Age-specific association of migraine with cryptogenic TIA and stroke

Population-based study

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ABSTRACT

Objective: To determine whether there is an association between previous migraine and cryptogenic TIA or ischemic stroke at older ages.

Methods: We determined the age-specific associations of history of migraine and Trial of Org 10172 in Acute Stroke Treatment (TOAST) subtype of TIA and ischemic stroke in a population-based cohort study (Oxford Vascular Study; 2002–2012).

Results: Among 1,810 eligible patients with TIA or ischemic stroke, 668 (36.9%) had cryptogenic events, of whom 187 (28.0%) had previous migraine. Migraine was more commonly associated with cryptogenic events than with those of known etiology (odds ratio [OR] 1.73, 95% confidence interval [CI] 1.38–2.16, $p < 0.0001$; cardioembolic 2.00, 1.50–2.66, $p < 0.0001$; large artery 1.75, 1.20–2.53, $p = 0.003$; small vessel 1.32, 0.95–1.83, $p = 0.096$). The association of migraine with cryptogenic events was independent of age, sex, and all measured vascular risk factors (RFs) (adjusted OR 1.68, 1.33–2.13, $p < 0.0001$) and was strongest at older ages (<55 years, OR 1.11, 0.55–2.23; 55–64 years, 1.48, 0.83–2.63; ≥65 years, 1.81, 1.39–2.36) and in patients without vascular RFs (0 RFs OR 2.62, 1.33–5.15; 1 RF 2.01, 1.35–3.01; 2 RFs 1.80, 1.21–2.68; 3 RFs 1.21, 0.71–2.07; 4 RFs 0.92, 0.28–2.99). Results were consistent for migraine with or without aura and for analyses excluding TIA or stratified by sex or vascular territory of event.

Conclusions: In this population-based study of stroke etiology stratified by age, migraine was most strongly associated with cryptogenic TIA and ischemic stroke, particularly at older ages, suggesting a causal role or a shared etiology. ***Neurology*® 2015;85:1444–1451**

GLOSSARY

CI = confidence interval; **HRT** = hormone replacement therapy; **MRA** = magnetic resonance angiography; **OR** = odds ratio; **OXVASC** = Oxford Vascular Study; **PFO** = patent foramen ovale; **RF** = risk factor; **TOAST** = Trial of Org 10172 in Acute Stroke Treatment; **WMC** = white matter changes.

In contrast to myocardial infarction and peripheral vascular disease, up to one-third of TIA and ischemic strokes are cryptogenic despite detailed diagnostic workup, resulting in roughly 400,000 cases annually in Western Europe alone.[1] Moreover, although absolute recurrence rates after cryptogenic TIA or ischemic stroke vary between studies, the prognosis is similar to that of large artery and cardioembolic strokes.[2] Better understanding of the pathogenesis of cryptogenic TIA and ischemic stroke is therefore important.

Although patent foramen ovale (PFO)–related paradoxical embolism and underdiagnosed paroxysmal atrial fibrillation have been proposed as causes of some cryptogenic TIA and strokes,[3–5] fewer than half of cases can be clearly attributed to these etiologies,[6–9] and so other risk factors (RFs) must be important. Migraine has been shown to be associated with a 2-fold increased risk of ischemic stroke in case-control and cohort studies,[10,11] but only 2 conflicting case-control studies of young stroke looked specifically at cryptogenic events.[12,13] Given that the majority of cryptogenic TIA or strokes occur at older ages, we aimed to study the associations of previous migraine and cryptogenic TIA or ischemic stroke in a population-based cohort study of all TIA and stroke irrespective of age.

