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Predictors of Migraine Subtypes in Young Adults With Ischemic Stroke

The Italian Project on Stroke in Young Adults

Alessandro Pezzini, MD; Mario Grassi, PhD; Corrado Lodigiani, MD, PhD; Rosalba Patella, MD; Carlo Gandolfo, MD; Federica Casoni, MD; Rossella Musolino, MD; Rocco Salvatore Calabrò, MD; Paolo Bovi, MD; Alessandro Adami, MD; Maria Luisa DeLodovici, MD; Elisabetta Del Zotto, MD; Lidia Luciana Rota, MD; Maurizia Rasura, MD; Massimo Del Sette, MD; Alessia Giossi, MD; Irene Volonghi, MD; Andrea Zini, MD; Paolo Cerrato, MD; Paolo Costa, MD; Mauro Magoni, MD; Licia Iacoviello, MD, PhD; Alessandro Padovani, MD, PhD; on behalf of the Italian Project on Stroke in Young Adults Investigators

Background and Purpose—The mechanisms underlying the relationship between migraine and ischemic stroke remain uncertain. The aim of the present study was to investigate the predictive value of major cardiovascular risk factors, cardiac interatrial abnormalities, and additional biological markers on migraine subtypes in young adults with ischemic stroke.

Methods—Ischemic stroke patients aged 45 years or younger were consecutively enrolled as part of the Italian Project on Stroke in Young Adults. A comprehensive evaluation was performed including assessment of self-reported migraine and cardiovascular risk factors, interatrial right-to-left shunt, and genotyping to detect factor V Leiden and the G20210A mutation in the prothrombin gene.

Results—Nine hundred eighty-one patients (mean age, 36.0 ± 7.6 years; 50.7% women) were included. The risk of migraine with aura increased with decreasing number of cardiovascular risk factors (OR, 0.50; 95% CI, 0.24–0.99 for 2 factors or more), increasing number of thrombophilic variants (OR, 2.21; 95% CI, 1.05–4.68 for carriers of at least 1 of the 2), and the presence of right-to-left shunt (OR, 2.41; 95% CI, 1.37–3.45), as compared to patients without migraine. None of these factors had influence on the risk of migraine without aura.

Conclusions—In young adults with ischemic stroke, low cardiovascular risk profile, right-to-left shunt, and an underlying procoagulant state are predictors of migraine with aura. The biological effects of these factors should be considered in future studies aimed at investigating the mechanisms linking migraine to brain ischemia. (*Stroke*. 2011;42:17-21.)

Key Words: migraine ■ patent foramen ovale ■ stroke

Although a large body of literature supports an association between migraine, especially migraine with aura (MA), and ischemic stroke,¹ the mechanisms underlying the relation between the 2 disorders remain to be elucidated. Several pathogenic processes have been advocated and, at least theoretically, might be operant synergistically. First, evidence indicating that MA is a risk factor for different ischemic

disorders, including cardiovascular death, stroke, myocardial infarction, angina, and claudication,^{2–4} has led to hypothesizing that MA may predispose to systemic atherosclerosis, which increases the risk for each of these vascular diseases through similar mechanisms. If this is the case, then a higher prevalence of risk factors known to be associated with cardiovascular disease among those with MA is expected.

