wall, leading to structural instability and predisposing to the damaging effect of temporarily active factors. In addition, observations collected from a few informative case–control studies and sparse case-series over the past 20 years have led to the shared opinion that most traditional pro-atherosclerotic factors have a marginal, if any, role in disease pathogenesis.[1] However, consistent epidemiological data to substantiate this assumption and to better characterize individuals at risk of developing sCeAD are still lacking.[3] Because of the biological and clinical implications of the above, we conducted a case–control study in the setting of the Italian Project on Stroke in Young Adults Cervical Artery Dissection (IPSYS CeAD), comprising one of the largest series of patients with sCeAD currently available, with the purpose of assessing the specific contribution of each factor on disease occurrence and evaluating the possibility that interventions aimed at modifying these factors might have an influence on such a risk.

Methods

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

Standard Protocol Approvals and Participant Consents

The Institutional Ethical Standards Committee on human experimentation at Brescia University Hospital provided approval for the study. Written informed consent was obtained for all participants or by proxy (next of kin).

Study Design and Participants Selection

The study was designed to compare the following 3 groups, (1) patients with sCeAD, (2) patients whose

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ischemic stroke was due to a cause other than sCeAD (non-CeAD IS), and (3) stroke-free control subjects, in a case–control analysis. We matched each patient with sCeAD to one patient with non-CeAD IS and one stroke-free control subject of the same age (± 3 years), sex, and race.

Patients With CeAD

Patients in this group were recruited in the setting of the IPSYS CeAD, a substudy of the IPSYS project[4] whose methods have been described previously.[5,6] Briefly, patients consecutively admitted to 39 hospitals who received the diagnosis of first-ever CeAD, were considered eligible provided they met predefined inclusion/exclusion criteria. The diagnosis of CeAD was based on established radiological criteria.[5] 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. The recruitment process took place prospectively from January 2000 through June 2019.[5] For the purpose of the present analysis, patients whose dissection occurred as an immediate consequence of a major trauma were excluded. 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 intra-thoracic pressure (eg, heavy lifting), which had occurred within 1 month prior to first symptoms of dissection. Traumatic events leading to medical examination or hospitalization were considered "major" and all others were "minor."[6]

Patients With Non-CeAD IS

Patients with IS due to a cause other than CeAD were selected from 2 prospective cohort studies: the IPSYS study and the Brescia Stroke Registry (BSR). The IPSYS study is a countrywide network of neurological centers with special interest in cerebral ischemia at a young age across Italy, aimed at prospectively recruiting consecutive patients with first-ever acute IS aged 18 to 45 years, in the setting of a hospital-based, multicenter, observational study. The recruitment period was January 2000 through December 2018.[4] The BSR is an ongoing, hospital-based, longitudinal study of patients with acute stroke from the contiguous catchment area. All patients consecutively admitted to the Department of Neurology at Brescia University Hospital between April 2015 and February 2018 who received the diagnosis of acute IS were screened for inclusion.[7] In both studies, stroke was defined as a sudden loss of global or focal cerebral function that persisted for > 24 hours with a probable vascular cause and imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) evidence of cerebral infarction. IS due to sinus venous thrombosis, vasospasm after subarachnoid hemorrhage, cardiac surgery, occurring as an immediate consequence of trauma, and iatrogenic strokes were excluded.[6,7] All patients received an initial diagnostic evaluation and treatment based on established guidelines.[8,9]

Control Group

Subjects in this group were selected from the staff members of participating hospitals provided they had no known history of vascular diseases. Study physicians interviewed each consented subject face-to-face in a structured, identical manner. The recruitment period was January 2000 through December 2018.[10]

