Migraine in cervical artery dissection and ischemic stroke patients

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ABSTRACT

Objective: Several small to medium-sized studies indicated a link between cervical artery dissection (CeAD) and migraine. Migrainous CeAD patients were suggested to have different clinical characteristics compared to nonmigraine CeAD patients. We tested these hypotheses in the large Cervical Artery Dissection and Ischemic Stroke Patients (CADISP) population.

Methods: A total of 968 CeAD patients and 653 patients with an ischemic stroke of a cause other than CeAD (non-CeAD IS) were recruited. CeAD patients with stroke ($CeAD_{stroke}$, n = 635) were compared with non-CeAD IS patients regarding migraine, clinical characteristics, and outcome. CeAD patients with and without migraine were compared in terms of clinical characteristics and outcome.

Results: Migraine was more common among $CeAD_{stroke}$ patients compared to non-CeAD IS patients (35.7 vs 27.4%, $p = 0.003$). The difference was mainly due to migraine without aura (20.2 vs 11.2%, $p < 0.001$). There were no differences in prevalence of strokes, arterial distribution, or other clinical or prognostic features between migrainous and nonmigrainous CeAD patients.

Conclusion: Migraine without aura is more common among $CeAD_{stroke}$ patients compared to non-CeAD IS patients. The mechanisms and possible causative link remain to be proved. Although CeAD is often complicated by stroke, our data do not support increased risk of stroke in migrainous CeAD patients. *Neurology*® 2012;78:1221–1228

GLOSSARY

CADISP = Cervical Artery Dissection and Ischemic Stroke Patients study; **CeAD** = cervical artery dissection; **CI** = confidence interval; **ICAD** = internal carotid artery dissection; **IHS** = International Headache Society; **IS** = ischemic stroke; **MA** = migraine with aura; **MO** = migraine without aura; **mRS** = modified Rankin Scale; **OR** = odds ratio; **NIHSS** = NIH Stroke Scale; **PFO** = patent foramen ovale; **TIA** = transient ischemic attack; **VAD** = vertebral artery dissection.

Cervical artery dissection (CeAD) is the most common single etiology of stroke in young adults.[1] The pathophysiology and risk factors for CeAD are unclear. Several factors, including migraine, have been suggested to be associated with CeAD.[2,3] It has also been proposed[4] that CeAD could be one of the links explaining the widely accepted association between migraine and stroke[5] in young adults. However, few case-control studies on relatively small samples are available in the literature, comparing the frequency of migraine in CeAD patients vs healthy controls or CeAD patients vs patients with ischemic stroke of a cause other than CeAD (non-CeAD IS). In the previous studies,[2,4,6] there was an association between CeAD and migraine, but the results on migraine aura status (migraine with aura [MA] or migraine without aura [MO]) and CeAD have been controversial. It also remains to be verified whether CeAD patients with migraine have different clinical characteristics compared to nonmigraine CeAD patients related to presenting symptoms[7] and the frequency of stroke.[8]

Supplemental data at www.neurology.org

Supplemental Data

CME

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Using a case-control design, we 1) assessed whether the frequency of migraine and its subtypes (presence or absence of an aura) differs between CeAD patients with stroke and non-CeAD IS patients, matched on age and gender; and 2) compared CeAD patients with and without migraine in terms of clinical presentation, putative risk factors, and outcome in the large multicenter Cervical Artery Dissection and Ischemic Stroke Patients (CADISP) study.[9]

METHODS

Study population. CADISP is an international observational study focusing on research on CeAD. The structure and methods of the CADISP study have been described in detail previously.[9] The aims of CADISP are to perform a genetic association study and clinical studies on various debated topics including risk factors, clinical presentation, and outcome predictors of CeAD. Between 2004 and 2009, as part of a multicenter effort comprising 20 centers in 9 countries, we have included consecutive patients evaluated in departments of neurology with a diagnosis of CeAD. A cohort of non-CeAD IS patients, frequency-matched on age (by 5-year intervals) and gender, was recruited as controls in the same centers. The inclusion and exclusion criteria are shown in table 1. For the clinical part of the CADISP study, altogether 983 CeAD patients and 658 patients with a non-CeAD IS were recruited in 18 centers in 8 countries. For a description of CADISP centers and a flow diagram of the participant selection process see figures e-1 and e-2 on the *Neurology*® Web site at www.neurology.org. Non-CeAD IS patients were classified into IS subgroups according to the TOAST criteria.[10,11]

