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Association Between Migraine and Cervical Artery Dissection
The Italian Project on Stroke in Young Adults

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IMPORTANCE Although sparse observational studies have suggested a link between migraine and cervical artery dissection (CEAD), any association between the 2 disorders is still unconfirmed. This lack of a definitive conclusion might have implications in understanding the pathogenesis of both conditions and the complex relationship between migraine and ischemic stroke (IS).

OBJECTIVE To investigate whether a history of migraine and its subtypes is associated with the occurrence of CEAD.

DESIGN, SETTING, AND PARTICIPANTS A prospective cohort study of consecutive patients aged 18 to 45 years with first-ever acute ischemic stroke enrolled in the multicenter Italian Project on Stroke in Young Adults was conducted between January 1, 2000, and June 30, 2015. In a case-control design, the study assessed whether the frequency of migraine and its subtypes (presence or absence of an aura) differs between patients whose IS was due to CEAD (CEAD IS) and those whose IS was due to a cause other than CEAD (non-CEAD IS) and compared the characteristics of patients with CEAD IS with and without migraine.

MAIN OUTCOMES AND MEASURES Frequency of migraine and its subtypes in patients with CEAD IS vs non-CEAD IS.

RESULTS Of the 2485 patients (mean [SD] age, 36.8 [7.1] years; women, 1163 [46.8%]) included in the registry, 334 (13.4%) had CEAD IS and 2151 (86.6%) had non-CEAD IS. Migraine was more common in the CEAD IS group (103 [30.8%] vs 525 [24.4%], $P = .01$), and the difference was mainly due to migraine without aura (80 [24.0%] vs 335 [15.6%], $P < .001$). Compared with migraine with aura, migraine without aura was independently associated with CEAD IS (OR, 1.74; 95% CI, 1.30-2.33). The strength of this association was higher in men (OR, 1.99; 95% CI, 1.31-3.04) and in patients 39.0 years or younger (OR, 1.82; 95% CI, 1.22-2.71). The risk factor profile was similar in migrainous and non-migrainous patients with CEAD IS (eg, hypertension, 20 [19.4%] vs 57 [24.7%], $P = .29$; diabetes, 1 [1.0%] vs 3 [1.3%], $P > .99$).

CONCLUSIONS AND RELEVANCE In patients with IS aged 18 to 45 years, migraine, especially migraine without aura, is consistently associated with CEAD. This finding suggests common features and warrants further analyses to elucidate the underlying biologic mechanisms.

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Editorial page 503

Supplemental content

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Although spontaneous cervical artery dissection (CEAD) is the most frequent cause of ischemic stroke (IS) in young and middle-aged adults, the mechanisms leading to vessel damage are still unclear.[1] A reason for this lack of clarity is the limited number of large epidemiologic studies aimed at investigating this unusual disease that have been conducted thus far. In particular, what is poorly defined is the effect that specific susceptibility factors might have on disease risk. This is especially true for migraine. Scarce reports, mainly derived from case series and case-control studies conducted on small cohorts, have observed a higher prevalence of migraine in patients with spontaneous CEAD compared with patients with an IS due to a cause other than CEAD (non-CEAD IS).[2] To our knowledge, the international Cervical Artery Dissection and Ischemic Stroke Patients (CADISP) case-control study[3] is the only study confirming these findings in a large cohort and providing support for the idea that such an association may vary according to migraine subtype, being stronger for migraine without aura. Apart from the contribution that these findings might have for better understanding the biology of arterial dissection, they also might have potential implications in elucidating the specific pathways underlying the widely accepted association between migraine and IS in young adults. In this regard, any association between this primary headache and spontaneous CEAD deserves to be further substantiated, and the characteristics of migrainous patients with IS caused by CEAD should be better defined. We aimed to evaluate the association between migraine and spontaneous CEAD, as well as the effect of specific migraine subtypes on disease risk, in the Italian Project on Stroke at Young Age (IPSYS), one of the largest registries of patients with early-onset IS that is currently available.

Key Points

Question Is there a link between migraine and cervical artery dissection?