Demographic Characteristics, Lifestyle Variables, and Risk Factor Definition

The dataset included information on participants' demographic characteristics (age, sex, and race), lifestyle variables, comprising alcohol consumption, smoking habit, and body measures (height, weight, and body mass index [BMI]), as well as on the following risk factors for cerebral ischemia: hypertension, diabetes mellitus, hypercholesterolemia, and migraine. Among migraine sufferers, we distinguished between "active migraine," which included participants with at least one self-reported migraine attack in the year preceding the baseline evaluation, and "prior (non-active) migraine," which included those who reported ever having had migraine but no attack in the year preceding the baseline evaluation. Participants who reported active migraine were asked about migraine-specific features, including migraine frequency. Categories for migraine frequency included the following: < 1 migraine attack per month and ≥ 1 migraine attack per month. Overweightness was defined as BMI ≥ 25 kg/m^2 and < 30 kg/m^2 and obesity as BMI ≥ 30 kg/m^2. We also collected information on the use of oral contraceptives and hormone replacement therapy and on family history of thrombosis in participants' first-degree relatives (parents or siblings or sons or daughters). Variables were determined by self-report or direct measurements, as previously described.[5]

Statistical Analyses

Differences among the 3 groups (patients with sCeAD, patients with non-CeAD IS, and stroke-free subjects) were examined with the χ^2 test and analysis of variance (ANOVA), when appropriate. A multinomial logistic

regression (generalized logit) model was used to test the association of age, sex, body weight (normal weight, overweightness, and obesity), hypertension, diabetes, current smoking, hypercholesterolemia, history of migraine and its subtypes (migraine without aura and migraine with aura), alcohol intake, and family history of vascular disease in first-degree relatives with each group. Using the same model, we also tested whether the associations observed in the whole group were confirmed in the 2 independent subgroups defined by sex (men and women). Then, we used binomial logistic regression models to test whether the associations found in the primary analysis were maintained in secondary, sensitivity analyses, including the following subgroups of patients with CeAD: (1) patients with internal carotid artery dissection and patients with vertebral artery dissection; and (2) patients with brain ischemia and patients without brain ischemia as clinical presentation. In addition, because migraine was found to be the variable most strongly associated with sCeAD, we conducted a further logistic regression analysis to test the association, within the subgroup of patients with personal history of migraine, between migraine frequency, and each of the 3 groups (patients with sCeAD, patients with non-CeAD IS, and stroke-free subjects). Finally, we estimated attributable risk (AR), which was defined as AR = P(F|D) × (RR-1)/RR, where P(F|D) is the prevalence of a given factor among the cases and RR denotes relative risk, estimated using odds ratios (ORs) from the logistic regression, including stroke-free control subjects with disease status as the outcome.[11] Results are given as ORs with 95% confidence intervals (CIs). The $p \leq 0.05$ determined with a 2-sided test was considered significant. Data were analyzed using SPSS, version 21.0 (http://www.spss.com).

Results

Of the 1,530 patients with CeAD included in the IPSYS CeAD registry, 62 (4.0%) were excluded from the present analysis because vessel dissection occurred as an immediate consequence of a major trauma. Therefore, the study group comprised 1,468 patients (mean age = 47.3 ± 11.3 years; men = 56.7%) with spontaneous events. At the time of diagnosis, 1,180 patients (80.4%) had an ischemic cerebral event (stroke/transient ischemic attack [TIA], 1,071/109) and 19 patients (1.3%) had a subarachnoid hemorrhage. The sCeAD affected predominantly a single artery (carotid = 870 patients [59.3%], and vertebral = 386 patients [26.3%]), whereas 212 patients (14.4%) had > 1 cervical artery involved. Based on the prespecified selection criteria, we matched non-CeAD IS cases and stroke-free control subjects 1:1 with sCeAD cases, for a total of 1,468 participants per group. Demographic and clinical characteristics of the study group according to disease status and the prevalence of selected risk factors are presented in Table 1, whereas the results of the multinomial logistic regression analysis comparing the 3 groups of subjects are summarized in Table 2.