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From the Dipartimento di Scienze Mediche e Chirurgiche (A. Pezzini, E.D.Z., A.G., I.V., P.C., A. Padovani), Clinica Neurologica, Università degli Studi di Brescia, Brescia, Italia; Dipartimento di Scienze Sanitarie Applicate (M.G.), Sezione di Statistica Medica e Epidemiologia, Università di Pavia, Pavia, Italia; Centro Trombosi (C.L., L.L.R.), IRCCS Istituto Clinico Humanitas, Rozzano-Milano, Italia; Stroke Unit (R.P., M.R.), Azienda Ospedaliera Sant'Andrea, Roma, Italia; Dipartimento di Neuroscienze (C.G.), Oftalmologia e Genetica, Università di Genova, Genova, Italia; Stroke Unit (F.C., A.Z.), Clinica Neurologica, Nuovo Ospedale Civile "S. Agostino Estense," AUSL Modena, Italia; Dipartimento di Neuroscienze (R.M.), Scienze Psichiatriche e Anestesiologiche Clinica Neurologica, Università di Messina, Messina, Italia; Istituto di Ricovero e Cura a Carattere Scientifico (R.S.C.), Centro Neurolesi Bonino-Pulejo, Messina, Italia; UO Neurologia (P.B.), Azienda Ospedaliera-Universitaria Borgo Trento, Verona, Italia; Stroke Center (A.A.), Dipartimento di Neurologia, Ospedale Sacro Cuore Negrar, Verona, Italia; Unità di Neurologia (M.L.D.), Ospedale di Circolo, Università dell'Insubria, Varese, Italia; Unità di Neurologia (M.D.S.), Ospedale S. Andrea, La Spezia, Italia; Dipartimento di Neuroscienze (P.C.), Stroke Unit, Università di Torino, Torino, Italia; Stroke Unit (M.M.), Neurologia Vascolare, Spedali Civili di Brescia, Brescia, Italia; Laboratori di Ricerca (L.I.), "RE ARTU," Centro di Ricerca e Formazione ad Alta Tecnologia nelle Scienze Biomediche, "Giovanni Paolo II," Università Cattolica del Sacro Cuore, Campobasso, Italia.

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Correspondence to Alessandro Pezzini, MD, Dipartimento di Scienze Mediche e Chirurgiche, Clinica Neurologica, Università degli Studi di Brescia, P.le Spedali Civili, 1, 25100 Brescia, Italia. E-mail ale_pezzini@hotmail.com

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Second, a number of investigators have reported an increased prevalence of patent foramen ovale, a potential risk factor for stroke among younger individuals, in patients with MA, prompting speculation that this cardiac interatrial abnormality may explain at least part of the ischemic risk in patients with MA.⁵ Third, migraine might predispose to ischemic stroke by inducing platelet-related hypercoagulability as a consequence of an underlying procoagulant state attributable to coexistent coagulation abnormalities and endothelial dysfunction.^{6,7} Besides the obvious implication in elucidating the biological mechanisms linking the 2 diseases, the identification of factors influencing such a relationship may help in stratifying subpopulations of those with migraines, enabling preventive strategies to be targeted at those subjects at higher risk for stroke. The Italian Project on Stroke in Young Adults (IPSYS) provides the opportunity to investigate these issues because of its large sample size, the homogeneous demographic characteristics and clinical phenotype of the subjects included, and the standard diagnostic work-up. Therefore, in the present study we aimed at evaluating whether individual cardiovascular risk profile varies according to migraine subtype, and whether specific risk factors clustering may be used as a predictive marker of migraine subtypes in a cohort of Italian ischemic stroke patients aged 45 years or younger.

Subjects and Methods

The study was approved by the local Ethics Committee. Informed consent was provided by all study participants. The IPSYS is a countrywide network of neurological centers with special interest in cerebral ischemia at a young age across Italy (see the online Appendix, available at <http://stroke.ahajournals.org>) aimed at recruiting patients with first-ever acute stroke who fulfill the following criteria: (1) age 18 to 45 years and 2) CT- or MRI-proven cerebral infarction in the setting of a hospital-based, multicentric, observational study. Centers are included in the network provided that the recruitment process of stroke cases takes place prospectively. Stroke was defined as a sudden loss of global or focal cerebral function that persisted for >24 hours with a probable vascular cause. Ischemic strokes attributable to sinus venous thrombosis, vasospasm after subarachnoid hemorrhage, cardiac surgery, occurring as an immediate consequence of trauma, and iatrogenic strokes were excluded. For the purpose of the present analysis, we screened data sets from patients consecutively admitted to 10 hospitals between January 2000 and July 2009.

