Vulnerability to Infarction During Cerebral Ischemia in Migraine Sufferers

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Background and Purpose—Cerebral hyperexcitability in migraine experiencers might sensitize brain tissue to ischemia. We investigated whether a personal history of migraine is associated with vulnerability to brain ischemia in humans.

Methods—Multicenter cohort study of patients with acute ischemic stroke who underwent a brain computed tomography perfusion and were scheduled to undergo reperfusion therapy. In a case–control design, we compared the proportion of subjects with no-mismatch, the volume of penumbra salvaged, as well as the final infarct size in a group of patients with migraine and a group of patients with no history of migraine.

Results—We included 61 patients with migraine (34 [55.7%] men; mean age, 52.2±15.1 years; migraine without aura/migraine with aura, 44/17) and 61 patients with no history of migraine. The proportion of no-mismatch among migraineurs was significantly higher than among nonmigraineurs (17 [27.9%] versus 7 [11.5%]; *P*=0.039) and was more prominent among patients with migraine with aura (6 [35.3%]; *P*=0.030) while it was nonsignificantly increased in patients with migraine without aura (11 [25.0%]; *P*=0.114). Migraine, especially migraine with aura, was independently associated with a no-mismatch pattern (odds ratio, 2.65; 95% CI, 0.95–7.41 for migraine; odds ratio, 5.54; 95% CI, 1.28–23.99 for migraine with aura), and there was a linear decrease of the proportion of patients with migraine with aura with increasing quartiles of mismatch volumes. Patients with migraine with aura had also smaller volumes of salvaged penumbra (9.8±41.2 mL) compared with patients with migraine without aura (36.4±54.1 mL) and patients with no migraine (45.1±55.0 mL; *P*=0.056). Conversely, there was no difference in final infarct size among the 3 migraine subgroups (*P*=0.312).

Conclusions—Migraine is likely to increase individual vulnerability to ischemic stroke during the process of acute brain ischemia and might represent, therefore, a potential new therapeutic target against occurrence and progression of the ischemic damage. **(*Stroke*. 2018;49:573-578. DOI: 10.1161/STROKEAHA.118.020554.)**

Key Words: brain ischemia ■ case-control studies ■ migraine disorders ■ migraine with aura ■ stroke

A large body of literature supports a link between migraine, especially migraine with aura, and ischemic stroke. This notwithstanding, the mechanisms underlying the relationship between the 2 disorders remain to be elucidated.[1] A recent hypothesis to explain the migraine–stroke association, based on experimental data obtained in mice expressing familial hemiplegic migraine type 1 mutations, is that the cerebral hyperexcitability phenotype associated with migraine might sensitize brain tissue to ischemia. Along with the observation that migraine mutants had an elevated minimum cerebral blood flow threshold required for tissue survival and developed larger infarcts, these findings directly support the hypothesis that brain tissue in migraineurs is more susceptible to ischemic injury.[2] The main drawback of this theoretical construct is that it comes from a transgenic animal model of monogenic migraine. Whether it applies to nonfamilial forms of migraine in humans has been insufficiently investigated thus far[3] and remains, therefore, currently unknown. Based on these premises, taking advantage of the reliability of computed tomography perfusion (CTP) imaging in the estimation of cerebral tissue viability in both clinical and research settings,[4] we conducted a case–control study comparing CTP

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maps of migraineurs and nonmigraineurs patients with acute ischemic stroke aimed at investigating whether a personal history of migraine is associated with vulnerability to brain ischemia.

Materials and Methods

Study Design

This was a multicenter cohort study of patients with acute stroke who underwent a CTP scan before recanalization therapy. The institutional review board at each site approved the study, and informed consent for participation was obtained from each patient or their next of kin. The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Subjects and Protocol

We retrospectively analyzed data from patients consecutively enrolled at 4 Italian hospitals between January 2016 and March 2017. Patients were eligible for participation in the study if they (1) were at least 18 years old; (2) had a proven anterior circulation acute ischemic stroke; (3) were scheduled to undergo reperfusion therapy for the stroke; (4) had undergone noncontrast CT (NCCT), CT angiography of the cervical and intracranial vessels, and CTP at admission, before scheduled therapy; (5) had follow-up NCCT within 24 to 36 hours after symptom onset; (6) had recanalization assessed on conventional angiography at end of the endovascular treatment or on follow-up CT angiography within 24 to 36 hours of admission when they were treated with intravenous thrombolysis with recombinant tissue-type plasminogen activator or did not receive any therapy; and (7) had a documented history of migraine (without aura or with aura). During the same study period, we also enrolled a group of control subjects who matched patients (1:1) by sex and age (±3 years) and fulfilled the inclusion criteria reported above, except they had no personal history of migraine.