Patients were recruited both retrospectively (n = 884) and prospectively (n = 737). Retrospective patients are participants who had a qualifying event before the beginning of the study or were interviewed after discharge, and were identified through local registries of CeAD or IS patients in each center. Over 96% of patients had a qualifying event between 1999 and 2009 (<4% had a qualifying event before 1999), and the interviews were performed between 2004 and 2009. The detailed questionnaire included items related to symptoms of dissection and stroke; NIH Stroke Scale (NIHSS) score at admission; imaging findings of dissection and stroke; medical history such as vascular risk factors, migraine, and traumas; and follow-up data at 3 months including modified Rankin Scale (mRS) score and major complications.

Standard protocol approvals, registrations, and patient consents. The study protocol was approved by relevant local authorities in all participating centers and was conducted according to the national rules concerning ethics committee approval and informed consents.

Variable definitions. Risk factors for CeAD were defined as follows. Hypertension: a history of antihypertensive treatment or blood pressure ≥140/90 mm Hg during nonacute phase. Hypercholesterolemia: lipid-lowering treatment or total cholesterol ≥6.20 mmol/L or low-density lipoprotein cholesterol ≥4.1 mmol/L, measured within 48 hours after admission to the hospital or diagnosed by the treating physician. Diabetes: fasting glucose >7 mmol/L during nonacute phase or use of an antidiabetic therapy. Hormonal therapy: use of oral contraceptives or postmenopausal substitution therapy at time of event. Smoking: Smokers were divided into current (smoking within a month) and past smokers. Lifetime history of migraine was classified according the International Headache Society (IHS) criteria.[12] Information on migraine was available for 968 (98.5%) CeAD patients and 653 (99.2%) non-CeAD IS patients of the CADISP population, included in the current study. Migraine type (migraine with aura [MA]/migraine without aura [MO]) was not defined for 22 patients.

Infection: An infection in the week preceding the dissection was defined by the presence of at least 1 typical symptom of infection, in combination with fever (temperature ≥38°C) or the presence of at least 1 typical symptom of infection with corresponding serologic, cultural, or radiologic findings indicating

Table 1 CADISP inclusion and exclusion criteria

Criteria	CeAD patients	Non-CeAD IS patients
Inclusion criteria	Typical radiologic aspect of dissection[a] in a cervical artery (carotid, vertebral); performed imaging modalities: cervical ultrasound 68.9%; MRA 80.2%; CTA 18.5%; DSA 16.8%	Recent ischemic stroke
		No signs of CeAD on ultrasound and angiography (MR or CT or DSA), performed <7 days after the stroke
Exclusion criteria	Purely intracranial dissection	Possible IS with normal cerebral imaging
	Iatrogenic dissection after endovascular procedure	CeAD cannot be ruled out (e.g., persistent arterial occlusion without mural hematoma)
	Monogenic disorder known to cause CeAD (e.g., vascular Ehlers-Danlos syndrome)	Endovascular or surgical procedure on coronary, cervical, or cerebral arteries <48 h
	Age <18 y at inclusion	Cardiopathies with very high embolic risk[b]
		Arterial vasospasm after subarachnoid hemorrhage
		Autoimmune disease possibly explaining IS
		Monogenic disease explaining IS[c]
		Age <18 y at inclusion

Abbreviations: CADISP = Cervical Artery Dissection and Ischemic Stroke Patients study; CeAD = cervical artery dissection; CTA = CT angiography; DSA = digital subtraction angiography; IS = ischemic stroke; MR = magnetic resonance; MRA = magnetic resonance angiography.
[a] Mural hematoma, pseudoaneurysm, long tapering stenosis, intimal flap, double lumen, or occlusion >2 cm above the carotid bifurcation revealing a pseudoaneurysm or a long tapering stenosis after recanalization.
[b] Mechanical prosthetic valves, mitral stenosis with atrial fibrillation, intracardiac tumor, infectious endocarditis, myocardial infarction <4 months.
[c] e.g., Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; Fabry disease; mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes; homocystinuria; sickle cell disease.