Patients With sCEAD Versus Stroke-Free Control Subjects

After adjustment for preselected variables, hypertension was associated with an increased risk of sCeAD (OR = 1.65, 95% CI = 1.37–1.98) and so were a personal history of migraine, both with aura (OR = 2.45, 95% CI = 1.74–3.34) and without aura (OR = 2.67, 95% CI = 2.15–3.32), and a family history of vascular disease in first-degree relatives (OR = 1.69, 95% CI = 1.39–2.05). Conversely, diabetes (OR = 0.65, 95% CI = 0.47–0.91), hypercholesterolemia (OR = 0.75, 95% CI = 0.62–0.91), and obesity (OR = 0.41, 95% CI = 0.31–0.54) were associated with a decreased risk of disease. Results remained substantially unchanged when stratifying the subgroup of patients with sCeAD on (1) the presence or absence of brain ischemia or (2) the site of arterial dissection (carotid or vertebral; Table 3).

Patients With sCeAD Versus Non-CeAD IS Patients

In the comparative analysis of patients with sCeAD with patients with non-CeAD IS, all traditional cardiovascular risk factors were associated with increased risk of non-CeAD IS, as opposed to migraine (OR = 1.42, 95% CI = 1.19–1.70), especially migraine without aura (OR = 1.81, 95% CI = 1.47–2.22), which was found to be associated with increased risk of sCeAD.

Patients With Non-CeAD IS Versus Control Subjects

As expected, traditional cardiovascular risk factors, including hypertension, hypercholesterolemia, active smoking, regular alcohol consumption, and history of vascular disease, among first-degree family members were associated with the subgroup of patients with non-CeAD IS. Similarly, a personal history of migraine was independently associated with non-CeAD IS (OR = 1.74, 95% CI = 1.41–2.14), although the strength of this association was more prominent for migraine with aura (OR = 2.43, 95% CI = 1.73–3.41) than for migraine without aura (OR = 1.47, 95% CI = 1.16–1.86).

Findings did not differ when patients with sCeAD were compared to the 2 control groups stratifying on sex (men and women; data not shown).

TABLE 1. Demographic and Clinical Characteristics of the Study Group

Variable	sCeAD (n = 1,468)	non-CeAD IS (n = 1,468)	Control subjects (n = 1,468)	*p*
Sex, males	832 (56.7)	832 (56.7)	832 (56.7)	
Age, yr ± SD	47.3 ± 11.3	47.5 ± 11.3	47.1 ± 11.8	0.621
Race				1.000
White	1,430 (97.4)	1,430 (97.4)	1,430 (97.4)	
Black	13 (0.9)	13 (0.9)	13 (0.9)	
Asian	25 (1.7)	25 (1.7)	25 (1.7)	
Body weight				≤ 0.001
Normal weight	1,003 (68.3)	1,083 (73.8)	1,069 (72.8)	
Overweightness	375 (25.5)	278 (18.9)	287 (19.6)	
Obesity	90 (6.1)	107 (7.3)	112 (7.6)	
Body mass index, kg/m^2	24.3 ± 3.7	26.6 ± 6.1	26.8 ± 6.1	≤ 0.001
Hypertension				≤ 0.001
Non-hypertensive	1,068 (72.8)	875 (59.6)	1,172 (79.8)	
Hypertensive under treatment	284 (19.3)	460 (31.3)	230 (15.7)	
Hypertensive not under treatment	116 (7.9)	133 (9.1)	66 (4.5)	
Diabetes				≤ 0.001
Non-diabetic	1,402 (95.5)	1,318 (89.8)	1,372 (93.5)	
Diabetic under treatment	51 (3.5)	129 (8.8)	76 (5.2)	
Diabetic not under treatment	15 (1.0)	21 (1.4)	20 (1.4)	
Hypercholesterolemia				≤ 0.001
Non-hypercholesterolemic	1,221 (83.2)	1,037 (70.6)	1,173 (79.9)	
Hypercholesterolemic under treatment with statins	91 (6.2)	291 (19.8)	225 (15.3)	
Hypercholesterolemic not under treatment	156 (10.6)	140 (9.5)	70 (4.8)	
Smoking habit				≤ 0.001
Never smoker	686 (46.7)	716 (48.8)	890 (60.6)	
Former smoker	307 (20.9)	191 (13.0)	148 (10.1)	
Current smoker	475 (32.4)	561 (38.2)	430 (29.3)	
Oral contraceptives[a]	135 (22.0)	195 (31.8)	130 (20.4)	≤ 0.001
Migraine				≤ 0.001
No migraine	1,052 (71.7)	1,156 (78.7)	1,257 (85.6)	
Migraine without aura	313 (21.3)	196 (13.4)	154 (10.5)	
Migraine with aura	103 (7.0)	116 (7.9)	57 (3.9)	
Alcohol, regular intake	609 (41.5)	743 (50.7)	628 (42.8)	≤ 0.001
Family history of vascular disease in first degree relatives	332 (22.6)	406 (27.6)	221 (15.1)	≤ 0.001