Findings In this cohort study of 2485 patients aged 18 to 45 years with first-ever acute ischemic stroke, a history of migraine, especially the subtype without aura, was independently associated with cervical artery dissection. The strength of this association was higher in men and in younger individuals.

Meaning In young patients with ischemic stroke, migraine is consistently associated with cervical artery dissection. This finding implicates possible common biologic mechanisms underlying the 2 disorders.

Methods

Study Design and Patients Selection

The IPSYS is a countrywide network of neurologic centers with a special interest in cerebral ischemia occurring at a young age across Italy, aimed at recruiting white patients with first-ever acute stroke who fulfill the following criteria: (1) age 18 to 45 years and (2) computed tomographic (CT)- or magnetic resonance imaging (MRI)–proven cerebral infarction in the setting of a hospital-based, multicenter, observational study. Centers are included in the network provided that the recruitment process of stroke cases takes place prospectively. For the purpose of the present analysis, we screened data sets from patients consecutively admitted to 26 hospitals. The recruitment period was January 1, 2000, through June 30, 2015. Stroke was defined as a sudden loss of global or focal cerebral function that persisted for more than 24 hours with a probable vascular cause. Ischemic stroke due to sinus venous thrombosis, vasospasm after subarachnoid hemorrhage, and cardiac surgery; IS occurring as an immediate consequence of trauma; and iatrogenic strokes were excluded.[4,5] All aspects of the study were approved by relevant local authorities at each study site (eAppendix 2 in the Supplement). Written informed consent was obtained from all patients or their guardians.

Risk Factor Definition

The following risk factors for premature cerebral ischemia were documented: hypertension, diabetes, cigarette smoking, hypercholesterolemia, and migraine. These variables were defined and dichotomized as follows: hypertension, with systolic blood pressure 140 mm Hg or higher and diastolic pressure 90 mm Hg or higher in 2 separate measurements after the acute phase or use of antihypertensive drugs before recruitment; diabetes, with a history of diabetes, use of a hypoglycemic agent or insulin, or fasting glucose level 126 mg/dL or higher (to convert to millimoles per liter, multiply by 0.0555); current smoking, including former smokers who had quit smoking for 6 months before the index event; and hypercholesterolemia, with cholesterol serum levels 220 mg/dL or higher (to convert to millimoles per liter, multiply by 0.0259) or use of cholesterol-lowering drugs.

Assessment of Migraine History

The personal history of headache was assessed in all patients by study physicians (all but M. Grassi, L.I., and A. Padovani) during a face-to-face interview in both the acute-phase and follow-up evaluations. A history of migraine before stroke occurrence was considered for the present analysis. The diagnoses of migraine without aura and migraine with aura were made according to the diagnostic criteria of the International Headache Society.[6,7]

Clinical and Laboratory Investigations

All patients underwent an etiologic workup, including complete blood cell count; biochemical profile; urinalysis; 12-lead electrocardiogram; chest radiography; Doppler ultrasonography, with frequency spectral analysis and B-mode echotomography of the cervical arteries; transcranial Doppler ultrasonography; and CT and/or MR angiography, to investigate extracranial and intracranial vessels. Coagulation testing included prothrombin and activated partial thromboplastin times, lupus anticoagulant, circulating antiphospholipid antibodies (anticardiolipin antibodies and anti-β_2-glycoprotein I antibodies), fibrinogen, protein C, protein S, activated protein C resistance, antithrombin III, and genotyping to detect factor V Leiden and the G20210A mutation in the prothrombin gene. Transthoracic and/or transesophageal echocardiography were performed to rule out cardiac sources of emboli.