Table 2 Characteristics of the study population[a]

	$CeAD_{stroke}$ (n = 635)	Non-CeAD IS (n = 653)	p Univariate	OR (95% CI)[b]	p Adjusted[b]
Age, y	43.9 ± 10.0	44.5 ± 10.5	0.312	1.01 (1.00–1.02)	0.201
Men	361 (56.9)	398 (60.9)	0.135	0.98 (0.76–1.26)	0.876
Hypertension	154/630 (24.4)	240/653 (36.8)	<0.001[c]	0.48 (0.67–0.63)[c]	<0.001[c]
Hypercholesterolemia	114/623 (18.3)	184/649 (28.4)	<0.001[c]	0.47 (0.35–0.62)[c]	<0.001[c]
Diabetes mellitus	13/632 (2.1)	55/653 (8.4)	<0.001[c]	0.23 (0.12–0.44)[c]	<0.001[c]
Hormonal therapy in women	108/274 (39.4)	97/255 (38.0)	0.745	1.19 (0.80–1.77)	0.389
BMI, kg/m^2	24.5 ± 3.8	25.8 ± 4.6	<0.001[c]	0.93 (0.90–0.96)[c]	<0.001[c]
Current smokers	183/629 (29.1)	305/651 (46.9)	<0.001[c]	0.52 (0.41–0.67)[c]	<0.001[c]
NIHSS on admission	5.95 ± 6.68	4.85 ± 5.49	0.179	1.03 (1.01–1.05)[c]	0.003[c]
mRS 0–2 at 3 months	498/605 (82.3)	510/592 (86.1)	0.069	0.82 (0.53–1.28)	0.393
mRS 0–1 at 3 months	379/601 (63.1)	374/591 (63.2)	0.937	1.15 (0.84–1.28)	0.377

Abbreviations: BMI = body mass index; $CeAD_{stroke}$ = cervical artery dissection presenting with stroke; CI = confidence interval; IS = ischemic stroke; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; non-CeAD IS = ischemic stroke without CeAD; OR = odds ratio.
[a] Values are n (%) or mean ± SD. The data are not available for all the patients.
[b] Regression analysis separately for each variable with group as dependent variable and age, gender, country of inclusion, and prospective/retrospective inclusion as covariates, and additionally NIHSS for outcome variables.
[c] Significant.

an acute infection or the combination of at least 2 typical corresponding symptoms.[13] A recent trauma was defined as physical impact on the head or neck (e.g., extreme neck movements, cervical manipulation, lifting up heavy loads) <1 month prior to the CeAD. If the trauma prompted a visit to a physician or hospitalization, the trauma was considered major. All other forms of traumas were considered mild.

Clinical and radiologic characteristics of CeAD patients. The following radiologic features at admission were recorded: arterial occlusion, stenosis, aneurysmal dilatation, and multiple dissections. Cervical pain and headache at the acute phase of CeAD and the occurrence of tinnitus and Horner syndrome were recorded.

Three-month outcome. Functional 3-month outcome was defined as favorable if mRS = 0–2 and excellent if mRS = 0–1. Major complications within 3 months included the following: stroke or TIA after admission, recurrent cervical artery dissection, intracranial hemorrhage, or major extracranial hemorrhage (i.e., leading to death, or requiring blood transfusion, surgery, or hospitalization). Putative risk factors and 3-month outcome were defined identically in CeAD and non-CeAD IS patients.

Statistical analyses. For comparisons between CeAD and non-CeAD IS patients, only CeAD patients presenting with stroke were included ($CeAD_{stroke}$, n = 635) so that the groups would differ in one aspect only (i.e., etiology of stroke). All 968 CeAD patients were included in the comparisons between CeAD patients with or without migraine. The groups ($CeAD_{stroke}$ vs non-CeAD IS and CeAD patients with vs without migraine) were compared by using χ^2, Mann-Whitney *U*, and *t* tests when appropriate. Thereafter, the comparisons were made by using logistic regression, adjusted for the following possible confounding factors: age, gender, country of inclusion, and prospective/retrospective recruitment. We additionally tested the results separately for prospective and retrospective patients, and this did not change the results (data not shown). Since CeAD and non-CeAD groups differ in terms of vascular risk factors, they were added as covariates to the comparisons regarding migraine and its subtypes. Since the frequency of migraine in women is higher than in men,[14] we performed additional analyses separately for both genders. Because of epidemiologic association of patent foramen ovale (PFO) and migraine,[15] a subgroup analysis of patients without PFO was run. The analyses were performed using PASW 18.0 for Windows. A 2-tailed value of $p < 0.05$ was considered statistically significant.