Abbreviations: IS = ischemic stroke; sCeAD = spontaneous cervical artery dissection; SD = standard deviation.
[a]Among female patients.

TABLE 2. Associations of Vascular Risk Factors with the Group of Patients with sCeAD, non-CeAD IS, and Stroke-Free Subjects Based on Multinomial Logistic Regression (Generalized Logit) Model

Variable	sCeAD vs control subjects	*p*	Attributable risk (%)	sCeAD vs non-CeAD IS	*p*	non-CeAD IS vs control subjects	*p*	Attributable risk (%)
Hypertension	1.65 (1.37–1.98)	< 0.001	+11	0.63 (0.53–0.74)	< 0.001	2.61 (2.19–3.11)	< 0.001	+17
Diabetes	0.65 (0.47–0.91)	0.011	−2	0.52 (0.38–0.71)	< 0.001	1.23 (0.93–1.64)	0.152	+1
Hypercholesterolemia	0.75 (0.62–0.91)	0.004	−6	0.53 (0.44–0.64)	< 0.001	1.40 (1.17–1.68)	< 0.001	+5
Current smoking	1.14 (0.97–1.34)	0.120	+4	0.77 (0.66–0.90)	0.001	1.47 (1.25–1.72)	< 0.001	+10
Alcohol consumption, regular	0.92 (0.79–1.07)	0.266	−4	0.69 (0.59–0.81)	< 0.001	1.32 (1.13–1.53)	0.001	+10
History of migraine								
No migraine	1			1		1		
Migraine without aura	2.67 (2.15–3.32)	< 0.001	+13	1.81 (1.47–2.22)	< 0.001	1.47 (1.16–1.86)	0.001	+4
Migraine with aura	2.45 (1.74–3.34)	< 0.001	+4	1.01 (0.75–1.35)	0.963	2.43 (1.73–3.41)	< 0.001	+7
Body weight								
Normal weight	1			1		1		
Overweightness	0.92 (0.77–1.10)	0.343	−1	0.85 (0.71–1.02)	0.079	1.07 (0.90–1.29)	0.434	0
Obesity	0.41 (0.31–0.54)	< 0.001	−4	0.47 (0.36–0.63)	< 0.001	0.87 (0.68–1.10)	0.236	−5
Family history of vascular disease in first-degree relatives	1.69 (1.39–2.05)	< 0.001	+9	0.82 (0.69–0.99)	0.035	2.04 (1.69–2.46)	< 0.001	+11

Note: Numbers are odds ratios and 95% confidence intervals.
Age, sex, body weight (normal weight, overweightness and obesity), hypertension, diabetes, current smoking, hypercholesterolemia, history of migraine and its subtypes (migraine without aura and migraine with aura), alcohol intake, and family history of vascular disease in first-degree relatives were entered into the model as covariates.
Abbreviations: IS = ischemic stroke; sCeAD = spontaneous cervical artery dissection.