Risk Factor Definition

The following risk factors for premature cerebral ischemia were retained: hypertension, diabetes mellitus, cigarette smoking, hypercholesterolemia, and oral contraceptive use. These variables were defined and dichotomized as follows: hypertension (systolic blood pressure ≥ 140 mm Hg and diastolic pressure ≥ 90 mm Hg in 2 separate measurements after the acute phase or use of antihypertensive drugs before recruitment), diabetes mellitus (history of diabetes, use of hypoglycemic agent or insulin, or fasting glucose ≥ 126 mg/dL), current smoking (including former smokers who had quit smoking for 6 months before the index event), hypercholesterolemia (cholesterol serum levels ≥ 220 mg/dL or use of cholesterol-lowering drugs), and oral contraceptive use (including former users who had quit using these medications for 1 month before the index event).

Assessment of Migraine History

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. History of migraine before stroke occurrence was considered for the present analysis. The diagnoses of migraine

without aura (MO) and MA were made according to the diagnostic criteria of the International Headache Society.⁸

Clinical and Laboratory Investigations

All patients underwent an etiologic work-up including complete blood cell count, biochemical profile, urinalysis, 12-lead ECG, chest roentgenography, 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. The performance of specialized coagulation testing (including prothrombin and activated partial thromboplastin times, antiphospholipid 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) was left to the discretion of the investigator in charge of the patient and no obvious cause of infarct was detected. Transthoracic and transesophageal echocardiography were performed to rule out cardiac sources of emboli. In particular, interatrial right-to-left shunt (RLS) was assessed in all patients with transesophageal echocardiography with a contrast study and Valsalva maneuver and/or transcranial Doppler sonography with intravenous injection of agitated saline. A RLS was considered present if any microbubble was seen in the left atrium within 3 cardiac cycles from maximum right atrial opacification on echocardiography.⁹ Transcranial Doppler sonography with intravenous injection of agitated saline was performed according to the Venice Consensus Conference.¹⁰ Briefly, it consists of the injection of 9 mL of saline solution and 1 mL air mixed with a 3-way stopcock by exchange of saline/air mixture between the syringes and injected as a bolus as a contrast-enhancing agent into the right cubital vein 5 seconds before the start of a 10-second Valsalva maneuver while recording the flow velocity of the middle cerebral artery, insonated through the temporal window on the right side at a depth of 50 to 60 mm, with a handheld probe. The appearance of transient spikes on the velocity spectral curve is considered positive for interatrial RLS. The method has an overall diagnostic accuracy comparable to that of transesophageal echocardiography with a contrast study and Valsalva maneuver.¹¹ Based on the results of such investigations, patients were classified according to a classification based on the Trial of Org 10172 in Acute Stroke Treatment criteria, accommodated and validated for the cause of stroke in the young,¹² and divided into 5 etiologic categories: (1) atherosclerotic vasculopathy; (2) nonatherosclerotic vasculopathy; (3) small-vessel disease; (4) cardioembolism; and (5) other (cerebral infarction that did not meet the criteria for 1 of the categories outlined). Stroke was classified as "anterior circulation stroke" when involving the areas of the brain supplied by carotid arteries and their branches, and as "posterior circulation stroke" when involving the brain stem, the cerebellum, or territories supplied by the posterior cerebral arteries.

Statistical Analysis

An individual proatherosclerotic score (from 0–4) was computed based on the number of major cardiovascular risk factors (hypertension, diabetes, smoking, and hypercholesterolemia). Similarly, a prothrombotic score (from 0–2) was obtained for each subject based on the individual status of carrier of factor V Leiden and the G20210A mutations. The median value of each score (1 for proatherosclerotic score and 0 for prothrombotic score) was used to get binary variables. Differences among the migraine groups (no migraine, MO, and MA) were examined with the χ^2 test, median test, and ANOVA *F* test, when appropriate. Categorical (multinomial) logistic regression model was planned to examine the conditional effect of RLS, proatherosclerotic risk profile, and thrombophilic defects in the prediction of migraine subgroups, and adjusted for age and gender. Results are given as OR (as measures of migraine-covariate interaction effects on disease risk) with 95% CI. *P* < 0.05 on 2-sided test was considered significant. Data were analyzed using the SPSS (version 16) package.