Clinical Assessment

Patients were classified into etiologic subgroups according to Trial of ORG 10172 in Acute Stroke Treatment criteria[5] while stroke severity was scored by the National Institutes of Health Stroke Scale.[6] Clinical outcome was measured by the modified Rankin Scale[7] at 3 months. Modified Rankin Scale ≤2 and > 2 were defined as good and poor outcomes, respectively.

Imaging Techniques

All imaging was conducted on 64-slice scanners and included (1) NCCT performed from the skull base to the vertex, (2) CT angiography performed from the carotid bifurcation to vertex, and (3) CTP that covered a total of 4 cm from the basal ganglia to the lateral ventricles. CTP studies were obtained with a dynamic first-pass bolus-tracking methodology according to a 1-phase imaging protocol consisting of an acquisition of 50-second continuous (cine) scans, which started 5 seconds after the automatic injection of 40 mL of nonionic contrast agent at the rate of 4 mL/s.

Imaging Processing

All CTP scans were assessed using a commercially available delay-sensitive deconvolution software (CT Perfusion 3; GE Healthcare, Waukesha, WI). For each CTP scan, time–density curves for the arterial input function and venous output functions were obtained from the anterior cerebral artery and superior sagittal sinus, respectively. The arterial input function was corrected for partial volume averaging using the venous output functions-time–density curves. Cerebral blood flow, cerebral blood volume (CBV), and mean-transit-time (MTT) CTP maps were generated for each patient by deconvolution of tissue time–density curves and the arterial input function. Cerebral blood flow, CBV, and MTT values were expressed in mL/min per (100 g)$^{-1}$, mL/100 g, and seconds, respectively. Large blood vessels were automatically excluded from calculation by the software. Color-coded functional CTP map scales were set at 0 to 100 mL/min per (100 g)$^{-1}$ for cerebral blood flow, 0 to 8 mL/100 g for CBV, and 0 to 20 seconds for MTT. After identification by visual inspection on MTT and CBV maps, 3 different regions of interest were drawn freehand on every section in which they were visible according to the classical CTP mismatch model[8]: (1) MTT lesion indicating total hypoperfusion; (2) CBV lesion referring to infarct core; (3) MTT-CBV lesion representing ischemic penumbra. This last regions of interest was outlined on MTT maps where the regions of interest corresponding to CBV defect were automatically superimposed (Figure I in the online-only Data Supplement). The sum of these lesion areas was then multiplied by slice thickness to obtain core and penumbra (CTP MTT-CBV mismatch) volumes, respectively. The proportion between MTT and CBV volumes was defined as mismatch ratio. By using an adaptation of the previously proposed method,[3] we defined no mismatch as CBV lesion volume >83% of MTT volume. Final infarct volume was measured on follow-up NCCT at 24 to 36 hours after symptom onset with a multislice planimetric method by summation of the hypodense areas, manually traced on each slice in which they were detectable, multiplied by slice thickness.[9] As described by Friedrich et al,[10] total hypoperfusion volume detected on MTT maps was considered as the potential final infarct volume and, therefore, the amount of rescued brain tissue (penumbra volume salvaged) was calculated according to the formula: penumbra volume on baseline CTP−penumbra volume that infarcted on 24 to 36 hours NCCT. Collateral supply was graded on a 4-point scale according to a previously published scoring system in which collaterals were categorized as absent (score, 0), >0% but ≤50% (score, 1), >50% but < 100% (score, 2) and 100% (score, 3) of the occluded territory.[11] Finally, in agreement with the EXTEND-IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial) trial,[12] recanalization was scored based on a modified version of the TIMI (Thrombolysis in Myocardial Infarction) grading system: complete occlusion (TIMI score, 0–1); partial recanalization (TIMI score, 2); full recanalization (TIMI score, 3).[13] Patients with TIMI scores 2 and 3 were classified as recanalized, whereas patients with TIMI scores 0 and 1 were classified as nonrecanalized. All neuroimaging data were independently reviewed by 2 neuroradiologist (G.B., E.F.) blinded to the patients' clinical history and outcome.