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Supplemental data at Neurology.org

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

METHODS Consecutive cases with a first TIA or ischemic stroke in the first 10 years (April 1, 2002, to March 31, 2012) of the Oxford Vascular Study (OXVASC) were studied. OXVASC is an ongoing population-based study of the incidence and outcome of cerebrovascular, cardiovascular, and peripheral vascular events. The study population comprises all 92,728 individuals, irrespective of age, registered with about 100 general practitioners in 9 general practices in Oxfordshire, UK. Methods of OXVASC have been reported previously.[14,15] Briefly, multiple overlapping methods of hot and cold pursuit are used to achieve near complete ascertainment of all individuals with TIA or stroke. These include (1) a daily, rapid access TIA clinic to which participating general practitioners and the local accident and emergency department refer all individuals with suspected, but not hospitalized, TIA or stroke; (2) daily searches of admissions to the medical, stroke, neurology, and other relevant wards; (3) daily searches of the local accident and emergency department attendance register; (4) daily searches of in-hospital death records via the Bereavement Office; (5) monthly searches of all death certificates and coroner's reports for out-of-hospital deaths; (6) monthly searches of general practitioner diagnostic coding and hospital discharge codes; and (7) monthly searches of all vascular imaging referrals. Stroke was defined as rapidly developing clinical symptoms or signs of focal, and at times global, loss of cerebral function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin. A TIA was defined as an acute loss of focal cerebral or ocular function with symptoms lasting less than 24 hours and which after adequate investigation was presumed to be due to a vascular cause.[14]

Detailed clinical history was recorded in all patients. Patients routinely had brain imaging (CT or MRI), vascular imaging (carotid Doppler or CT angiography/magnetic resonance angiography [MRA] or digital subtraction angiography), 12-lead ECG, and standard blood tests. Echocardiography, 24-hour ECG (Holter), and 5-day ambulatory ECG monitoring were done when clinically indicated (e.g., potential cryptogenic TIA/stroke; multiterritory infarct; patients at high risk of endocarditis, with known valve problems, or with other cardiologic complaints). During the 10-year study period, OXVASC had different imaging protocols in different time periods. From April 1, 2002, to March 31, 2010 (phase 1), CT brain and carotid Doppler were the first-line imaging modalities with MRI/MRA performed in selected cases when clinically indicated (e.g., cryptogenic TIA/stroke, patients <55 years old, and patients with suspected posterior circulation events). From April 1, 2010, to March 31, 2012 (phase 2), MRI brain and MRA of extracranial and intracranial vessels became the first-line imaging modality.

All cases were reviewed by a senior neurologist (P.M.R.) and etiology was classified according to the modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[16] Presence of hypertension and diabetes was not taken into account in classifying events.[17] The patients were classified as cryptogenic TIA or stroke only if the diagnostic workup included at least brain imaging, ECG, and vascular imaging, and no clear etiology was found. Patients with incomplete investigation were classified as unknown TIA or stroke. Incomplete investigation was usually due to early death or severe illness. For these same reasons there was also a risk of underascertainment of a history of migraine in patients with incomplete investigation due to lack of face-to-face interview or only a limited interview. In order to avoid bias due to underestimation of the prevalence of migraine in strokes of unknown etiology (and hence potential overestimation of the association of migraine and cryptogenic events), the TOAST unknown cases were excluded from analyses. Cases with cervical artery dissection or PFO were also excluded because of known associations with migraine.

RFs were collected both from face-to-face interview and primary care records using a structured questionnaire. History of migraine included diagnosed migraine any time before the index event. It was further divided into migraine with or without aura based on the clinical history. We used structured questions, including (1) Have you ever been diagnosed with migraine? (2) Have you ever had any aura (e.g., visual/sensory/speech disturbance or limb weakness) associated with the migraine? (3) Have you ever had any aura lasting for longer than 1 hour? Hypertension, hypercholesterolemia, and diabetes were defined based on documented diagnosis reported by the patient or in the medical records or the use of relevant medication. Cancer was defined as any previous solid tumor or hematologic malignancy. Previous venous thrombosis included at least one previous diagnosis of pulmonary embolism or deep vein thrombosis. Previous autoimmune disease was defined as having at least one of the following conditions: rheumatoid arthritis, type I diabetes, pernicious anemia, psoriasis, antiphospholipid syndrome, systemic lupus erythematous, Sjögren syndrome, autoimmune-related thyroid disease, Crohn disease, and myasthenia gravis. We also collected family history of stroke of first-degree relatives. Moreover, markers of small vessel disease on brain imaging were prospectively coded in OXVASC and have been published previously.[18] The Age-Related White Matter Changes (ARWMC) scale was applied for both CT and MRI, rating 5 different regions in both hemispheres according to a 0–3 score. Total score was categorized as absent (0), mild (1–5), moderate (6–10), or severe (>10) white matter disease (WMC).[19]

