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ORIGINAL ARTICLE

Migraine improvement after spontaneous cervical artery dissection the Italian Project on Stroke in Young Adults (IPSYS)

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Abstract

Objective Whether migraine modifies after spontaneous cervical artery dissection (sCeAD) more than after other stroke etiologic subtypes has never been adequately investigated.

Methods In the setting of the Italian Project on Stroke in Young Adults (IPSYS), we compared the course of migraine before and after acute brain infarct in a group of migraine patients with sCeAD and a group of migraine patients whose ischemia was due to a cause other than CeAD (non-CeAD IS), matched by sex, age (± 3 years), and migraine subtype.We applied linear mixed models to evaluate pre-event vs post-event changes and differences between sCeAD and non-CeAD IS patients.

Results Eighty-seven patients per group (migraine without aura/migraine with aura, 67/20) qualified for the analysis. After the acute event, migraine headaches disappeared in 14.0% of CeAD patients vs 0.0% of non-CeAD IS patients ($p \leq 0.001$). Migraine frequency (patients suffering at least 1 attack, from 93.1 to 80.5%, $p = 0.001$), pain intensity (from 6.7 ± 1.7 to 4.6 ± 2.6 in a 0 to 10 pain scale, $p \leq 0.001$), and use of acute anti-migraine medications (patients taking at least 1 preparation, from 81.6 to 64.4%, $p = 0.007$) also improved significantly after CeAD as opposed to that observed after non-CeAD IS.

Conclusion The spontaneous improvement of migraine after sCeAD reinforces the hypothesis of a pathogenic link between the two conditions.

Keywords Cervical artery dissection · Stroke in young adults · Migraine

Introduction

A personal history of migraine can be found in nearly half the patients suffering spontaneous dissection of the cervical arteries (sCeAD) [1] and, notably, the two conditions appear strongly associated, according to the results of recent case-control studies conducted on large cohorts of patients with ischemic stroke (IS) at young age [2, 3]. This suggests a potential pathophysiological link, at least in a proportion of migraineurs. In this regard, the sparse observations that the natural course of migraine tends to improve after spontaneous dissection of the neck vessels [4, 5] might represent a further argument in favor of the hypothesis of a relation between the two conditions and support the idea that arterial-endothelial factors may play a role. We, therefore, aimed at addressing the issue of the biologic link between migraine and sCeAD in a case-control study in which we evaluated the course of migraine before and after acute brain infarct in the setting of the Italian Project on Stroke in Young Adults (IPSYS).

Methods

Study design and patient selection

The Italian Project on Stroke in Young Adults (IPSYS) is a countrywide network of neurological centers with special

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interest in cerebral ischemia at young age across Italy, aimed at recruiting white patients aged 18 to 45 years, with first-ever acute IS in the setting of a hospital-based, multicenter, observational study, as previously described [6, 7]. For the purpose of the present study, we included a group of patients whose IS was due to sCeAD and were migraine sufferers and, as control subjects, a group of patients whose IS was due to a non-cardioembolic cause other than CeAD (non-CeAD IS), matched to sCeAD patients (1:1) by sex, age (± 3 years), and migraine subtype (migraine without aura or migraine with aura). The recruitment period was January 1, 2000, through June 30, 2015.

Risk factor definition

Hypertension was defined as systolic blood pressure ≥ 140 mmHg and diastolic pressure ≥ 90 mmHg in two separate measurements after the acute phase or use of antihypertensive drugs before recruitment. Diabetes mellitus as history of diabetes mellitus, use of hypoglycemic agent or insulin, or fasting glucose ≥ 7.0 mmol/L. Smoking history was defined as "current smoking," including former smokers who had quit smoking for 6 months before the index event, vs "ever smoking" or "never smoking." Hypercholesterolemia as cholesterol serum levels ≥ 5.7 mmol/L or use of cholesterol-lowering drugs. Current use of oral contraceptives included current user as well as former users who had quit taking these medications for 1 month before the index event [6, 7].