Assessment of Migraine Characteristics

Personal history of headache was assessed in all subjects by study physicians during a face-to-face interview with patients or family members in both acute phase and follow-up evaluations. The diagnosis of migraine without aura and migraine with aura was made according to the diagnostic criteria of the International Headache Society.[14] Patients were also asked to rate the severity of their migraine by indicating (1) the frequency of attacks, (2) the duration of migraine, and (3) the number and type of acute and preventive medications.

Statistical Analysis

For subgroup comparisons, we used the χ^2 test, the Student t test, and the Mann–Whitney U test, when appropriate. Demographic and stroke features with $P \leq 0.1$ in the univariate comparison between patients with mismatch and patients with no mismatch on CT perfusion maps were entered into a binomial logistic regression model aimed at examining the conditional effect of such covariates in the prediction of mismatch itself (outcome variable). Results are given as odds ratio with 95% CI. $P \leq 0.05$ on 2-sided test was considered significant. Data were analyzed using the SPSS (version 21.0) package (www.spss.com).

Results

We identified 61 patients with acute ischemic stroke and personal history of migraine (34 [55.7%] men; mean age, 52.2±15.1 years; migraine without aura/migraine with aura, 44/17) and 61 patients with acute ischemic stroke and no personal history of migraine who qualified for the

analysis. Demographic features and clinical data of patients with migraine as well as of the selected nonmigraineurs control subjects are summarized in Table 1. Patients with migraine more often had other determined pathogenesis, especially cervical artery dissection, as likely cause of brain ischemia, and had a longer time interval from symptom onset to CT in comparison with patients with no history of migraine.

The analysis of CTP maps displayed larger ischemic core, smaller penumbra, and smaller penumbra salvaged in the group of patients with migraine, especially migraine with aura, compared with that of patients with no history of migraine, although differences were not significant (Tables I and II in the online-only Data Supplement). Conversely, we observed a significantly higher proportion of no-mismatch among migraine experiencers as compared with nonmigraineurs (17 [27.9%] versus 7 [11.5%]; P=0.039). This was even more prominent among patients with migraine with aura (6 [35.3%]; P=0.030) while it was nonsignificantly increased in patients with migraine without aura (11 [25.0%]; P=0.114). Besides migraine, sex, National Institutes of Health Stroke Scale score, and time from symptoms onset to CT were the only variables, among the preselected demographic

Table 1. Demographic and Clinical Characteristics of the Study Group According to Migraine Status

	Migraine (n=61)	No Migraine (n=61)	*P* Value
Age, y±SD	52.2±15.1	52.9±13.7	0.784
Sex, male	34 (55.7)	34 (55.7)	1.000
Hypertension	29 (47.5)	35 (57.4)	0.277
Diabetes mellitus	5 (8.2)	13 (21.3)	0.072
Hypercholesterolemia	26 (42.6)	22 (36.1)	0.459
Current smoking	29 (47.5)	20 (32.8)	0.096
Coronary artery disease	4 (6.6)	7 (11.5)	0.529
Cause of stroke*			0.601
Large-vessel disease	19 (31.1)	18 (29.5)	
Cardiac embolism	23 (37.7)	26 (42.6)	
Small-vessel disease	1 (1.6)	3 (4.9)	
Other determined pathogenesis	11(18.0)	6 (9.8)	
Undetermined pathogenesis	7 (11.5)	8 (13.1)	
Site of arterial occlusion			0.757
MCA-M1	27 (44.3)	32 (52.5)	
MCA-M2	16 (26.2)	15 (24.6)	
Proximal ICA	13 (21.3)	9 (14.8)	
T occlusion	5 (8.2)	5 (8.2)	
Collateral score			0.223
0	0 (0.0)	3 (4.9)	
1	15 (24.6)	18 (29.5)	
2	26 (42.6)	19 (31.1)	
3	20 (32.8)	21 (34.4)	
NIH Stroke Scale	13.7±6.6	14.8±6.4	0.349
Serum glucose, mg/dL	126.4±50.3	120.5±29.7	0.426
IV thrombolysis/endovascular treatment	40/18 (95.1)	41/12 (86.9)	0.205
Time from symptom onset to CT, min	186.7±112.3	166.8±75.6	0.268
Recanalization rate	43 (70.5)	49 (80.3)	0.207