Results

The current study targets 1017 patients enrolled in the IPSYS registry. Among these, patients with missing migraine history

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

Variable	No Migraine	Migraine Without Aura	Migraine With Aura	<i>P</i>
Age, mean±SD, y	36.0±7.6	36.0±7.4	35.6±7.4	0.893
Sample size	746 (76.0)	161 (15.8)	74 (7.3)	
Women	335 (44.9)	111 (68.9)	50 (67.6)	<0.001
Right-to-left shunt	248 (33.9)	55 (34.6)	43 (58.1)	<0.001
Hypertension	176 (23.6)	30 (18.6)	11 (14.9)	0.114
Diabetes mellitus	34 (4.6)	4 (2.5)	0 (0.0)	0.086
Current smokers	292 (39.1)	62 (38.5)	21 (28.4)	0.197
Hypercholesterolemia	199 (26.7)	39 (24.5)	12 (16.2)	0.135
Proatherosclerotic risk profile (0–4)				0.012
>1 factor	183 (24.5)	29 (18.2)	8 (10.8)	
≤1 factor	563 (75.5)	130 (81.8)	66 (89.2)	
Oral contraceptive users*	118 (36.8)	37 (33.3)	18 (36.7)	0.905
Factor V Leiden G1691A	32 (5.5)	4 (3.1)	5 (8.9)	0.262
Prothrombin G20210A	33 (5.7)	7 (5.4)	7 (12.5)	0.121
Combined thrombophilic defects (0–2)†				0.053
≥1	60 (10.5)	10 (7.8)	11 (19.6)	
None	513 (89.5)	118 (92.2)	45 (80.4)	
Stroke etiologic subtypes				<0.001
Large-vessel atherosclerosis	91 (12.1)	9 (5.6)	4 (5.4)	
Nonatherosclerotic vasculopathy	136 (18.2)	27 (16.8)	12 (16.2)	
Small-vessel disease	47 (6.3)	5 (3.1)	2 (2.7)	
Cardioembolism/transcardiac embolism	210 (28.2)	42 (26.1)	36 (48.6)	
Other	262 (35.1)	78 (48.4)	20 (27.0)	
Location of the infarct				0.833
Posterior circulation	248 (33.7)	57 (35.8)	21 (28.8)	

*For women only.

†259 genotypes missing.

Values shown are n (%) unless otherwise indicated.

(n=36) were excluded, leaving a final sample size of 981 (mean age, 36.0±7.6 years; 50.7% women) for the analysis. Demographic characteristics of the study population grouped according to migraine status and the prevalence of selected risk factors are presented in Table 1. Large-vessel atherosclerosis and small-vessel disease were the presumed cause of infarct in 112 (11.0%) cases and 55 (5.4%) cases, respectively, nonatherosclerotic vasculopathy in 179 (17.6%) cases, cardiac/transcardiac embolism in 301 (29.6%) cases, and other etiologies in the remaining 369 (36.3%) cases. Patients who did not have migraines were more often males, more often had hypertension, diabetes mellitus, and hypercholesterolemia, were more often smokers, and, overall, were more likely to have an unfavorable vascular risk profile compared to patients with migraine, especially with the specific MA subtype. Conversely, RLS and individual and combined prothrombotic genotypes were more frequent in the subgroup of patients with MA than in the subgroup of patients with no history of migraine, and in the subgroup of patients with MO. There were no differences in the prevalence of oral contraceptive users between females with or without personal history of migraine.