RESULTS

CeAD vs non-CeAD IS. Demographic features and history of vascular risk factors in $CeAD_{stroke}$ and non-CeAD IS patients are shown in table 2. The majority of the 635 $CeAD_{stroke}$ patients (56.9%) were men. According to the TOAST classification, the cause of infarction in the non-CeAD IS group was large artery atherosclerosis in 86 (13.1%), cardioembolism in 239 (36.6%), small vessel disease in 44 (6.7%), other determined etiology in 19 (2.9%), and undetermined etiology in 265 (40.6%), of which 34 (5.2% of all IS patients) had multiple possible causes for stroke. All traditional vascular risk factors were less frequent in $CeAD_{stroke}$ patients compared to non-CeAD IS patients (table 2).

Migraine characteristics of $CeAD_{stroke}$ vs non-CeAD IS groups. Migraine was more common in $CeAD_{stroke}$ patients (35.7 vs 27.4%, $p = 0.003$). In terms of migraine subtypes, there was a higher frequency of MO in $CeAD_{stroke}$ compared to non-CeAD IS patients (20.2 vs 11.2%, $p < 0.001$), but the frequencies of MA were not different (13.1 vs 15.8%, $p = 0.322$) (table 3). Migraine and migraine without aura were more common among $CeAD_{stroke}$ patients in both men and women, but after adjusting for

Table 3 Prevalence of migraine in patients with $CeAD_{stroke}$ and non-CeAD ischemic stroke

	$CeAD_{stroke}$ (n = 635), n (%)	Non-CeAD IS (n = 653), n (%)	*p* Univariate	OR (95% CI)[a]	*p* Adjusted[a]
All					
Migraine	227 (35.7)	179 (27.4)	0.001[c]	1.51 (1.15–1.99)[c]	0.003[c]
MO	128 (20.2)	73 (11.2)	<0.001[c]	2.09 (1.46–2.99)[c]	<0.001[c]
MA[b]	83 (13.1)	103 (15.8)	0.168	0.83 (0.57–1.20)	0.322
Men	No. = 361	No. = 398			
Migraine	94 (26.0)	73 (18.3)	0.011[c]	1.68 (1.14–2.49)[c]	0.009[c]
MO	59 (16.3)	27 (6.8)	<0.001[c]	3.09 (1.79–5.31)[c]	<0.001[c]
MA[b]	31 (8.6)	44 (11.1)	0.255	0.773 (0.44–1.36)	0.370
Women	No. = 274	No. = 255			
Migraine	133 (48.5)	106 (41.6)	0.107	1.40 (0.94–2.08)	0.100
MO	69 (25.2)	46 (18.0)	0.047[c]	1.52 (0.93–2.49)	0.096
MA[b]	52 (19.0)	59 (23.1)	0.240	0.84 (0.51–1.40)	0.503

Abbreviations: $CeAD_{stroke}$ = cervical artery dissection presenting with stroke; CI = confidence interval; IS = ischemic stroke; non-CeAD IS = ischemic stroke without CeAD; MA = migraine with aura; MO = migraine without aura; OR = odds ratio.
[a] Logistic regression, adjusted for age, sex (first 3 lines), country of inclusion, prospective/retrospective inclusion, hypertension, hypercholesterolemia, current smoking, diabetes mellitus, body mass index, and use of oral contraceptives or hormone replacement therapy in women.
[b] Including subjects with pure MA and subjects with both MO and MA.
[c] Significant.

baseline characteristics (table 3), the differences did not reach statistical significance in women.

Non-CeAD IS patients with PFO had higher percentages of migraine, especially MA, compared with other etiologies for IS (overall migraine 36.4 vs 23.4%, $p = 0.001$; MO 12.3 vs 10.7%, $p = 0.559$; MA 23.6 vs 12.4%, $p < 0.001$). When all patients with PFO (n = 197 non-CeAD IS and 36 $CeAD_{stroke}$ patients) were excluded from the analyses, and only patients in whom echocardiography was done were analyzed, the difference between $CeAD_{stroke}$ and non-CeAD IS groups regarding overall migraine was even clearer (37.8 vs 23.4, $p < 0.001$), but the difference in MA remained statistically insignificant (12.2 vs 12.4%, $p = 0.938$).