Assessment of migraine characteristics

Personal history of headache was assessed in all patients by study physicians during a face-to-face interview in both acute phase and follow-up evaluations, according to the diagnostic criteria of the International Headache Society [8, 9]. On the occasion of the baseline (acute vascular event) as well as follow up visits, patients were asked to rate the severity of their migraine in the last 6 months by indicating (1) the frequency, (2) the intensity of the attacks, and (3) the number and type of acute and preventive medications. Scales were used to evaluate the frequency (no attacks; < 1 per month; 1 to 3 per month; 1 to 3 per week; > 3 per week) and the intensity (from 0, no pain, to 10, intolerable pain) of headache episodes. For each item, values were averaged across the last 6 months. A total final value was obtained for each item as the average of values obtained at each follow up visit. This value was compared with the one obtained at the enrollment. The difference between baseline and final values was defined as outcome. We defined migraine improvement as at least one among (1) any decrease of migraine frequency, (2) improvement of pain intensity (at least 3 points), and (3) discontinuation of acute or prophylactic anti-migraine agents. All patients were allowed to take the preferred anti-migraine medications whenever necessary, throughout the study period.

Statistical analysis

Continuous variables are expressed as mean ± SD and were compared by a two-sided, paired *t* test. Categorical variables are reported as counts and percentages. We applied linear mixed models to evaluate pre-event vs post-event changes (*time*), differences between CeAD and non-CeAD IS, and differences between migraine subtypes (migraine without aura vs migraine with aura). To take into account for intra-subject variability (each subject was measured before and after the acute vascular event), we added random effect (1|*id*) to the models. Frequency of migraine attacks (both ordinal and binary variables), pain intensity (both continuous and binary variables), and acute and prophylactic anti-migraine treatments was considered as outcomes (y). Because of the low frequency of patients taking prophylactic medications, a clog-log logistic regression was applied to estimate the *time*, groups, and migraine effects. For each outcome measure, we fitted two models, one model with only *time*, patient group (case or control), and migraine subtype as fixed effects and *id* as random effect, and one model adjusted for sex, migraine characteristics [age at onset; duration (years)], and major cardiovascular risk factors. Finally, we planned a binomial logistic regression model to examine the conditional effect of attack frequency, pain intensity, and use of acute and prophylactic anti-migraine medications in the prediction of migraine improvement, within the subgroup of patients with CeAD (case-only analysis), and adjusted for age and sex. Results are given as odds ratio (OR) with 95% confidence intervals (CIs). $p \leq 0.05$ on two-sided test was considered significant. Data were analyzed using the SPSS (version 21.0) package (www.spss.com).

Results

Study group

Among the 334 patients with CeAD included in the IPSYS database, 103 (30.8%) were migraine sufferers[3]. Three recruiting centers did not participate to the present longitudinal study, leading to the exclusion of 16 (15.5%) patients. The study group, therefore, comprised 87 patients (36 [41.4%] males; mean age, 36.8 ± 7.0 years; migraine without aura/migraine with aura, 67/20) fulfilling the inclusion criteria, who were followed-up for a total of 2516 person-months (median follow-up time, 36.0 months [25th to 75th percentile,

Table 1 Demographic characteristics and evolution of migraine headaches after ischemic stroke in the group of patients with spontaneous cervical artery dissection (sCeAD) and the group of patients whose brain ischemia was due to a non-cardioembolic cause other than CeAD (non-CeAD IS)