As summarized by the migraine–covariate interaction OR reported in Table 2, females had >2-fold increased risk for migraine (OR, 2.37; 95% CI, 1.42–3.95 for MA; OR, 2.72;

95% CI, 1.88–3.94 for MO) as compared to the reference group of stroke patients without migraine. In addition, we observed a reduction in the risk of migraine with increasing number of the atherothrombotic risk factors. In particular, such a reduction (OR, 0.50; 95% CI, 0.24–0.99 for 2 factors or more) was significant only in the subgroup of patients with MA in comparison with the subgroup without migraines. A similar interactive effect of migraine with the 2 genetic thrombophilic variants was also observed: carriers of factor V Leiden mutation, the G20210A mutation in the prothrombin gene, or both the prothrombotic genotypes had >2-fold increased risk for MA (OR, 2.21; 95% CI, 1.05–4.68 as compared to stroke patients without migraine; OR, 2.83; 95% CI, 1.13–7.07 as compared to stroke patients with MO). Finally, the status of RLS carrier was associated with >2-fold increased risk of MA when compared to the other 2 subgroups (OR, 2.41; 95% CI, 1.37–3.45 as compared to stroke patients without migraine; OR, 2.58; 95% CI, 1.45–4.59 as compared to stroke patients with MO). None of these predisposing factors had significant interaction with MO.

Discussion

The hypothesis that people with MA have a higher prevalence of traditional risk factors known to be associated with cardiovascular disease recently has been suggested to explain

Table 2. Migraine–Covariate Interaction OR of Age, Gender, Right-to-Left Shunt, Proatherosclerotic Risk Profile, and Thrombophilic Defects According to Multinomial Logistic Regression Model

	MA vs No Migraine		MO vs No Migraine		MA vs MO	
	OR	95% CI	OR	95% CI	OR	95% CI
Age*	1.06	(0.90–1.25)	1.06	(0.94–1.19)	1.00	(0.83–1.21)
Women	2.37	(1.42–3.95)	2.72	(1.88–3.94)	0.87	(0.48–1.58)
Right-to-left shunt	2.41	(1.47–3.95)	0.93	(0.63–1.36)	2.58	(1.45–4.59)
Proatherosclerotic risk profile (>1 factor)	0.50	(0.24–0.99)	0.71	(0.44–1.14)	0.71	(0.30–1.66)
Combined thrombophilic defects (at least 1)	2.21	(1.05–4.68)	0.78	(0.37–1.63)	2.83	(1.13–7.07)

MA indicates migraine with aura; MO, migraine without aura.

*OR changes by 5-year units step.

the association between this migraine subtype and ischemic vascular disease, especially cerebral ischemia. If MA is associated with an unfavorable cardiovascular risk profile, then it would be likely that the increased propensity to ischemic disease observed in those with MA is the consequence of common comorbidities rather than of migraine-specific mechanisms. In line with this hypothesis, the population-based Genetic Epidemiology in Migraine study indicated that those with migraines, particularly those with aura, were more likely to smoke, have a parental history of myocardial infarction, an unfavorable cholesterol profile, elevated blood pressure, and high Framingham risk score, leading to speculation that MA may be a marker of progressive atherosclerosis.¹³ Data from the population-based American Migraine Prevalence and Prevention study recently provided further support to the perception that those with migraines have a higher probability of having an unfavorable risk factor profile.¹⁴ Intriguingly, a number of large-scale epidemiological analyses conducted over the past years have questioned these findings and suggested that the migraine–stroke association is particularly present in the absence of traditional cardiovascular risk factors,^{15,16} reinforcing the assumption that biological mechanisms other than those atherosclerosis-mediated may link migraine to ischemic stroke. The results of the present study support this hypothesis and prompt speculation that migraine alone might be insufficient to increase the risk of ischemic stroke and additional, nonproatherosclerotic factors might be necessary, and that these factors might be of help in identifying the subgroup of those with migraines in which cerebral ischemia is more likely to occur. Actually, within a large cohort of young adults with ischemic stroke, we found that the coexistence of migraine and cerebral infarcts is more frequent in those patients with a lower vascular risk factor profile, a higher prevalence of RLS, and underlying hypercoagulability. In particular, the fact that such a relation was limited to stroke patients with MA is an argument in favor of the idea that MA, RLS, and thrombophilic disorders are comorbid conditions acting together in a synergistic way and their effect is more pronounced and clinically apparent when not overcome by that of major cardiovascular risk factors. A number of data indirectly support this view. First, although controversial, there is evidence that MA may be associated

