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Abstract

Objective: To assess the association between migraine and cryptogenic ischemic stroke (CIS) in young adults, with subgroup analyses stratified by sex and presence of patent foramen ovale (PFO).

Methods: We prospectively enrolled 347 consecutive patients aged 18-49 with a recent CIS and 347 age- and sex-matched (±5 years) stroke-free controls. Any migraine and migraine with (MA) and migraine without aura (MO) were identified by a screener, which we validated against a headache-neurologist. We used conditional logistic regression adjusting for age, education, hypertension, diabetes, waist-to-hip ratio, physical inactivity, current smoking, heavy drinking, and oral estrogen use to assess independent association between migraine and CIS. The effect of PFO on the association between migraine and CIS was analyzed with logistic regression in a subgroup investigated with transcranial Doppler bubble screen.

Results: The screener performance was excellent (Cohen's Kappa >0.75) in patients and controls. Compared with non-migraineurs, any migraine (odds ratio [OR] 2.48, 95% confidence interval 1.63-3.76) and MA (OR 3.50, 2.19-5.61) were associated with CIS, whereas MO was not. The association emerged both in women (OR 2.97 for any migraine, 1.61-5.47; OR 4.32 for MA, 2.16-8.65) and men (OR 2.47 for any migraine, 1.32-4.61; OR 3.61 for MA, 1.75-7.45). Specifically for MA, the association with CIS remained significant irrespective of PFO. MA prevalence increased with increasing magnitude of the right-to-left shunt in patients with PFO.

Interpretation: MA has a strong association with CIS in young patients, independent of vascular risk factors and presence of PFO.

Introduction

Ischemic stroke is an increasing global problem due to increasing incidence, high morbidity, mortality and risk of recurrence, as well as other long-term consequences.[1] Despite the high prevalence of traditional well-documented risk factors in young ischemic stroke patients,[2,3] recent hospital- and population-based studies suggest that a substantial proportion (33% to 50%) of ischemic strokes at younger ages remain cryptogenic after complete diagnostic work-up.[4-6] Many young patients with cryptogenic ischemic stroke (CIS) are diagnosed with patent foramen ovale (PFO), suggesting paradoxical embolism as one of the main causes based on evidence from observational studies and secondary prevention trials comparing PFO closure to medical treatment.[7] However, about 25% of individuals have PFO in general, and, as causality of PFO remains a challenge to determine at individual level, strong recommendations in favor of PFO closure have not been given.[8]

Migraine is another frequently encountered feature in young stroke patients. Pooling case-control and cohort studies, a 2010 meta-analysis found migraine to be associated with about 2-fold overall increase in the risk of all ischemic strokes independent of vascular risk factors.[9] The risk estimate was slightly lower in a 2017 meta-analysis including prospective cohort studies (relative risk ~1.64).[10] Notably, the increased risk of ischemic stroke is mostly established for women having migraine with aura (MA).[9,10] It is also known that MA prevalence is more than 3-fold in individuals with PFO compared to those without PFO.[11] Suggesting that CIS, migraine, and PFO are intertwined, prior studies showed that any type of migraine[12] and MA[13-15] emerge more frequently in patients with CIS harboring PFO compared to those without PFO. Nevertheless, studies assessing the strength of association between migraine and ischemic stroke are scarce specifically for young patients with CIS.

It is further not known, whether sex and PFO modulate the risk. To our knowledge, three studies[16-18] — of which two compared stroke patients with non-stroke controls and one with stroke patients with determined etiology — have assessed the strength of association between migraine and CIS. These associations were, however, influenced by confounders, consisting of known vascular risk factors (Supplemental Table s1).

The gold standard in migraine diagnosis is an interview by a headache specialist following the diagnostic criteria of the International Classification of Headache Disorders (ICHD).[19] This strategy is often not feasible in patients with an acute stroke or in multicenter research settings, however. Multiple migraine screeners are available, but only one of these, the Migraine Screener for Stroke (MISS) is validated specifically in stroke patients.[20] MISS showed a high negative predictive value (NPV) and a reasonable positive predictive value (PPV) for any type of migraine, but a low PPV for MA. To study the associations between migraine subtypes in patients with recent stroke in a multicenter setting, a standardized migraine screener that is simple to use by study personnel and with sufficient reliability in establishing migraine diagnosis and its subtypes is desirable.