Standard protocol approvals, registrations, and patient consents. Written informed consent or assent from relatives was obtained in all participants. OXVASC was approved by the local research ethics committee (OREC A: 05/Q1604/70).

Statistical analysis. Values are reported as absolute numbers with percentages for categorical variables and as means with SDs for continuous variables. χ^2 and t tests were performed respectively to compare categorical and continuous variables between groups.

We compared the prevalence of history of migraine (any type, migraine with or without aura) between cryptogenic TIA/stroke cases and cases of determined etiology combined and individually using χ^2 test and logistic regression. We then determined the independent association between migraine and cryptogenic cases using logistic regression adjusting for other RFs (age, sex, hypertension, diabetes, angina, myocardial infarction, peripheral vascular disease, history of smoking, hypercholesterolemia, previous venous thrombosis, cancer, and autoimmune disease), and also stratified by number of vascular RFs (hypertension, diabetes, smoking, and hypercholesterolemia). Analyses were also stratified by age, sex, and vascular territory (carotid vs vertebrobasilar vs ocular events). Sensitivity analysis was performed excluding TIA cases and patients on β-blockers premorbidly (to explore potential impact of medication for migraine on any observed association between migraine and stroke). All analyses were performed using SPSS version 20 (SPSS Inc., Chicago, IL).

RESULTS Among 1,810 patients presenting with a first-in-the-study-period ischemic event (stroke = 1,114, TIA = 696), 668 (36.9%) had cryptogenic events, 534 (29.5%) cardioembolic, 236 (13.0%)

large artery disease, 277 (15.3%) small vessel disease, 65 (3.6%) multiple, and 30 (1.7%) other causes. Only one patient had a migrainous infarct. Baseline characteristics are shown in table 1.

Compared to events with determined etiology, patients with cryptogenic events most often had a history of migraine: 187/668 (28.0%) vs 210/1,142 (18.4%) in those with a determined etiology (odds ratio [OR] 1.73, 95% confidence interval [CI] 1.38–2.16, $p < 0.0001$). The same trend was seen for migraine with aura (123/604 vs 134/1,066; OR 1.78, 1.36–2.33, $p < 0.0001$) and migraine without aura (55/536 vs 52/984, OR 2.05, 1.38–3.04, $p = 0.0003$), and in analysis stratified by sex and vascular territory (table 2 and table e-1 on the *Neurology*® Web site at Neurology.org). Sensitivity analyses excluding TIA cases or cases on premorbid β-blocker also showed consistent results (tables e-2 and e-3).

Migraine was also more frequent in patients with cryptogenic events when compared with other individual subtypes: vs cardioembolic (OR 2.00, 1.50–2.66, $p < 0.0001$); vs large artery (1.75, 1.20–2.53, $p = 0.003$); vs small vessel (1.32, 0.95–1.83, $p = 0.096$, table 3), both for migraine with aura and migraine without aura (table 3). Results were consistent in analyses confined to patients aged ≥65 years (table e-4).