CeAD patients with and without migraine. Migraine was twice more common in women than in men (213/422, 50.5% vs 128/546, 27.1%, $p < 0.001$). The comparisons of CeAD patients with and without migraine are presented in table 4. There was no difference between migraineurs and nonmigraineurs in terms of body mass index, hypertension, hypercholesterolemia, diabetes, smoking, admission NIHSS score, or prior minor trauma.

In the acute phase, migraineurs more often had headache (73.7% vs 63.2%, $p = 0.001$). CeAD patients with ischemia (stroke or TIA) had as often migraine as patients with local signs only (36.9% vs 38.6%, $p = 0.650$). On the other hand, CeAD patients with migraine had as often cerebral infarct as the nonmigraineurs (62.9 vs 67.2%, $p = 0.170$, table 4). Stroke rates did not differ significantly between MA and MO patients (63.4 and 60.7%, respectively, $p = 0.618$). Nor was there difference between CeAD patients with and without migraine regarding the dissected vessel (ICA vs VA), vessel patency (occluded vs nonoccluded), presence of dissecting aneurysm, or the number of dissections (multiple vs single dissections). Presence or absence of migraine did not affect prognosis in CeAD patients in terms of favorable outcome (mRS 0–2 in 85.8% in migraine group and 80.4% in nonmigraineurs) or complications.

DISCUSSION We found that migraine, especially migraine without aura, is more common in CeAD patients than in non-CeAD ischemic stroke patients. As in the general population,[14] migraine was more common among women. The vascular risk factor profile was similar in CeAD patients with or without migraine. Migraine was not associated with cerebral ischemia in CeAD patients and did not influence the prognosis in CeAD.

It has been shown before that 1) patients with migraine, particularly MA, have increased risk of stroke,[5] 2) CeAD patients have more migraine than non-CeAD ischemic stroke patients,[6,16] and that 3) CeAD patients have more migraine than healthy controls.[4,6,16] The association between ischemic stroke and migraine is probably multifactorial. It may be related to increased frequency of some vascular risk factors among migraineurs, altered vascular reactivity, neurogenic inflammation, and excessive neuronal activation during migraine attacks, these changes being more pronounced in MA.[3,17]

In the light of our present data, it seems plausible that migraine accelerates or contributes to those pathogenetic processes that may lead to CeAD in otherwise susceptible patients. The fact that we observed no substantial difference in the frequency of migraine between CeAD patients with or without stroke indicates that the occurrence of stroke in CeAD patients is independent of migraine history. We could thus not confirm the findings of a previous study,[8] suggesting a lower prevalence of migraine among CeAD patients with stroke. Stroke in CeAD depends on the characteristics of the vessel wall damage, i.e., whether thromboembolism or significant hemodynamic changes occur or not. As hypothesized before,[6] 1) patients with migraine might be at increased risk of extracellular matrix degradation, and subsequently increased risk of CeAD; 2) endothelium-dependent vasodilatation is impaired in both CeAD and migraine patients, suggesting that there could be a common generalized vascular disorder predisposing

Table 4 Differences between CeAD patients with or without migraine[a]