In particular, the presence of patent foramen ovale (PFO) was assessed in all patients with transesophageal echocardiography with a contrast study and Valsalva maneuver or transcranial Doppler sonography with intravenous injection of agitated saline (contrast-enhanced transcranial Doppler), according to validated protocols.[4,5]

Diagnosis of CEAD

Four-vessel conventional angiography, MRI with MR angiography (3-dimensional time of flight), and/or CT angiography of the brain and neck were included in the diagnostic workup. The presence of the double-lumen sign (a false lumen or an intimal flap), luminal narrowing with the "string sign," and gradual tapering ending in total occlusion of the lumen (flame-like occlusion) were considered reliable angiographic findings of CEAD, whereas a narrowed lumen surrounded by a semilunar-shaped intramural hematoma on axial T1-weighted images was considered the pathognomonic MRI sign.[8]

Definition of Traumatic CEAD

We considered the mechanisms of trauma associated with CEAD to be (1) any direct mechanical impact to the neck region, (2) any impact to the head with indirect involvement of the neck region, or (3) any mechanical activity causing greatly increased intrathoracic pressure (eg, heavy lifting) that had occurred within 1 month before the first symptoms of dissection. Traumatic events leading to medical examination or hospitalization were considered major, and all other events were considered minor.[9] Dissections occurring as an immediate consequence of a major trauma were excluded.

For the purpose of the present analysis, patients included in the registry were dichotomized into 2 groups: IS due to spontaneous CEAD (CEAD IS) and IS due to a cause other than CEAD (non-CEAD IS). Patients with non-CEAD IS were classified into etiologic subgroups according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria.[10]

Statistical Analysis

Differences between the 2 subgroups (CEAD IS and non-CEAD IS) were examined with the χ^2 test, an unpaired, 2-tailed *t* test, and the Mann-Whitney test, when appropriate. A categorical (multinomial) logistic regression model was planned to examine the conditional effects of hypertension, diabetes, smoking, hypercholesterolemia, and history of migraine and its subtypes (migraine without aura and migraine with aura) in the prediction of each subgroup, and was adjusted for age and sex. To evaluate whether the magnitude of migraine effect may vary according to sex and age, we conducted the same analysis separately for men and women and for 2 different strata defined by median age. We additionally investigated whether, within the subgroup of patients with CEAD (case-only analysis), the vascular risk factor profile differed between patients with migraine and patients without migraine. Finally, because of the suggested association between PFO and migraine,[11] we conducted subgroup analyses based on the individual status of carrier or noncarrier of this cardiac interatrial septal abnormality. Results are given as odds ratios (ORs) with 95% CIs. $P \leq .05$ determined with a 2-sided test was considered significant. Data were analyzed using SPSS, version 16.0 (http://www.spss.com).

Results

The present study targeted 2485 patients enrolled in the IPSYS registry. Among these, 334 patients (13.4%) had a diagnosis of CEAD IS and 2151 individuals (86.6%) had a diagnosis of non-CEAD IS. The mean (SD) age of the patients was 36.8 (7.1) years, and 1163 participants (46.8%) were women. As expected, patients with non-CEAD IS were more likely to have an unfavorable cardiovascular risk factor profile, including diabetes, hypercholesterolemia, and current smoking status. Migraine was more common in the subgroup of patients with CEAD IS (103 [30.8%] vs 525 [24.4%], $P = .01$). This was mainly due to difference in the frequency of migraine without aura (80 [24.0%] vs 335 [15.6%], $P < .001$), while the frequency of migraine with aura did not differ significantly in the 2 subgroups (21 [6.3%] vs 190 [8.8%], $P = .12$). The demographic characteristics of the study population grouped according to disease status and the prevalence of selected risk factors are presented in **Table 1**.

After adjustment for the preselected variables, migraine without aura was significantly associated with the subgroup of CEAD IS (OR, 1.74; 95% CI, 1.30-2.33), but we did not detect any significant association between migraine with aura and CEAD IS (OR, 0.80; 95% CI, 0.49-1.29). Conversely, there was a significant association with diabetes (OR, 3.84; 95% CI, 1.38-11.11), current smoking (OR, 1.38; 95% CI, 1.07-1.78), and hypercholesterolemia (OR, 1.38; 95% CI, 1.03-1.88) with non-CEAD IS. A personal history of migraine was significantly associated with the subgroup of CEAD IS only in men. Similarly, although migraine without aura was associated with dissection in both sexes and it was independent of the patients' age, the magnitude of this association was higher in men than in women (OR, 1.99; 95% CI, 1.31-3.04 vs OR, 1.53; 95% CI, 1.04-2.25) and in the subgroup of younger compared with older patients (OR, 1.82; 95% CI, 1.22-2.71 vs OR, 1.55; 95% CI, 1.04-2.31) (**Table 2**).