Migraine Frequency and Risk of sCeAD

We observed a relationship between increasing frequency of migraine attacks and the risk of sCeAD (Table 4). In the logistic regression models, including participants with personal history of any migraine, increasing frequency of attacks was associated with sCeAD in comparison with both patients with non-CeAD IS (OR = 2.03, 95% CI = 1.33–3.33 for patients with < 1 migraine attack per month; OR = 4.54, 95% CI = 2.85–7.69 for patients with ≥ 1 migraine attack per month; reference, non-active migraine) and control subjects (OR = 3.98, 95% CI = 2.06–7.71 for patients with ≥ 1 migraine attack per month; reference, non-active migraine). Findings did not change substantially when we restricted the analysis to participants with personal history of migraine without aura (patients with sCeAD vs patients with non-CeAD IS: OR = 1.92, 95% CI = 1.12–3.22 for patients with < 1 migraine attack per month; OR = 4.16, 95% CI = 2.32–7.69 for patients with ≥ 1 migraine attack per month; patients with sCeAD vs control subjects: OR = 4.72, 95% CI =2.22–10.02 for patients with ≥ 1 migraine attack per month; reference, non-active migraine). Conversely, we did not detect any association between the frequency of attacks of migraine with aura and sCeAD, nor did we find any relation of migraine frequency with non-CeAD IS.

In line with the results reported above, within the subgroup of patients with migraine, patients with sCeAD were found to be taking migraine preventive medications at a lower rate than subjects in the other 2 groups, a finding that was most evident for beta-blocker agents (Table 5).

Discussion

The findings of the present study provide information on the specific risk profile of patients with sCeAD as well as on the impact of each factor on the risk of disease

TABLE 3. Association of Vascular Risk Factors with Specific Subgroups of Patients With sCeAD

	Carotid artery dissection	*p*	Vertebral artery dissection	*p*	sCeAD with brain ischemia	*p*	sCeAD without brain ischemia	*p*
Hypertension	1.48 (1.19–1.80)	≤ 0.001	1.73 (1.32–2.27)	≤ 0.001	1.59 (1.32–1.93)	≤ 0.001	1.28 (0.94–1.74)	0.116
Diabetes	0.53 (0.35–0.81)	0.003	1.08 (0.68–1.71)	0.732	0.68 (0.48–0.97)	0.034	0.32 (0.14–0.71)	0.006
Hypercholesterolemia	0.74 (0.59–0.93)	0.012	0.85 (0.62–1.15)	0.299	0.71 (0.57–0.87)	0.001	0.86 (0.61–1.20)	0.386
Current smoking	1.16 (0.96–1.40)	0.108	1.03 (0.80–1.34)	0.769	1.19 (0.97–1.41)	0.083	0.92 (0.69–1.24)	0.616
Alcohol consumption, regular	0.90 (0.75–1.07)	0.255	0.87(0.68–1.11)	0.273	0.91 (0.77–1.07)	0.259	1.02 (0.78–1.34)	0.838
History of migraine								
No migraine	1		1		1		1	
Migraine without aura	2.65 (2.07–3.38)	≤ 0.001	2.32 (1.68–3.21)	≤ 0.001	2.32 (1.84–2.92)	≤ 0.001	3.97 (2.85–5.53)	≤ 0.001
Migraine with aura	2.38 (1.62–3.51)	≤ 0.001	2.12 (1.28–3.52)	0.004	2.08 (1.45–3.00)	≤ 0.001	3.69 (2.19–6.21)	≤ 0.001
Body weight								
Normal weight	1		1		1		1	
Overweightness	0.75 (0.52–1.10)	0.151	1.15 (0.74–1.79)	0.525	0.86 (0.62–1.18)	0.368	0.61 (0.33–1.13)	0.122
Obesity	0.69 (0.56–0.86)	0.001	0.73 (0.54–0.99)	0.045	0.69 (0.57–0.84)	≤ 0.001	0.84 (0.70–0.99)	0.043
Family history of vascular disease in first-degree relatives	1.49 (1.19–1.87)	≤ 0.001	1.69 (1.26–2.27)	≤ 0.001	1.69 (1.38–2.07)	≤ 0.001	1.69 (1.38–2.07)	≤0.001

Note: Numbers are odds ratios and 95% confidence intervals.
Adjustments were made as in Table 2.
Abbreviations: sCeAD = spontaneous cervical artery dissection.

compared with both patients whose brain ischemia is caused by mechanisms other than dissection and stroke-free control individuals. In particular, we found the following peculiar patterns of association: (1) hypertension, history of migraine (especially migraine without aura), and family history of vascular disease in first-degree relatives were directly associated with sCeAD, whereas other major conventional cardiovascular risk factors, namely diabetes, hypercholesterolemia, and obesity, were inversely associated to disease occurrence in comparison with stroke-free