	CeAD with migraine (n = 361)	CeAD, no migraine (n = 607)	*p* Univariate	OR (95% CI)	*p* Adjusted[b]
Age, y	42.6 ± 9.8	44.9 ± 9.9	<0.001[e]	0.99 (0.97–1.00)	0.065
Men, %	148 (41.0)	398 (65.6)	<0.001[e]	0.38 (0.29–0.50)[e]	<0.001[e]
Hypertension	88/359 (24.5)	159/603 (26.4)	0.524	1.09 (0.79–1.52)	0.591
Hypercholesterolemia	56/357 (15.7)	124/595 (20.8)	0.049[e]	0.90 (0.62–1.30)	0.566
Diabetes mellitus	5/360 (1.4)	15/605 (2.5)	0.250	0.70 (0.24–2.02)	0.509
BMI, kg/m^2	24.1 ± 4.0	24.7 ± 3.9	0.027[e]	1.00 (0.97–1.04)	0.834
Current smokers	93/358 (26.0)	175/603 (29.0)	0.309	0.81 (0.59–1.10)	0.181
Infection within 1 week	77/355 (21.7)	109/597 (18.3)	0.197	1.29 (0.91–1.82)	0.150
Prior (<1 mo) minor trauma	144/356 (40.4)	243/599 (40.6)	0.971	0.95 (0.71–1.27)	0.723
ICA/VA dissection[c]	221/123 (64.2/35.8)	387/200 (65.9/34.1)	0.602	1.09 (0.81–1.47)	0.579
Headache	261/354 (73.7)	371/587 (63.2)	0.001[e]	1.43 (1.05–1.93)[e]	0.023[e]
Neck pain	178/354 (50.3)	287/590 (48.6)	0.626	0.96 (0.73–1.27)	0.790
Horner syndrome	167/590 (28.3)	100/354 (28.2)	0.985	1.10 (0.81–1.50)	0.555
Tinnitus	36/354 (10.2)	35/590 (5.9)	0.017[e]	1.49 (0.90–2.47)	0.122
Occlusion	119/361 (33.0)	208/607 (34.3)	0.679	0.97 (0.72–1.29)	0.811
Dissecting aneurysms	49/361 (13.6)	75/607 (12.4)	0.584	1.10 (0.73–1.66)	0.639
Multiple dissection	58/361 (16.1)	89/607 (14.7)	0.556	1.02 (0.70–1.49)	0.924
Cerebral ischemia	276/361 (76.5)	475/607 (78.3)	0.650	0.86 (0.61–1.19)	0.355
Cerebral infarct	227/361 (62.9)	408/607 (67.2)	0.170	0.82 (0.62–1.09)	0.175
TIA	79/361 (21.9)	117/607 (19.3)	0.329	1.00 (0.71–1.40)	0.983
NIHSS on admission if infarction	6.0 ± 6.7	5.9 ± 6.7	0.654	1.01 (0.98–1.04)	0.517
mRS 0–2 at 3 mo if infarction	187/218 (85.8)	311/387 (80.4)	0.078	1.01 (0.60–2.06)	0.590
mRS 0–1 at 3 mo if infarction	138/217 (63.6)	241/384 (62.8)	0.368	1.14 (0.70–1.84)	0.603
Complications by 3 mo	23/350 (6.6)	35/583 (6.0)	0.728	1.00 (0.58–1.81)	0.945
Recurrent stroke	7/350 (2.0)	12/583 (2.1)	0.951	0.78 (0.30–2.09)	0.626
TIA	4/350 (1.1)	8/583 (1.4)	0.763	0.69 (0.20–2.39)	0.557
Hemorrhage[d]	6/350 (1.7)	4/583 (0.7)	0.140	2.01 (0.53–7.53)	0.303
Recurrent dissection	10/350 (2.9)	13/583 (2.2)	0.550	1.51 (0.62–3.70)	0.369

Abbreviations: BMI = body mass index; CeAD = cervical artery dissection; CI = confidence interval; ICA = internal carotid artery; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; OR = odds ratio; VA = vertebral artery.
[a] Values are n (%) or mean ± SD. The data are not available for all the patients.
[b] Adjusted for age, gender, prospective/retrospective inclusion and country of inclusion, and NIHSS for outcome variables.
[c] Both single and multiple dissections are included. Patients with CeAD in both ICA and VA are excluded. One patient with a dissection of the left common carotid and left subclavian arteries was not included in the statistics comparing ICA and VA.
[d] Intracranial hemorrhage or severe extracranial bleeding: lethal bleeding, or bleeding requiring hospitalization.
[e] Significant.

to both conditions—the origin of this vasculopathy is likely multifactorial, resulting from a combination of genetic and environmental factors that remain to be discovered.[9,18,19]

It has been unclear whether CeAD is linked to MA or MO or both. However, there were differences in the study designs and the control groups used in the different previous series (ischemic stroke controls and healthy controls), and each study involved patients of one nationality only.[4,6,16] The 2 latest case-control studies on migraine in CeAD, which partly overlap with the present study population,[4,18] have the largest patient numbers. In a Finnish study,[4] CeAD patients were compared with healthy controls. Particularly MA was more common in CeAD patients than in healthy controls, and the association of MO and CeAD was parallel, but did not reach statistical significance. An Italian study[18] consisted of CeAD and non-CeAD IS patients and healthy controls. Compared with healthy controls, both MA and MO were more common in CeAD patients, whereas compared with the non-CeAD IS group, CeAD patients had more MO, not MA, which is consistent with our study. Furthermore, non-CeAD IS patients had more MA compared to healthy controls,[18] in line with literature on migraine and stroke. Considering

that our control group consists of patients who had an ischemic stroke, it is likely that MA is overrepresented in non-CeAD IS patients compared to healthy controls. This is likely to be one of the factors explaining why our CeAD patients did not differ from controls regarding MA. The following conclusions seem feasible based on the present and previous studies: 1) both MA and MO are more frequent in CeAD patients compared to healthy controls; 2) non-CeAD IS patients have more MA than healthy controls, but the rates of MO are similar; 3) CeAD patients have more MO than non-CeAD IS patients.