CT indicates computed tomography; IV, intravenous; ICA, internal carotid artery; MCA, middle cerebral artery; and NIH, National Institutes of Health.

*According to Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria.[5]

Table 2. Demographic and Clinical Characteristics of the Study Group According to Penumbra/Core Ratios (Mismatch)

	Mismatch (n=98)	No-Mismatch (n=24)	*P* Value
Age, y±SD	52.9±14.3	51.2±14.8	0.616
Sex, male	51 (52.0)	17 (70.8)	0.113
Hypertension	52 (53.1)	12 (50.0)	0.788
Diabetes mellitus	16 (16.3)	2 (8.3)	0.522
Hypercholesterolemia	37 (37.8)	11 (45.8)	0.468
Current smoking	39 (39.8)	10 (41.7)	0.896
Coronary artery disease	9 (9.2)	2 (8.3)	1.000
Cause of stroke			0.455
Large-vessel disease	27 (27.6)	10 (41.7)	
Cardiac embolism	42 (42.9)	7 (29.2)	
Small-vessel disease	4 (4.1)	0 (0.0)	
Other determined pathogenesis	14 (14.3)	3 (12.5)	
Undetermined pathogenesis	11 (11.2)	4 (16.7)	
Site of arterial occlusion			0.327
MCA-M1	47 (48.0)	12 (50.0)	
MCA-M2	28 (28.6)	3 (12.5)	
Proximal ICA	16 (16.3)	6 (25.0)	
T occlusion	7 (7.1)	3 (12.5)	
Collateral score			0.528
0	2 (2.0)	1 (4.2)	
1	24 (24.5)	9 (37.5)	
2	38 (38.8)	7 (29.2)	
3	34 (34.7)	7 (29.2)	
NIH Stroke Scale	13.2±6.1	18.4±6.6	≤ 0.001
Serum glucose, mg/dL	122.4±43.5	127.7±30.6	0.572
IV thrombolysis/endovascular treatment	65/22 (88.8)	16/8 (100.0)	0.119
Time from symptom onset to CT, min	144.8±61.5	184.1±100.9	0.090
Recanalization rate	74 (75.5)	18 (75.0)	1.000

CT indicates computed tomography; ICA, internal carotid artery; IV, intravenous; MCA, middle cerebral artery; and NIH, National Institutes of Health.

*According to Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria.[5]

characteristics and stroke features, which showed a relationship with no-mismatch (Table 2) and were, therefore, entered into the logistic regression model.

We found association between personal history of migraine and no-mismatch (odds ratio, 2.95; 95% CI, 0.98–8.82). As opposed to migraine without aura, migraine with aura turned out to be significantly associated with no-mismatch in the model, including migraine subtypes among the covariates (Table 3). These results remained consistent after stratification for time to CT, individual National Institutes of Health Stroke Scale score, recanalization rate, and collateral supply (Table III in the online-only Data Supplement). Similarly, when we divided the individual penumbra/core ratio (mismatch) values into quartiles, we found a linear decrease of the proportion of patients with migraine with aura with increasing quartiles but were unable to detect any specific distribution of frequencies across quartiles in the subgroups of patients with migraine without aura and patients with no migraine (Figure).