TABLE 4. Association Between Frequency of Migraine Attacks and the Group of Patients With sCeAD, Patients With Non-CeAD IS, and Stroke-Free Subjects

	sCeAD vs control subjects			sCeAD vs non-CeAD IS			non-CeAD IS vs control subjects		
Migraine frequency	Any migraine	Migraine without aura	Migraine with aura	Any migraine	Migraine without aura	Migraine with aura	Any migraine	Migraine without aura	Migraine with aura
Non-active migraine	1	1	1	1	1	1	1	1	1
< 1/mo	0.69 (0.40–1.22)	0.78 (0.42–1.73)	0.34 (0.06–1.75)	2.03 (1.33–3.33)	1.92 (1.12–3.22)	2.70 (0.98–6.14)	0.89 (0.17–1.09)	0.83 (0.18–1.60)	0.70 (0.02–1.01)
≥ 1/mo	3.98 (2.06–7.71)	4.72 (2.22–10.02)	2.08 (0.38–11.40)	4.54 (2.85–7.69)	4.16 (2.32–7.69)	5.69 (0.94–20.00)	0.71 (0.37–1.34)	0.88 (0.41–1.92)	0.41 (0.04–1.15)

Note: Numbers are odds ratios and 95% confidence intervals.

TABLE 5. Study Subgroups Defined by Migraine Features (Migraine Frequency and Migraine Preventive Medications) Among Patients With sCeAD, Patients With Non-CeAD IS, and Stroke-Free Subjects

	Any migraine				Migraine without aura				Migraine with aura			
Variable	sCeAD (n = 416)	non-CeAD IS (n = 312)	Control subjects (n = 210)	*p*-value	sCeAD (n = 313)	non-CeAD IS (n = 196)	Control subjects (n = 154)	*p*-value	sCeAD (n = 103)	non-CeAD IS (n = 116)	Control subjects (n = 56)	*p*-value
Migraine frequency												
Non-active migraine	43 (10.3)	79 (25.3)	24 (11.4)	<0.001	36 (11.5)	51 (26.0)	21 (13.6)	<0.001	7 (6.8)	28 (24.1)	3 (5.4)	<0.001
< 1/mo	184 (44.3)	159 (51.0)	156 (74.3)		144 (46.0)	102 (52.0)	115 (74.7)		40 (38.8)	57 (49.1)	41 (73.2)	
≥ 1/mo	189 (45.4)	74 (23.7)	30 (14.3)		133 (42.5)	43 (22.0)	18 (11.7)		56 (54.4)	31 (26.8)	12 (21.4)	
Prophylactic therapy	23 (5.5)	35 (11.3)	35 (16.7)	<0.001	16 (5.1)	25 (12.8)	24 (15.6)	<0.001	7 (6.8)	10 (8.6)	11 (19.6)	0.029
Beta-blocker	3 (0.7)	15 (4.8)	13 (6.2)	<0.001	2 (0.6)	11 (5.6)	8 (5.2)	<0.001	1 (1.0)	4 (3.4)	5 (8.9)	0.037
Calcium-channel blocker	4 (1.0)	8 (2.6)	6 (2.9)	0.157	4 (1.3)	5 (2.6)	5 (3.2)	0.332	0 (0.0)	3 (2.6)	1 (1.8)	0.273
Tricyclic antidepressants	8 (1.9)	2 (0.6)	7 (3.3)	0.76	5 (1.6)	2 (1.0)	6 (3.9)	0.129	3 (2.9)	0 (0.0)	1 (1.8)	0.194
Antiepileptic drugs	8 (1.9)	10 (3.2)	9 (4.3)	0.227	5 (1.6)	7 (3.6)	5 (3.2)	0.321	3 (2.9)	3 (2.6)	4 (7.1)	0.289

Note: Numbers are no. (%).
Abbreviations: IS = ischemic stroke; sCeAD = spontaneous cervical artery dissection.

control subjects, and (2) all traditional cardiovascular risk factors, except for migraine without aura, were inversely associated with sCeAD in the comparative analysis with the group of patients with non-CeAD IS. Overall, migraine without aura emerged as the condition most strongly associated with sCeAD, a finding that was further corroborated by the observation of a direct relationship between increasing frequency of migraine attacks and the risk of disease.