As expected, the frequency of reported migraine decreased with age in the overall cohort: <55 years, 45/159 (28.3%); 55–64 years, 64/240 (26.7%); ≥65 years, 288/1,411 (20.4%), $p_{trend} = 0.004$. However, the frequency of history of migraine did not fall with age in patients with cryptogenic TIA or stroke ($p_{trend} = 0.52$, table 2), such that in analysis stratified by age, the association of migraine and cryptogenic events was strongest at older ages (table 2): <55 years (OR 1.11, 95% CI 0.55–2.23); 55–64 years (1.48, 0.83–2.63); ≥65 years (1.81, 1.39–2.36).

In a multivariable analysis, the association of migraine and cryptogenic events was independent of

Table 1 Baseline characteristics among ischemic stroke/TIA subtypes

	Cryptogenic (n = 668)	CE (n = 534)	LAD (n = 236)	SVD (n = 277)	MULT (n = 65)	Other (n = 30)	Total (n = 1,810)	p Value
Risk factors, n (%)								
Age, y, mean (SD)	70.7 (12.7)	78.3 (11.5)	73.5 (9.9)	70.1 (12.6)	78.4 (8.6)	63.5 (18.0)	73.4 (12.5)	<0.0001
Male	325 (48.7)	244 (45.7)	141 (59.7)	166 (59.9)	42 (64.6)	13 (43.3)	931 (51.4)	<0.0001
Hypertension	365 (54.6)	387 (72.5)	179 (75.8)	170 (61.4)	51 (78.5)	18 (60.0)	1,170 (64.6)	<0.0001
Diabetes	83 (12.4)	64 (12.0)	46 (19.5)	50 (18.1)	10 (15.4)	0 (0)	253 (14.0)	0.003
Atrial fibrillation	3 (0.4)	488 (91.4)	12 (5.1)	4 (1.4)	55 (84.6)	2 (6.7)	564 (31.2)	<0.0001
Angina	73 (10.9)	129 (24.2)	47 (19.9)	34 (12.3)	23 (35.4)	3 (10.0)	309 (17.1)	<0.0001
Myocardial infarction	53 (7.9)	99 (18.5)	33 (14.0)	16 (5.8)	12 (18.5)	3 (10.0)	216 (11.9)	<0.0001
Peripheral vascular disease	27 (4.0)	50 (9.4)	36 (15.3)	14 (5.1)	11 (16.9)	3 (10.0)	141 (7.8)	<0.0001
Hypercholesterolemia	227 (34.0)	196 (36.7)	117 (49.6)	97 (35.0)	26 (40.0)	10 (33.3)	673 (37.2)	0.002
Body mass index, mean (SD)	26.3 (5.2)	26.3 (6.5)	26.5 (4.4)	26.9 (5.3)	25.7 (5.5)	25.5 (4.1)	26.4 (5.5)	0.55
Current smoker	112 (16.8)	35 (6.6)	43 (18.2)	66 (23.8)	10 (15.4)	4 (13.3)	270 (14.9)	<0.0001
Ex-smoker	255 (38.3)	235 (44.2)	108 (45.8)	104 (37.5)	34 (52.3)	14 (46.7)	750 (41.5)	0.044
Previous venous thrombosis	43 (6.4)	37 (6.9)	18 (7.6)	6 (2.2)	2 (3.1)	5 (16.7)	111 (6.1)	0.007
Cancer	90 (13.5)	110 (20.6)	45 (19.1)	38 (13.7)	13 (20.0)	10 (33.3)	306 (16.9)	0.001
Autoimmune disease	95 (14.2)	100 (18.7)	33 (14.0)	29 (10.5)	13 (20.0)	5 (16.7)	275 (15.2)	0.036
Migraine	187 (28.0)	87 (16.3)	43 (18.2)	63 (22.7)	11 (16.9)	6 (20.0)	397 (21.9)	<0.0001
Migraine with aura[a]	123 (18.7)	52 (9.9)	29 (12.5)	43 (16.0)	6 (9.4)	4 (13.8)	257 (14.5)	0.001
Investigation								
CT/MR brain imaging/autopsy[b]	647 (96.9)	498 (93.3)	221 (93.6)	276 (99.6)	64 (98.5)	28 (93.3)	1734 (95.8) [b]	<0.001
Extracranial vascular imaging	668 (100.0)	315 (59.0)	234 (99.2)	263 (94.9)	56 (86.2)	23 (76.7)	1559 (86.1)	<0.0001
Intracranial vascular imaging	308 (46.1)	85 (15.9)	114 (48.3)	92 (33.2)	21 (32.3)	15 (50.0)	635 (35.1)	<0.0001
Transthoracic echocardiography	308 (46.1)	336 (62.9)	106 (44.9)	126 (45.5)	50 (76.9)	9 (30.0)	935 (51.7)	<0.0001
Prolonged cardiac monitoring	148 (33.0)	84 (15.9)	48 (29.1)	49 (23.9)	12 (18.8)	5 (19.2)	346 (24.1)	<0.0001