with patent foramen ovale.⁵ Second, in line with our findings, sparse reports indicate that the prevalence of migraine is higher among stroke patients with patent foramen ovale.^{17–19} Third, epidemiological evidence supports the assumption of a biological link between migraine and hypercoagulability,⁶ as well as its venous thromboembolic consequences.¹⁶ Finally, the reported relation among prothrombotic states, patent foramen ovale, and ischemic stroke²⁰ in a complex triangular pattern indirectly strengthens this hypothesis.

Although such a biological mechanism seems likely, an alternative interpretation of our data is also plausible. According to recent findings, vascular alterations may be the initial step of a cascade of events leading to neuronal dysfunction in those with migraines, and not the other way around.^{21,22} The emerging hypothesis is that brief cerebral hypoxic-ischemic episodes induced by microembolization could trigger cortical spreading depolarization of neurons and, thus, a migraine attack, whereas prolonged occlusion of the same vessels might cause cerebral ischemia.²³ In this regard, stroke and MA should be considered different clinical phenotypes of a common process of focal cerebral hypoperfusion. Lending support to this view, it might be that the coexistence of RLS and hypercoagulability we found in our stroke patients with MA increases the probability that small and clinically insignificant cerebral emboli shunted from the heart trigger spreading depolarization of neurons and cause MA in the same way they may induce major cerebral infarcts. Among other aspects, it is assumed that the duration is the main difference between spreading depolarization associated with MA and spreading depolarization associated with ischemic stroke.^{24–26} If this were true, then MA should be conceptualized as a marker of increased stroke risk, not as a stroke risk factor. The assumption of a pathogenic link between RLS and MA may also provide a potential interpretation for the weak association between migraine and myocardial infarction, as opposed to the strong association between migraine and ischemic stroke observed in numerous epidemiological studies.¹

Several strengths of the present study should be noted, including the large number of participants, the homogeneous demographic characteristics and clinical phenotype of the cohort, the standardized diagnostic work-up and evaluation of risk factors, and the clinical diagnosis of migraine and its subtypes, which constitute the gold standard for a valid

diagnosis with respect to alternative methods adopted in other studies. Some limitations also should be considered. First, because of the retrospective migraine ascertainment in our stroke patients, a recall bias cannot be theoretically excluded. However, because patients were unaware of the hypothesis undergoing study, there is no reason why they should have reported migraine symptoms more frequently. Second, because we did not assess migraine frequency and severity, as well as frequency of auras, in our cohort, we cannot evaluate whether the observed association differs according to specific migraine patterns. However, whether migraine frequency is a measure of migraine severity remains to be demonstrated. Third, because the transcranial Doppler technique prevents the assessment of atrial septal aneurysms, any further analyses comparing the prevalence of MA in stroke patients with RLS, atrial septal aneurysms, or both are hindered by the lack of precise data on the frequency of atrial septal aneurysms in our series. Furthermore, our protocol did not include any measurement, albeit semiquantitative, of the RLS diameter, an anatomic marker that may allow the identification of patients at high risk for embolism. Finally, although we adjusted for major potential confounders, residual confounding is possible given the observational design of the study. The implications of these missing data are noteworthy, but it seems unlikely that they have altered the main findings of the present analysis.

Conclusion

In conclusion, the results of our study reinforce the prevailing idea that multiple factors contribute to migraine, especially MA, and stroke susceptibility. In particular, they indicate that in young adults with cerebral ischemia, MA, as opposed to MO, is related to a low cardiovascular risk profile and it is strongly associated with RLS and inherited prothrombotic disorders. Although it seems premature to conclude that approaches aimed at modifying these factors may modify the risk of ischemic stroke in those with migraines, their biological effects should be taken into account in future studies aimed at investigating the mechanisms linking migraine to brain ischemia.

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Disclosures

None.

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