Most of our findings, particularly on the relationship between traditional cardiovascular risk factors and sCeAD, are substantially in line with those of the only observational study conducted so far, including a large series of patients with sCeAD (which partly overlaps with the present one), a group of patients with non-CeAD IS and a group of stroke-free control subjects,[12] as well as with those of other smaller studies.[3,13–15] Overall, these results underscore a neutral or inverse association of classic proatherosclerotic risk factors with disease risk in comparison with the 2 control groups, with the only notable exception of hypertension, which is confirmed in our analysis as a major susceptibility factor for sCeAD.[3] Similarly, the hypothesis of a link between migraine and sCeAD, based on the results of 2 previous large studies[16,17] and a few other smaller ones,[18] is essentially confirmed by the results of the present analysis. Notwithstanding, our study represents a substantial step forward compared to previous analyses and some of their inherent methodological limitations. Specifically, the variable migraine was not entered into the comprehensive analysis of the Cervical Artery Dissection and Ischemic Stroke Patients (CADISP) project,[12] whereas heterogeneity in the method of selection of stroke-free control subjects might theoretically represent a source of bias in the setting of an international multicenter study.[3] On the other hand, both the large studies focused on exploring the effect of migraine on the risk of disease lacked a group of stroke-free control subjects.[16,17] Unlike the previous registries, the IPSYS CeAD database allows us to adequately assess the strength of the association between all the individual variables and sCeAD within the same logistic model, and, hence, to define which among them is most likely to impact disease risk. This approach provides a more precise definition of the individual risk profile.

Concerning migraine, in addition to the hypotheses put forward so far to explain the possible relation with

arterial dissection, including increased extracellular matrix degradation, impairment of endothelium-dependent vasodilatation, and hormonal influences,[19] the assumption of a common genetic background has been recently reinforced by the observation of an extensive genetic sharing between the 2 conditions,[20] which further supports our findings and the idea of shared biologic mechanisms. The other noteworthy result that emerges from the present analysis is the association between migraine frequency, again, mostly migraine without aura, and the risk of sCeAD. According to our data, active migraine is associated with ~ 2-fold increased risk of sCeAD when the frequency is < 1 attack per month and ~ 4-and-a-half-fold increased risk when it is ≥ 1 attack per month in comparison with patients with non-CeAD IS, whereas this risk is ~ 4-fold increased when the frequency is ≥ 1 attack per month in comparison with the group of stroke-free control subjects. The hypothesis of a relationship between migraine frequency, in that case, migraine with aura, and ischemic stroke has been suggested previously[21,22] but has never been consistently confirmed and no data are available in the literature regarding such a relationship within the group of patients with arterial dissection. Hence, our findings need to be replicated in independent datasets before we can make any assumption on the role of migraine as a "modifiable factor" in sCeAD biology and the possibility that treatments aimed at reducing migraine frequency might reduce the risk of sCeAD. As obvious as these considerations may be, our additional observation that, at the time of dissection, patients were receiving treatment with migraine preventive agents, particularly beta-blockers, less frequently than subjects in the 2 control groups, strengthens this view and gives a rationale for future research perspectives and therapeutic opportunities. Although the role of beta-blockers in preventing sCeAD has never been formally investigated, it seems biologically plausible. Apart from being first-line medications in migraine prevention treatment,[23] beta-blockers reduce heart rate and blood pressure and are essential in managing aortic dissection,[24] where beta-blockade has been shown to reduce aneurysmal degeneration, dissection-related aortic procedures, and mortality.[25]