Abbreviations: CE = cardioembolic; LAD = large artery disease; MR = magnetic resonance; MULT = multiple causes; SVD = small vessel disease.
[a] Thirty-three missing values.
[b] Incomplete brain imaging was mostly among patients with amaurosis fugax, retinal artery occlusion, or fatal stroke.

Table 2 Frequency (%) of migraine in patients with cryptogenic events vs events with determined etiology stratified by age, sex, and vascular territory

	Cryptogenic (% migraine)	Determined etiology (% migraine)[a]	OR (95% CI)	p Value
Age, y				p_{trend} = 0.17
<55	26/89 (29.2)	19/70 (27.1)	1.11 (0.55-2.23)	0.77
55-64	32/103 (31.1)	32/137 (23.4)	1.48 (0.83-2.63)	0.18
≥65	129/476 (27.1)	159/935 (17.0)	1.81 (1.39-2.36)	<0.0001
Sex				
Male	70/325 (21.5)	90/606 (14.9)	1.57 (1.11-2.23)[b]	0.01
Female	117/343 (34.1)	120/536 (22.4)	1.80 (1.33-2.43)[b]	<0.001
Territory				
Ocular only	22/55 (40.0)	13/39 (33.3)	1.33 (0.57-3.14)	0.51
Carotid	122/419 (29.1)	165/903 (18.3)	1.84 (1.40-2.41)	<0.0001
VB	65/249 (26.1)	45/239 (18.8)	1.52 (0.99-2.34)	0.05

Abbreviations: OR = odds ratio; VB = vertebrobasilar territory.
[a] Cases of determined etiology included cases of large artery disease, cardioembolic disease, small vessel disease, multiple, and other causes.
[b] Age-adjusted ORs were consistent (male 1.45, 1.02-2.06, p = 0.04; female 1.69, 1.24-2.29, p = 0.001).

age, sex, hypertension, diabetes, angina, myocardial infarction, peripheral vascular disease, hypercholesterolemia, smoking, previous venous thrombosis, cancer, and autoimmune disease (table 4, table e-5). Moreover, the association with cryptogenic events was strongest in cases with few vascular RFs (0 RFs OR 2.62, 1.33–5.15; 1 RF 2.01, 1.35–3.01; 2 RFs 1.80, 1.21–2.68; 3 RFs 1.21, 0.71–2.07; 4 RFs 0.92, 0.28–2.99, p_{trend} = 0.032, figure), particularly in patients aged ≥65 years (0 RFs OR 2.70, 1.18–6.15; 1 RF 2.25, 1.38–3.67; 2 RFs 2.04, 1.30–3.20; 3 RFs 1.17, 0.63–2.17; 4 RFs 0.58, 0.11–3.16, p_{trend} = 0.028, figure). Similarly, there tended to be stronger associations of migraine with cryptogenic events in patients with no family history of stroke (without family history 1.86, 1.39–2.50, $p < 0.0001$; with family history 1.44, 0.97–2.13, $p = 0.07$) or with less burden of small vessel disease on brain imaging (no or mild WMC 1.95, 1.49–2.56, $p < 0.0001$; moderate or severe WMC 1.09, 0.68–1.75, $p = 0.71$).