Finally, in the case-only analysis restricted to patients with CEAD IS, we observed an increased prevalence of women with migraine compared with men with migraine, with or without aura (62 [60.2%] vs 41 [39.8%], $P \leq .001$), but did not find significant differences in the vascular risk factor profile between patients with and without migraine (**Table 3**).

The status of PFO carrier had no apparent influence on our findings. Although the prevalence of migraine, especially with aura, was higher in patients with PFO compared with those without PFO (any migraine, 239 [30.3%] vs 389 [22.9%], $P < .001$; migraine without aura, 129 [16.3%] vs 286 [16.9%]; $P = .74$; migraine with aura, 110 [13.9%] vs 101 [6.0%], $P < .001$), the exclusion of PFO carriers from the analysis (763 non-CEAD IS and 26 CEAD IS) did not modify the association between migraine categories, especially migraine without aura, and CEAD (any migraine, 89 [28.9%] vs 300 [21.6%], $P = .006$; migraine without aura, 71 [23.1%] vs 215 [15.5%]; $P = .001$;

Table 1. Demographic and Clinical Characteristics of the Study Group

Characteristic	CEAD IS (n = 334)	Non-CEAD IS (n = 2151)	*P* Value for Univariate	OR (95% CI)	*P* Value for Adjusted
Age, mean (SD), y	37.4 (6.8)	36.7 (7.1)	.11	1.01 (1.00-1.03)	.06
Male, No. (%)	182 (54.5)	1140 (53.0)	.62	0.83 (0.65-1.06)	.14
Hypertension, No. (%)	77 (23.1)	448 (20.8)	.89	1.13 (0.84-1.52)	.41
Diabetes, No. (%)	4 (1.2)	95 (4.4)	.002	0.26 (0.09-0.72)	.01
Hypercholesterolemia, No. (%)	70 (21.0)	574 (26.7)	.03	0.72 (0.53-0.97)	.03
Smoking, No. (%)	104 (31.1)	825 (38.4)	.01	0.72 (0.56-0.93)	.01
Oral contraceptives, No. (%)[a]	51 (33.6)	402 (39.8)	.13		
Any migraine, No. (%)	103 (30.8)	525 (24.4)	.01	1.44 (1.11-1.88)	.006
Without aura	80 (24.0)	335 (15.6)	<.001	1.74 (1.30-2.33)	<.001
With aura	21 (6.3)	190 (8.8)	.12	0.80 (0.49-1.29)	.3
Migraine with aura, smoking, and oral contraceptives[a]	4 (2.6)	14 (1.4)	.28		
Dissected vessel, No. (%)	NA				
Internal carotid artery	189 (56.6)				
Vertebral artery	117 (35.0)				
Multiple vessels[b]	28 (8.4)				
Cause of stroke, No. (%)[c]	NA				
Large-vessel disease		287 (13.3)			
Nonatherosclerotic vasculopathy (other than CEAD)		70 (3.3)			
Cardiac embolism		707 (32.9)			
Small-vessel disease		300 (13.9)			
Other causes or undetermined origin		787 (36.6)			

Abbreviations: CEAD, cervical artery dissection; NA, not applicable; OR, odds ratio.

[a] In women.

[b] More than 1 vessel was involved (51.6% of the dissected vessels in this group were not related to a cerebral ischemic event).