As a further support to what above, we found significantly smaller volumes of salvaged penumbra in the subgroup of patients with migraine with aura compared with those in the other 2 subgroups at follow-up imaging performed between 24 and 36 hours poststroke occurrence (no migraine, 45.1±55.0 mL; migraine without aura, 36.4±54.1 mL; migraine with aura, 9.8±41.2 mL; P=0.05). Conversely, final infarct size measured at the same time point did not differ significantly among the 3 migraine subgroups (no migraine, 33.7±50.6 mL; migraine without aura, 44.0±58.1 mL; migraine with aura, 56.3±73.5 mL; P=0.312; Table II in the online-only Data Supplement), and the same was for the 3-month clinical outcome (good outcome: no migraine, 33 [54.1%] patients; migraine without aura, 24 [54.5%] patients; migraine with aura, 9 [52.9%] patients; P=0.994). Finally, none of the predefined migraine characteristics (migraine duration, frequency of attacks, number and type of acute and preventive medications) had any apparent relationship with mismatch (Table IV in the online-only Data Supplement).

Discussion

The main finding of the present study is the observation that a personal history of migraine is associated with no-mismatch pattern on CT perfusion scan performed in the acute phase of brain ischemia and that such an association is more robust in the subgroup of patients with migraine with aura. In this regard, our findings are consistent with those of the sparse experimental studies in transgenic mouse models,[2] as well as of the only clinical study in humans[3] that evaluated the potential influence of migraine on the biology of acute brain ischemia. Specifically, in the retrospective case–control study of Mawet et al,[3] which had the same design as ours but used magnetic resonance imaging instead of CT to investigate cerebral perfusion patterns, a no-mismatch profile was observed in ≈22% of migraineurs and ≈36% of migraineurs with aura, frequencies which are similar to those observed in the present study among migraine patients with a CT-based mismatch profile. In addition to the imaging modalities, there are also some methodological differences between the 2 studies that are worth to be noticed. First, our decision to match cases and control subjects for age and sex to reduce confounding should be regarded as a strength of the present study. Second, because our analyses were conducted on brain images obtained before any acute reperfusion intervention, they are more likely to provide an unbiased evaluation of the biology of acute brain ischemia in migraineurs. Third, to reduce the risk of misclassification, the diagnosis of migraine was systematically assessed by an expert in headaches unaware of the hypothesis under investigation through a direct interview in all subjects who entered into our analysis. Forth, we provided information on specific migraine characteristics (ie, frequency of attacks, acute and prophylactic antimigraine medications) that might potentially influence the rate of progression to infarction. Some limitations also should be considered, including the relatively small number of participants and the heterogeneous demographic characteristics and clinical phenotype of the cohort. Furthermore, migraine status relied on patient self-report, and it was diagnosed retrospectively, that is, after stroke had occurred. This might theoretically introduce a recall bias. However, it is unlikely that this potential bias explains the observed association because both cases and controls were patients with acute stroke, and they were unaware of the hypothesis under study. Finally, the case–control design inevitably exposes to the risks of selection bias. However, the recruitment was prospective and consecutive, and demographic variables and migraine subtypes were equally balanced in the 2 subgroups.

Table 3. Predictors of No-Mismatch According to Multivariable Logistic Regression Model

	OR	95% CI	P Value
Sex, male	3.03	0.80–8.33	0.111
Time from symptom onset to CT	0.99	0.98–1.00	0.056
NIH Stroke Scale	1.18	1.07–1.31	0.001
Migraine without aura	2.15	0.65–7.09	0.205
Migraine with aura	8.74	1.62–47.17	0.012

CT indicates computed tomography; NIH, National Institutes of Health; and OR, odds ratio.

Potential Biological Mechanisms

Biological mechanisms underlying our findings, as well as those of Mawet et al,[3] are matter of speculation because of the characteristics and the design of the 2 studies. One interpretation might be that migraine has an influence in increasing individual vulnerability to cerebral ischemia.[15] In particular, in the cascade of events leading to ischemic stroke, migraine might act as a susceptibility factor by rendering the brain more sensitive to ischemic depolarizations. If this is the case, one would expect, based also on the results of previous experimental studies on mice,[2] larger infarct core and final infarct volumes in patients with stroke who are migraine experiencers. An alternative interpretation of these results, as pointed out by Tietjen and Sacco,[16] might be that the greater proportion of no-mismatch among migraineurs is a consequence of more effective compensatory mechanisms to brain ischemia. People experiencing migraine would be, in other terms, more tolerant against the injurious effects of acute brain ischemia in comparison with nonmigraineurs. If this is the case, migraine