There was also a trend towards a stronger association of migraine and cryptogenic cases in patients who were currently on hormone replacement therapy (HRT) (TIA and ischemic stroke on HRT 3.63, 0.74–17.81, $p = 0.10$; not on HRT 1.74, 1.28–2.37, $p = 0.0004$; ischemic stroke alone on HRT 9.00, 0.91–88.58, $p = 0.046$; not on HRT 2.05, 1.33–3.14, $p = 0.001$).

DISCUSSION In this population-based study, we found that cryptogenic TIA and ischemic stroke had the strongest independent association with previous migraine. Moreover, the association was strongest in patients aged ≥65 years, and in those with no vascular RFs. These findings suggest a causal role or a shared etiology between migraine

Table 3 Associations of migraine and cryptogenic cases vs other etiologic stroke subtypes

	Any migraine		Migraine with aura[a]		Migraine without aura[a]	
Cases (migraine/migraine with aura)	**OR (95% CI)**	**p Value**	**OR (95% CI)**	**p Value**	**OR (95% CI)**	**p Value**
Cryptogenic (187/123) vs						
CE (87/52)	2.00 (1.50-2.66)	<0.0001	2.20 (1.55-3.12)	<0.0001	2.04 (1.25-3.34)	0.004
LAD (43/29)	1.75 (1.20-2.53)	0.003	1.70 (1.10-2.64)	0.016	2.21 (1.10-4.42)	0.022
SVD (63/43)	1.32 (0.95-1.83)	0.096	1.27 (0.87-1.87)	0.216	2.04 (1.07-3.89)	0.027
MULT (11/6)	1.91 (0.98-3.73)	0.055	2.30 (0.97-5.47)	0.059	1.54 (0.54-4.43)	0.416
Other (6/4)	1.56 (0.63-3.87)	0.338	1.53 (0.52-4.50)	0.436	2.74 (0.36-20.68)	0.307

Abbreviations: CE = cardioembolic; CI = confidence interval; LAD = large artery disease; MULT = multiple causes; OR = odds ratio; SVD = small vessel disease.
[a] Reference group: no migraine.

Table 4 Multivariable analysis of associations of migraine and cryptogenic cases vs cases of determined etiology

Risk factors	Odds ratio	95% CI	*p* Value
Migraine	1.68	1.33–2.13	<0.0001
Age (per 10 y)	0.84	0.78–0.92	<0.0001
Male	0.79	0.64–0.98	0.03
Hypertension	0.60	0.48–0.75	<0.0001
Diabetes	1.03	0.76–1.40	0.85
Angina	0.65	0.47–0.90	0.01
Myocardial infarction	0.81	0.56–1.17	0.26
Peripheral vascular disease	0.48	0.31–0.76	0.002
History of smoking	1.03	0.84–1.27	0.76
Hypercholesterolemia	1.05	0.84–1.32	0.66
Previous venous thrombosis	1.27	0.84–1.91	0.26
Cancer	0.72	0.55–0.96	0.02
Autoimmune disease	0.85	0.64–1.13	0.27