[c] According to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria.[10]

Table 2. Risk of Spontaneous CEAD According to Migraine Status in Sex and Age Categories

Characteristic	Migraine, OR (95% CI)[a]		
	Any	Without Aura	With Aura
All	1.44 (1.11-1.88)	1.74 (1.30-2.33)	0.80 (0.49-1.29)
Sex			
Men	1.48 (1.01-2.18)	1.99 (1.31-3.04)	0.60 (0.26-1.42)
Women	1.30 (0.92-1.85)	1.53 (1.04-2.25)	0.89 (0.50-1.59)
P value for IOR	.88	.36	.46
Age, y			
≤39.0	1.54 (1.08-2.21)	1.82 (1.22-2.71)	1.04 (0.56-1.93)
>39.0	1.18 (0.82-1.70)	1.55 (1.04-2.31)	0.55 (0.26-1.15)
P value for IOR	.30	.58	.19

Abbreviations: CEAD, cervical artery dissection; IOR, interaction odds ratio; OR, odds ratio.

[a] Conditional effect of age, sex, risk factors (hypertension, diabetes, hypercholesterolemia, and smoking), and history of migraine and its subtypes (migraine without aura and migraine with aura) in the prediction of CEAD in each subgroup.

migraine with aura, 16 [5.2%] vs 85 [6.1%], $P = .53$), which provides further support for our observations.

Discussion

In this large cohort study of patients with IS aged 18 to 45 years, we found a consistent association between migraine and spontaneous CEAD. This association persisted after adjustment for traditional vascular risk factors, and it was apparent for the migraine subtype without aura more than for migraine with aura, for men more than for women, and for the younger rather than older age group. We also found no significant differences in risk factor profile between patients with CEAD IS with migraine and those without migraine, despite an expected preponderance of women among migraineurs.

Comparison With Other Studies

Most studies evaluating the association between migraine and spontaneous CEAD have been limited to small cohorts, some of which, but not all,[12,13] provided evidence of association. A pooled meta-analysis of these data suggested that a history of migraine increases the risk of spontaneous CEAD by 2-fold.[2] As stated by the authors, despite this evidence, the results of the meta-analysis leave some remaining uncertainties. In particular, there are inconsistencies regarding the potential modifying effects of migraine aura status and sex, because of the low number of migraineurs with aura in individual studies, the small proportion of studies with sex-stratified data available, and differences among the control groups, including IS controls in some studies and healthy participants in others. The results of our analysis are in line with those recently derived from the CADISP registry, the largest cohort study of patients

Table 3. Comparison of Demographics and Vascular Risk Factors in CEAD IS Patients With Migraine vs Without Migraine

Characteristic	No. (%)		*P* Value
	Migraine (n = 103)	No Migraine (n = 231)	
Age, mean (SD), y	36.9 (6.6)	37.7 (6.8)	.33
Sex			
Male	41 (39.8)	141 (61.0)	<.001
Female	62 (60.2)	90 (39.0)	
Hypertension	20 (19.4)	57 (24.7)	.29
Diabetes	1 (1.0)	3 (1.3)	>.99
Hypercholesterolemia	28 (27.2)	42 (18.2)	.06
Smoking	39 (37.9)	65 (28.1)	.08
Dissected vessel			
Internal carotid artery	64 (62.1)	125 (54.1)	.21
Vertebral artery	29 (28.2)	88 (38.1)	
Multiple vessels[a]	10 (9.7)	18 (7.8)	

Abbreviation: CEAD, cervical artery dissection.

[a] More than 1 vessel involved.

with CEAD.[3] In that study, as in ours, migraine was associated with a higher risk of CEAD than of non-CEAD IS, and this risk was especially evident for the migraine subtype without aura. At variance with that study, we observed an age-dependent association between migraine and CEAD, which was stronger in the subgroup of the youngest patients.