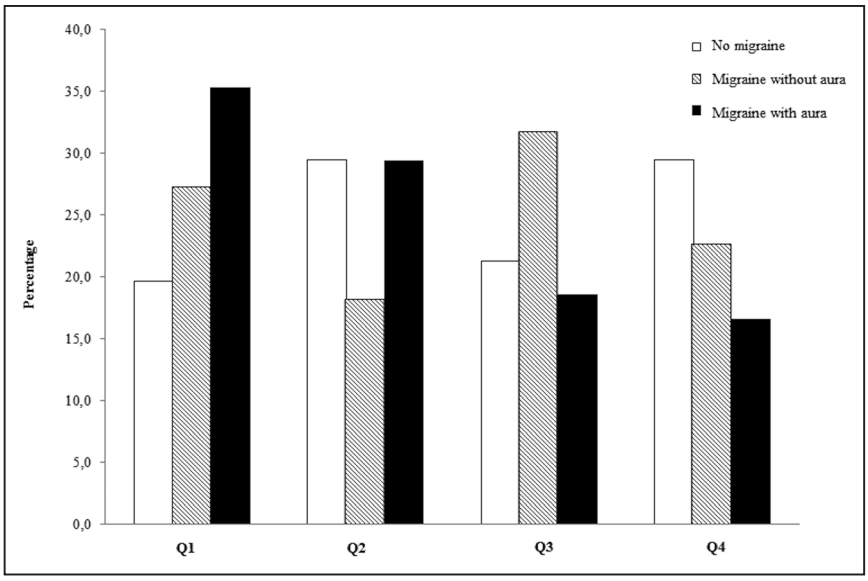

Figure. Histogram of percentage of subjects for quartiles of penumbra/core ratio (mismatch) in the subgroup with no migraine, migraine without aura, and migraine with aura. Q indicates quartile.

experiencers are expected to develop smaller infarct core and final infarct volumes. Although sparse data are available supporting this view,[17] the low level of disability from an ischemic cerebral event observed among migraineurs with aura in a subanalysis of the Women's Health Study[18] would indirectly strengthen this hypothesis. In the present analysis, we were unable to detect any differences in the infarct core volumes and final infarct size among the 3 subgroups defined by migraine status, which leaves the issue unsolved. This notwithstanding, there are several notable arguments in favor of the first hypothesis, which make it a more likely interpretation of our findings. First, although we are aware that our cohort is probably too small to allow significant differences to be detected, we observed an obvious trend toward larger infarct core and final infarct volumes, together with smaller penumbra size and penumbra volume salvaged in the subgroup of migraineurs. Second, the results of a recent preliminary study suggested that patients with migraine, especially migraine with aura, are more prone to develop larger infarcts than nonmigraineurs.[19] These findings implicate that, regardless of the size of cerebral hypoperfusion which may also depend on different compensatory mechanisms to circulatory dysfunction, people experiencing migraine are more likely to have a lower critical tissue perfusion level below which an infarction ensues (viability threshold) and, therefore, are more prone to incorporate the penumbra into the ischemic core.

Conclusions

Our findings in patients with ischemic stroke provide support to the experimental observations and the sparse data in humans that migraine is likely to increase individual vulnerability to ischemic stroke during the process of acute brain ischemia. Although further work is needed to elucidate the exact biological mechanisms underlying this effects, migraine might be conceptualized as a potential new therapeutic target against occurrence and progression of the ischemic damage.

Contributions

Dr Pezzini participated in manuscript drafting/revising, study design, data analysis and interpretation, data acquisition, statistical analysis, and study supervision. All authors participated in manuscript drafting/revising and data acquisition. Drs Pezzini and Padovani performed study supervision. Dr Fainardi performed manuscript drafting/revising, study design, data analysis and interpretation, data acquisition, and study supervision. The manuscript adheres to the American Heart Association Journals' implementation of the Transparency and Openness Promotion Guidelines.

Disclosures

None.

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