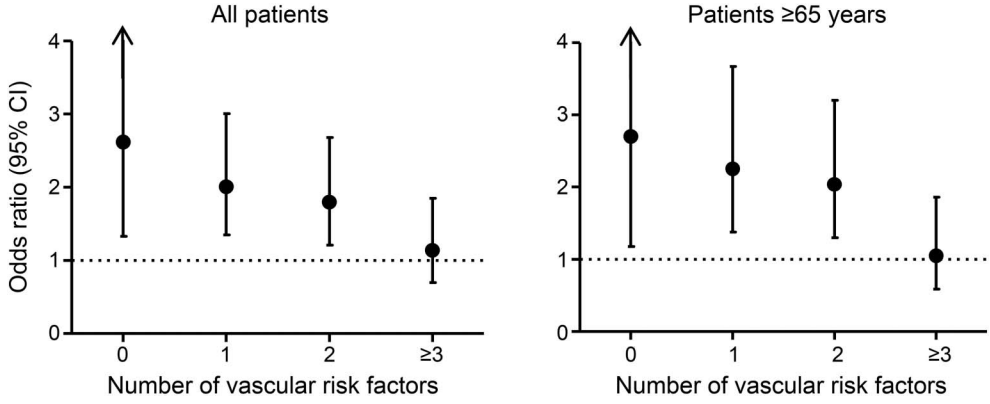
Abbreviation: CI = confidence interval.

and cryptogenic TIA or ischemic stroke even at older ages.

Previous studies have shown that migraine is associated with vascular disease, including acute cerebrovascular events,[11,20–22] asymptomatic brain lesions,[23–25] cardiac disease,[26,27] retinal vasculopathy,[28] and vascular mortality.[29] The risk of ischemic stroke seems to increase with increasing migraine attack frequency,[30,31] and is higher for migraine with aura and among young women.[11] However, despite a large number of individual cohort and case-control studies and meta-analyses on migraine and ischemic stroke risk,[11,20,21] only 2 small case-control studies looked at migraine-associated risk by etiologic subtype of ischemic stroke with conflicting results. While one found that patients with cryptogenic stroke (n = 192) were approximately twice as likely as controls to have previous migraine with visual aura,[12] the other reported similar prevalence of migraine in cryptogenic cases (n = 42) vs controls.[13] Neither of these studies compared the prevalence of migraine between etiologic stroke subtypes and they were both done in young populations (<50 years old). Moreover, case-control studies can be undermined by difficulties in selecting representative controls. Our findings, based on case-case comparisons within a population-based study without selection bias, add new evidence to support the distinct association between migraine and cryptogenic TIA or ischemic stroke. We showed that patients with cryptogenic events were more likely to have previous migraine than cases of determined etiology. Moreover, we showed that when compared to cases of determined etiology, the association of migraine and cryptogenic cases was independent of other vascular RFs. This is supported by one prospective cohort study that found that more than half of the ischemic strokes (35 out of 64) in women migraineurs were cryptogenic, whereas none was apparently due to atherothrombotic or atheroembolic mechanisms.[32]

We found that migraine was associated with cryptogenic cases independently of age, sex, hypertension, diabetes, hypercholesterolemia, and smoking. The association was strongest in patients with no other vascular RFs, suggesting that the possible mechanism of migraine in cryptogenic cases is independent of vascular burden, which is consistent with previous evidence that migraine-associated stroke risk is highest in patients without overt vascular disease.[12,33] There are several potential mechanisms that might explain these findings. First, migraine is associated with other rare causes of stroke, such as PFO[34] and cervical artery dissection.[35,36] However, all of the

Figure Odds of a history of migraine in patients with cryptogenic events vs events of determined etiology stratified by number of vascular risk factors (hypertension, diabetes, smoking, and hypercholesterolemia)



CI = confidence interval.