Potential Biological Mechanisms

The mechanisms by which migraine might increase the individual propensity to CEAD remain unproven, but there are convincing arguments for common biological pathways underlying the 2 disorders. Among these, shared genetic susceptibility and endothelial dysfunction seem to be plausible. The recent genome-wide association study of CEAD conducted by the CADISP consortium found a strong association between a genetic variant in the *PHACTR1* gene located on chromosome 6 and spontaneous CEAD.[14] The same protective allele had also been previously identified by a genome-wide association study to be associated with a reduced risk of migraine.[15] Additional suggestive genetic risk loci for CEAD, including *LRP1* and *FHL5*, have also been associated with migraine.[16] Finally, sparse reports indicate that the transforming growth factor β (TGF-β) pathway may be involved in the pathogenesis of migraine and CEAD. This hypothesis is indirectly supported by the observation of increased cerebrospinal fluid[17] or plasma[18] levels of TGF-β_1 in migraineurs and by the identification of a locus near *TGFBR2* in a large genome-wide association study,[15] which implicates a biological role in migraine. The well-known involvement of TGF-β in Marfan syndrome or in Loeys-Dietz syndrome, 2 autosomal-dominant connective tissue disorders characterized by large artery anomalies,[19,20] also provides evidence for a role of this biological pathway in the occurrence of arterial dissection. Finally, endothelial dysfunction, that is, a reduction in vasodilator activities, increase in endothelial-derived vasoconstrictors, and consequent impairment of the vascular reactivity, has been consistently documented in the 2 conditions. A genetic predisposition to the impaired endothelium-dependent vasodilatation observed in patients with CEAD and in those with migraine[21,22] cannot be excluded, suggesting that there could be a common generalized vascular disorder related to both entities. Conversely, in line with the results from the CADISP consortium, the possibility that people with migraine have an increased propensity to develop CEAD because of a nonfavorable vascular risk factor profile seems unlikely, based on our findings.

Strengths and Limitations

Our study has several strengths, including the prospective design, large number of participants, standardized evaluation of vascular disease risk factors, confirmation of migraine diagnosis by neurologists in all centers, and homogeneous demographic characteristics and clinical phenotype of the cohort, which may reduce confounding. Moreover, the fact that all of the patients enrolled in the IPSYS registry underwent a standard workup for early-onset stroke, including MR angiography investigation, reduces the possibility that some CEAD cases remained unrecognized in our series. This possibility is expected to be more likely in studies including patients with CEAD with no ischemic symptoms.[23] Several limitations also should be considered when interpreting our findings. First, because the IPSYS is a hospital-based study, the results might be susceptible to hospital referral selection bias. However, inaccurate capture of the incident cases is highly unlikely, because young patients with stroke are usually referred to academic centers during the course of the disease. Second, because we did not assess migraine frequency and severity or the frequency of auras, we cannot evaluate whether the observed association differs according to specific migraine patterns. Similarly, no information on the use of migraine-specific medications was available. However, whether migraine frequency is a measure of migraine severity remains to be demonstrated, and there is no evidence of a direct effect of migraine-specific drugs on vessel wall integrity. Third, at least theoretically, we cannot exclude the possibility that differences in group sizes might have introduced bias into the analysis of data. Fourth, since participants in this study were aged 18 to 45 years and white, with a documented acute cerebral infarct, generalizability to other populations might be lim-

ited. Finally, residual confounding cannot be definitively ruled out, as our data are observational.

Implications of Findings

The results of our study support the findings of other case-control studies[2] linking migraine with an increased risk of CEAD. At variance with most epidemiologic studies that found an association between the migraine subtype with aura and an increased risk of IS at a young age, our findings, as well as those of others, point toward the apparently paradoxical conclusion that, at least for CEAD, the most frequent cause of early-onset brain ischemia, this risk is mainly driven by the migraine subtype without aura. However, for complex diseases, such as migraine, identification of the phenotype is challenging due to the lack of objective markers and uncertainty about the cause of the disease. Furthermore, as the recent large genetic studies on migraine have suggested, the phenotypes commonly used (migraine without aura and migraine with aura) are probably not the most adequate to capture the heterogeneity of the many disease subtypes.[24]

Conclusions

Our data support consideration of a history of migraine as a marker for increased risk of IS caused by CEAD, as well as a putative susceptibility factor for CEAD, regardless of its clinical features. This finding emphasizes the need for further analyses to investigate the nature and mechanisms of elevated risk in migraineurs and to elucidate whether this risk applies to only specific subsets of patients with migraine.

ARTICLE INFORMATION

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Study concept and design: De Giuli, Pezzini.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: De Giuli, Pezzini.
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Group Information: The Italian Project on Stroke in Young Adults (IPSYS) Investigators are listed in the eAppendix in the Supplement.

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