Therefore, beyond the indirect confirmation of the biological effect of hypertension on the risk of disease, our results prompt to hypothesize that the reduction of blood pressure and arterial wall stress by beta-blockers might be effective in protecting against sCeAD, with no major adverse consequences. In addition to their antihypertensive effect, beta-blockers could also influence the individual propensity to arterial dissection by modifying the intrinsic elastic properties of the vessel wall. Actually, although the results in this regard are somewhat contradictory, sparse reports suggest that these agents can improve specific biomechanical parameters of the aorta, such as arterial stiffness and distensibility, in patients with early stage Marfan syndrome,[26–28] and suppress TGFβ expression, thus increasing matrix turnover[29–32] and reducing mechanical stress on arterial collagen fibers, in patients with Ehlers-Danlos syndrome type IV.[31,32] Because CeAD may be a phenotypic manifestation of these diseases, such observations provide indirect support to our findings.

Strength and Limitations

This is the largest case–control analysis of patients with sCeAD conducted so far, which ensures results, unlike other previous analyses including smaller series of patients, that are statistically stable and, therefore, reliable. IPSYS CeAD, IPSYS, and BSR are pragmatic registries combining the advantages of facilitating consecutive enrollment and follow-up of the patients with the strengths of a comprehensive clinical quality register. In addition, the inclusion of 2 groups of age-, sex-, and race-matched controls comprising patients with non-CeAD IS and stroke-free subjects provides epidemiological information that are specific to patients with dissection. Notwithstanding, the study also has some limitations. First, it covers a long period of time which makes it subject to variability in vascular imaging technology and estimation of the prevalence of historical risk factors. Furthermore, data on some variables (ie, migraine and migraine features) were self-reported which cannot exclude the unavoidable risk of misclassification. Second, the recruitment of control subjects among hospital employees might theoretically introduce a bias because of the different background and the reported healthier lifestyle of these individuals compared with the cases. Although the potential implications of this are noteworthy, the characteristics of our stroke-free control subjects and the prevalence of risk factors in this group are substantially comparable to those of the Italian population of the same age, according to the data provided by the Osservatorio Epidemiologico Cardiovascolare/Health Examination Survey (OEC/HES), the most comprehensive national evaluation of cardiovascular risk factors conducted in Italy.[33,34] Therefore, it seems unlikely that our results could be influenced by the criteria we adopted for the selection of the stroke-free control group. Third, because of the preponderance of patients with sCeAD who were hospitalized for acute ischemic stroke it cannot be excluded that the results of our analysis may be biased toward the most severe forms of disease. In addition, the prevalence of subjects taking prophylactic anti-migraine medications in the 3 groups is overall low. Therefore, despite statistical significance, our effect estimates carry some degree of uncertainty, which should caution strong conclusions on the clinical implication that

these agents, particularly beta-blockers, might be an effective preventive therapy against sCeAD. At this stage, results emerging from the analysis of selected patient subgroups should be interpreted as hypothesis-generating and additional studies involving a large number of well-characterized patients are needed to clarify this issue.

Conclusion

We confirmed that patients with sCeAD have a peculiar risk factor profile. In particular, migraine, especially migraine without aura, emerges as the variable with the highest impact on disease risk. Although our findings provide some hints in this regard, it remains to be established whether anti-migraine preventive medications aimed at reducing migraine frequency, namely beta-blockers, can actually reduce the risk of sCeAD and whether these agents might be a reasonable option for the long-term treatment of all patients with personal history of CeAD, regardless of whether or not they suffer from migraine.

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Author Contributions

A.P., E.D.Z., and M.G. contributed to the conception and design of the study. M.L.Z., A.Z., A.B., C.G., G.S., C.B., P.C., C.L., S.M., M.P., A.S., M.C., M.D.S., A.C., E.M.L., M.L.D., M.G., M.M., M.P., C.A., M.V.C., E.G., M.B., P.L.S., F.M., R.T., V.T., R.S.C., V.P., A.G., S.S., C.Z., M.M., I.C., C.D., P.N., V.B., A.A., R.B., R.P., and ZK contributed to the acquisition and analysis of data. A.P. and E.D.Z. contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

Nothing to report.

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