cryptogenic cases in OXVASC had at least carotid imaging, excluding cervical artery dissection, and although screening for PFO was not routine, the risks of recurrent cardioembolic stroke or acute peripheral artery disease with presumed embolic origin did not differ between cryptogenic cases with or without previous migraine (data not shown). However, there is evidence of an association of PFO and cryptogenic stroke at older ages.[4] Given that we found that the association of migraine and cryptogenic events was also stronger at older ages, it is possible that PFO might explain some of the associations between migraine and stroke at older ages. Second, there was a trend towards a stronger association between migraine and cryptogenic TIA or ischemic stroke in patients currently taking HRT in our study. HRT is known to increase the risk of ischemic stroke,[37] but little is known about any interaction with migraine. Despite the known synergistic effect of migraine on the risk of ischemic stroke due to oral contraceptive pill use in younger women,[20] current HRT guidelines do not raise any concerns about use of HRT in older women with migraine.[38] Our finding, although not statistically significant, warrants further research, but given the small proportion of women taking HRT it did not explain the overall association between migraine and cryptogenic events. Third, it is possible that drugs used in the management of migraine, such as β-blockers, triptans, and ergotamine, might have caused some cryptogenic events. However, no patients had stroke induced by acute use of triptans or ergotamine and although a quarter of our patients were on β-blockers, the sensitivity analysis excluding patients using β-blockers showed consistent results of higher frequency of previous migraine in cryptogenic cases. Therefore, migraine drug use is unlikely to explain the association between cryptogenic stroke and migraine.

Despite the doubling of the relative risk of ischemic stroke, in absolute terms ischemic stroke remains a rare complication in migraineurs.[10] Moreover, most of the ischemic events in migraineurs happen many years after their first migraine attack. Therefore, the association of migraine and cryptogenic cases or ischemic stroke overall is unlikely to be directly causal. Rather, given that migraine has a strong genetic component,[39] the association of migraine and cryptogenic stroke is possibly explained at the genetic level or by shared RFs that are unknown.

Although we consider our results to be valid, the study has several limitations. First, TOAST classification was applied to classify TIA as well as stroke subtypes (table e-6). Although the etiologic classification systems were not originally developed for TIA patients, the usefulness of the TOAST criteria in TIA has been validated in previous studies.[40] Moreover, the analysis excluding TIAs was consistent with the main analyses. Second, migraine history was collected from face-to-face interviews with the participants using a structured but simple questionnaire. As OXVASC patients were mainly elderly patients, a recall bias cannot be entirely ruled out. However, primary medical records were used to cross-check all relevant diagnoses. Moreover, as interviews were done by the same staff using the same protocol, the accuracy of reporting should not differ between different etiologic subtypes. Furthermore, any misclassification of exposure status may tend to bias any true association towards the null. Nevertheless, we still found associations between previous migraine and cryptogenic TIA or ischemic stroke. Third, since we did not screen all patients for PFO, we were not able to address this possible link between migraine and stroke. Fourth, given our cross-sectional design, a survival bias is also a potential limitation if migraine had an effect on hyperacute outcome in some determined stroke subtypes. Fifth, since we did not include a control group with no history of stroke or TIA, we were not able to determine whether stroke subtypes of determined etiology were associated with migraine, albeit less strongly than cryptogenic stroke. Finally, similar to previous studies,[12,32] only self-reported migraine history was collected in OXVASC. Thus we were not able to differentiate between active migraine vs history of migraine or between different frequencies of migraine. However, there has been consistent evidence suggesting an increased risk of ischemic stroke with any migraine.[20]

Our findings have several implications. First, as the associations between migraine and ischemic stroke differed by subtype, stratifying outcome by stroke subtypes in future cohort studies may help clarify the mechanism underlying migraine and stroke. Second, mechanistic studies of the association between migraine and cerebral ischemic stroke should focus on patients with cryptogenic cerebrovascular events. Finally, given that the association of migraine and cryptogenic stroke was strongest in the elderly, screening for potentially migraine-associated etiology, including hypercoagulable state, PFO, or genetic mutations, should not be confined to young strokes.

AUTHOR CONTRIBUTIONS

L.L.: study design, acquisition of data, draft and revision of the manuscript, statistical analysis, and interpretation of data. U.G.S.: acquisition of data and revision of the manuscript. W.K.: acquisition of data and revision of the manuscript. P.M.R.: study concept and design, draft and revision of the manuscript, analysis and interpretation of data, study supervision and funding.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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