	CeAD						Non-CeAD IS					
	Any migraine ($n = 87$)		MO ($n = 67$)		MA ($n = 20$)		Any migraine ($n = 87$)		MO ($n = 67$)		MA ($n = 20$)	
Age, years ± SD	36.8 ± 7.0		37.1 ± 6.9		36.1 ± 7.4		36.0 ± 6.9		36.2 ± 7.0		35.4 ± 6.5	
Sex, male	36 (41.4)		30 (44.8)		6 (30.0)		36 (41.4)		30 (44.8)		6 (30.0)	
Hypertension	17 (19.5)		16 (23.9)		1 (5.0)		13 (14.9)		11 (16.4)		2 (10.0)	
Diabetes	1 (1.1)		1 (1.5)		0 (0.0)		5 (5.7)		3 (4.5)		2 (10.0)	
Hypercholesterolemia	23 (26.4)		14 (20.9)		9 (45.0)		19 (21.8)		15 (22.4)		4 (20.0)	
Smoking	31 (36.0)		24 (36.4)		7 (35.0)		30 (34.5)		27 (40.3)		3 (15.0)	
Oral contraceptives	21 (41.2)		14 (37.8)		7 (50.0)		15 (29.4)		10 (27.0)		5 (35.7)	
Migraine characteristics												
Duration of symptoms (years)	17.9 ± 8.7		17.7 ± 8.6		18.7 ± 9.3		13.3 ± 6.9		14.0 ± 7.1		11.0 ± 6.0	
Frequency of migraine attacks	Baseline	Post-event	Baseline	Post-event	Baseline	Post-event	Baseline	Post-event	Baseline	Post-event	Baseline	Post-event
None	6 (6.9)	17 (19.5)	6 (9.0)	16 (23.9)	0 (0.0)	1 (5.0)	5 (5.7)	12 (13.8)	4 (6.0)	10 (14.9)	1 (5.0)	2 (10.0)
< 1 per 4 week	27 (31.0)	45 (51.7)	18 (26.9)	33 (49.3)	9 (45.0)	12 (60.0)	27 (31.0)	35 (40.2)	21 (31.3)	27 (40.3)	6 (30.0)	8 (40.0)
1–3 per 4 week	39 (44.8)	22 (25.3)	29 (43.3)	15 (22.4)	10 (50.0)	7 (35.0)	33 (37.9)	29 (33.3)	27 (40.3)	22 (32.8)	6 (30.0)	7 (35.0)
4–12 per week	11 (12.6)	2 (2.3)	11 (16.4)	2 (3.0)	0 (0.0)	0 (0.0)	14 (16.1)	8 (9.2)	9 (13.4)	5 (7.5)	5 (25.0)	3 (15.0)
> 12 per 4 week	4 (4.6)	1 (1.1)	3 (4.5)	1 (1.5)	1 (5.0)	0 (0.0)	8 (9.2)	3 (3.4)	6 (9.0)	3 (4.5)	2 (10.0)	0 (0.0)
Pain intensity (0 to 10)	6.7 ± 1.7	4.6 ± 2.6	6.8 ± 1.5	4.5 ± 2.7	6.3 ± 2.3	5.0 ± 2.2	7.5 ± 1.8	6.9 ± 1.7	7.4 ± 1.8	6.8 ± 1.7	7.6 ± 1.9	7.4 ± 1.7
Anti-migraine medications												
Acute drugs	71 (81.6)	56 (64.4)	58 (86.6)	41 (61.2)	13 (65.0)	15 (75.0)	77 (88.5)	68 (78.2)	59 (88.1)	51 (76.1)	18 (90.0)	17 (85.0)
Prophylactic drugs	7 (8.9)	7 (8.9)	7 (10.4)	4 (6.0)	0 (0.0)	3 (15.0)	9 (10.3)	8 (9.1)	7 (10.4)	6 (9.0)	2 (10.0)	2 (10.0)

SD standard deviation, *MO* migraine without aura, *MA* migraine with aura

Table 2 Baseline and post-stroke use of anti-migraine and anti-thrombotic medications in the group of patients with spontaneous cervical artery dissection (sCeAD) and the group of patients whose brain ischemia was due to a non-cardioembolic cause other than CeAD (non-CeAD IS)

	CeAD		non-CeAD IS	
Anti-migraine medications				
Acute therapy	*Baseline*	*Post-event*	*Baseline*	*Post-event*
NSAIDs	53 (60.9)	33 (37.9)	56 (64.4)	54 (62.0)
Triptans	16 (18.4)	15 (17.2)	20 (23.0)	12 (13.9)
Other drugs	2 (2.3)	8 (9.2)	1 (1.1)	2 (2.3)
No drugs	16 (18.4)	31 (35.6)	10 (11.5)	19 (21.8)
Preventive therapy				
Beta-blockers	3 (3.4)	1 (1.1)	2 (2.3)	2 (2.3)
Calcium-channel blockers	0 (0.0)	0 (0.0)	5 (5.7)	5 (5.7)
Tricyclic antidepressant	4 (4.6)	6 (6.9)	2 (2.3)	1 (1.1)
No drugs	80 (92.0)	80 (92.0)	78 (89.7)	79 (90.9)
Anti-thrombotic medications				
Anti-platelet agents	44 (50.6)	62 (71.3)	87 (100.0)	87 (100.0)
Oral anti-coagulants	43 (49.4)	0 (0.0)	0 (0.0)	0 (0.0)
None	0 (0.0)	25 (28.7)	0 (0.0)	0 (0.0)