There are conflicting results about the frequency of vascular risk factors in migraineurs compared to the general population.[17,20,21] In our study, CeAD patients with or without migraine did not differ in this aspect. Yet, it is known[22] that CeAD patients are a special subgroup in terms of vascular risk factors, as the frequency of hypercholesterolemia and body mass index are lower in CeAD patients compared to healthy controls. However, CeAD patients have more hypertension than the general population. It may be that migrainous CeAD patients represent a special subgroup also among migraineurs in terms of vascular risk factors.

Our results about the more frequent headache in the acute phase of CeAD in patients with migraine are consistent with a French study.[7] We could not verify the results of an earlier study,[23] indicating a higher prevalence of migraine in aneurysmal CeAD patients.

It should be noted that the distribution of TOAST categories in CADISP non-CeAD IS patients may not be representative of the distribution in the general stroke population. Some high-risk cardiac sources of embolism and other etiologies were not included by design so that patients with unknown stroke etiology may be overrepresented (table 2). Our non-CeAD patients are young adults (mean age 44.5). It was shown previously that in this age group the percentage of strokes with undetermined etiology is >30%, more than in older IS patients.[1,24] Epidemiologic associations between PFO vs stroke and PFO vs migraine have been debated over the years with conflicting results.[15,25] Non-CeAD IS patients in whom PFO was the only etiologic cause for stroke were overrepresented in our study due to recruitment criteria. Considering the possibility that our analyses could have been confounded by the non-CeAD patients with PFO, we performed a secondary analysis comparing CeAD and non-CeAD IS patients after excluding patients with PFO. PFO was indeed linked with migraine, especially MA. While our conclusion about the association between migraine and CeAD was unaffected by this subgroup analysis, PFO may explain some of the differences in the literature regarding MO/MA ratio,[6] and should be adjusted for in future research.

The strengths of the CADISP project are the large sample size and standardized collection of extensive clinical information in diverse populations. The limitations of our study include the following: our patients were recruited primarily in departments of neurology from tertiary academic centers, which may bias toward fewer CeAD patients with mild symptoms only. Patients with very severe strokes requiring intensive care were also less likely to be included. The lack of migraine data from healthy controls is of minor importance, since there are solid data showing that IS patients have more migraine than the general population.[5] This fact allows for the conclusion that CeAD patients also have more migraine than healthy controls. Both CeAD and non-CeAD IS patients were recruited retrospectively in part. There is no reason to assume that the potential recall bias concerning past migraine would be different among non-CeAD and CeAD patients. We did not correct for multiple testing.

Our study clearly verifies the association between migraine and CeAD which, compared with non-CeAD IS controls, was due to MO, while the mechanisms and possible causative link remain to be proved. We could not detect excess of brain infarction, specific arterial distribution, or other clinical or prognostic features characteristic to migrainous CeAD patients. Further studies exploring the mechanisms underlying the association between migraine and CeAD are warranted.

AUTHOR CONTRIBUTIONS

Dr. Metso: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis, obtaining funding. Dr. Tatlisumak: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, contribution of vital reagents/tools/patients, acquisition of data, study supervision, obtaining funding. Dr. Debette: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision, obtaining funding. Dr. Dallongeville: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, statistical analysis, study supervision, obtaining funding. Dr. Engelter: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data, obtain funding. Dr. Lyrer: study concept or design, analysis or interpretation of data, acquisition of data. Dr. Thijs: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. Dr. Bersano: drafting/revising the manuscript, acquisition of data. Dr. Aboud: study concept or design, contribution of vital reagents/tools/patients, acquisition of data. Dr. Leys: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision, obtaining funding. Dr. Grond-Ginsbach: drafting/revising the manuscript, study concept or design, contribution of vital reagents/tools/patients. Dr. Kloss: drafting/revising the manuscript, contribution of vital reagents/tools/patients. Dr. Touzé: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. Dr. Pezzini: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis. Dr. Metso: drafting/revising the manuscript, study concept or design, analysis

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