NSAIDs non-steroidal anti-inflammatory drugs

61.5]; Tables 1 and 2). Non-included cases were not significantly different from those who entered into the final analysis with regard to baseline characteristics (not shown). After the acute vascular event, migraine headaches disappeared in 13 (14.9%) CeAD patients vs 0 (0.0%) in the non-CeAD IS group ($p \leq 0.001$) and improved in 53 (60.9%) CeAD patients vs 38 (43.7%) in the non-CeAD IS group ($p = 0.023$). Headaches remained unchanged in 16 CeAD patients (18.4%), while 4 patients (4.6%) experienced transient and 1 patient (1.2%) persistent worsening of their headaches. The number of patients suffering at least 1 attack across the last 6 months switched from 93.1% before CeAD to 80.5% after CeAD ($p = 0.001$). Pain intensity (from 6.7 ± 1.7 to 4.6 ± 2.6, $p \leq 0.001$), and the use of acute anti-migraine medications (number of patients taking at least 1 preparation, from 81.6 to 64.4%, $p = 0.007$) also improved after CeAD, despite no change in the number of patients taking prophylactic anti-migraine agents.

Outcome

The unadjusted linear mixed model displayed a significant reduction in the frequency of migraine attacks (~ 72%), in the prevalence of patients taking acute anti-migraine medications (~ 72%), as well as of pain intensity after stroke occurrence, compared to pre-event values. These effects were all significant for patients with sCeAD as compared to those with non-CeAD IS, while we were unable to detect any significant influence of migraine subtype (migraine without aura vs migraine with aura). None of the pre-specified variables had any effect on the assumption of anti-migraine prophylactic therapy (Table 3). Similar results were obtained in the linear mixed model adjusted for the selected covariates (Table 4). Finally, in the subgroup of patients with CeAD, advanced age (age > 39; OR, 3.31; 95% CI, 1.16 to 9.41; $p = 0.025$), high frequency of migraine attacks (> 1 attacks/month; OR, 3.50; 95% CI, 1.19 to 10.28; $p = 0.022$), and high pain intensity (pain scale > 5;

Table 3 Outcomes of migraine characteristics in the linear mixed model including *time*, patient group (CeAD vs non-CeAD IS), and migraine subtype (migraine without aura vs migraine with aura)

	Time	CeAD vs non-CeAD IS	MO vs MA
Frequency of migraine attacks	0.28 (0.18–0.43)	0.58 (0.35–0.97)	1.25 (0.69–2.28)
At least 1 attack	0.26 (0.14–0.45)	0.61 (0.34–1.10)	1.09 (0.55–2.15)
Pain intensity	0. 00 (1.69^{-08}–1.93^{-05})	0.00 (6.89^{-10}–3.43^{-06})	0.86 (0.05–14.57)
Anti-migraine medications			
Acute drugs	0.28 (0.10–0.72)	0.49 (0.16–1.49)	0.88 (0.30–2.54)
Prophylactic drugs	0.99 (0.13–7.35)	0.51 (0.04–6.94)	0.97 (0.06–17.11)

Numbers are odds ratios with 95% confidence intervals

MO migraine without aura, *MA* migraine with aura, *time* before vs after stroke occurrence

Table 4 Outcomes of migraine characteristics in the adjusted linear mixed model including *time*, patient group (CeAD vs non-CeAD IS), and migraine subtype (migraine without aura vs migraine with aura)

	Time	CeAD vs non-CeAD IS	MO vs MA
Frequency of migraine attacks	0.28 (0.18–0.44)	0.56 (0.33–0.97)	1.24 (0.67–2.27)
At least 1 attack	0.27 (0.15–0.47)	0.64 (0.35–1.19)	1.06 (0.53–2.13)
Pain intensity	0.12 (0.04–0.36)	0.04 (0.00–0.31)	0.97 (0.20–4.66)
Anti-migraine medications			
Acute drugs	0.29 (0.11–0.72)	0.66 (0.22–1.94)	1.08 (0.39–2.96)
Prophylactic drugs	0.18 (0.03–1.08)	4.01 (0.39–41.83)	0.11 (0.00–3.64)

Covariates were: sex, migraine characteristics [age at onset; duration (years)], and major cardiovascular risk factors. Numbers are odds ratios with 95% confidence intervals

MO migraine without aura, *MA* migraine with aura

OR, 4.00; 95% CI, 1.24 to 12.87; $p = 0.020$) before stroke occurrence turned out to be independent predictors of post-stroke migraine improvement.

Discussion

In this large, multicentric, prospective registry of young ischemic stroke patients, we observed a marked improvement of migraine after sCeAD. In particular, migraine was abolished in ~15% of these patients and improved in more than 60%. Even more impressive, the magnitude of such an effect was significantly more prominent than in other pathogenic stroke subgroups.

The biologic interpretation of our findings remains speculative at present. Obviously, we cannot theoretically exclude the interference of a number of factors in altering the migraine course in our patients, among which the spontaneous variability of migraine as well as the effect of stroke itself and of medical treatment could have played a role [10]. This notwithstanding, there are also arguments against these interpretations, which indirectly strengthen the hypothesis of a pathophysiological link between migraine and sCeAD. First, although the natural waning of migraine with aging is a well-known phenomenon, it cannot fully explain the sudden disappearance or relief of headache attacks we observed soon after stroke. Second, the effect of anti-platelet agents, including acetylsalicic acid, on migraine has never been firmly established. Furthermore, we observed migraine improvement even in those sCeAD cases who, unlike non-CeAD IS patients, received short-term warfarin therapy and then did not undergo any long-term anti-thrombotic treatment. Third, changes in psychological status and lifestyle after stroke could have influenced the natural course of migraine. Even accepting this interpretation, it would be, however, difficult to explain why all these factors should consistently improve, and often abolish, migraine, more frequently in patients with sCeAD than in patients with other stroke etiologies without assuming that the two diseases might have some biologic mechanisms in common. Finally, as a further support to our results, the observation of migraine improvement after CeAD has previously been reported in small series. Artto and coworkers detected alleviation of migraine activity after sCeAD in 50% of the 36 patients who suffered an ischemic stroke [4], while Censori and coworkers observed total disappearance of migraine as well as migraine relief more frequently in a group of 11 CeAD patients than in the group of patients with other stroke etiologies [5].

There are some methodological limitations of our analysis worthy of consideration. The case-control design inevitably exposes to the risks of selection and recall bias. However, the recruitment was prospective and consecutive, and demographic variables and migraine subtypes were equally balanced in the two subgroups. Therefore, it seems most unlikely that the results are explained by different natural history. Though the present series represents the largest study group on which to test the hypothesis under investigation, the number of subjects included is still relatively small, which makes the results of the analysis somewhat unstable. Our decision to define the improvement of migraine when at least one of the three selected items showed an improvement is questionable, since individual items can change in opposite directions. Finally, because of the characteristics of the IPSYS protocol, we did not have the opportunity to explore whether the effect of the underlying vascular disease on migraine history might change over time during follow up. The potential implications of these theoretical shortcomings are noteworthy. Notwithstanding, our results provide evidence that sCeAD might modify, at least in the midterm, the spontaneous course of migraine and prompt to the speculation that the improvement might be related to specific, hitherto unknown, arterial factors. This reinforces the hypothesis of possible common biologic mechanisms underlying migraine and sCeAD and supports the basis for further studies aimed at investigating this relation.

Authors' contributions Valeria De Giuli: manuscript drafting/revising, study design, data analysis and interpretation, and data acquisition. All authors: manuscript drafting/revising and data acquisition. Francesca Graziano, Mario Grassi, and Alessandro Pezzini: statistical analysis.

Alessandro Pezzini: manuscript drafting/revising, study design, data analysis and interpretation, data acquisition, statistical analysis, and study supervision.

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Compliance with ethical standards

All aspects of the study were approved by the Ethics Committee of the coordinating Center (University of Brescia) and then of each study site. Written informed consent was obtained from all patients (or next of kin).

Role of the sponsor The sponsor had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; the preparation, review or approval of the manuscript; or the decision to submit the manuscript for publication.

Alessandro Pezzini had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Appendix

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