Based on existing evidence and clinical experience we hypothesized that migraine would have relatively strong association with CIS at younger age and that sex and the presence of PFO might modulate the association. To answer these questions, we set up a prospective multicenter case-control study, and, to allow diagnosis and subtyping of migraine, we developed a screening tool and compared it against the gold standard.

Methods

Study population

Searching for Explanations for Cryptogenic Stroke in the Young: Revealing the Etiology, Triggers, and Outcome (SECRETO; NCT01934725) is an international prospective multicenter case-control study of young adults presenting with a first-ever CIS. The study was approved by the Ethics Committee of the Helsinki and Uusimaa Hospital District (362/13/03/00/2012) and local Ethics Committees at each recruiting center (Supplemental Table s2). Written informed consent was obtained from all participants.

Methods of the study have been described previously in detail.[21] For the present study, consecutive patients aged 18-49 years were included after standardized and timely diagnostic work-up demonstrating no definite cause for the stroke, between October 2013 and April 2020. Ischemic lesion had to be visualized by neuroimaging. All patients underwent brain magnetic resonance imaging, imaging of intracranial and extracranial vessels with either computed tomography angiography or magnetic resonance angiography, routine laboratory testing, 12-lead electrocardiography (ECG), prolonged continuous ECG for a minimum of 24 hours, as well as both transthoracic and transesophageal echocardiography. Transcranial Doppler ultrasound with bubble screen (TCD-BS) was performed at selected study centers. Ancillary testing was performed at the discretion of local investigator. CIS was defined after initial diagnostic work-up according to ASCO classification as absence of disease (grade 0), or any of grade II (causality uncertain) or grade III (unlikely a direct cause) pathology using diagnostic testing with the highest grade of evidence.[22] Echocardiography studies followed standardized protocol.[23] Patients with PFO-related strokes and migrainous

infarction[19] were included in the present study given the uncertainty in their causality and pathophysiologic mechanisms. None of the patients underwent PFO closure prior to study assessments.

One sex- and age-matched (±5 years) stroke-free control for each patient from the same region was searched locally at each study center. Sources to identify control subjects included random search through population registers where feasible, patients' nonrelated proxies, and hospital staff unrelated to the study.

Cardiovascular risk factors and comorbidities

Detailed clinical history was obtained from all participants using medical records and a structured interview during a study visit. Level of education was classified as (1) primary or lower secondary education, (2) upper secondary education, and (3) post-secondary non-tertiary or tertiary education. Registered cardiovascular risk factors included history of hypertension (prior diagnosis of hypertension, prior antihypertensive medication, or a mean of two office blood pressure measures over 140/90 at study visit), diabetes mellitus (prior diagnosis of any diabetes and/or prior antidiabetic medication), cardiovascular disease (history of coronary heart disease, congestive heart failure, peripheral arterial disease, or atrial fibrillation), history of venous thrombosis, current tobacco smoking (smoking at least one cigarette during the preceding year prior to index stroke), waist-to-hip ratio (obesity defined as >0.85 in women, >0.90 in men), physical inactivity, heavy alcohol use, and for women, use of oral estrogen. Physical inactivity was assessed using the short version of the International Physical Activity Questionnaire,[24] defined as not meeting any of the criteria for either

moderate or high levels of physical activity. Adaptation of the World Health Organization Alcohol, Smoking and Substance Involvement Screening Test[25] was used to assess alcohol use, with heavy use defined as at least five doses of alcohol per day or 16 doses per week for women, and at least 7 doses of alcohol per day or 24 doses per week for men.[26] Stroke severity in patients on admission was assessed with the National Institutes of Health Stroke Scale (NIHSS).

Diagnosis of PFO

For the present study, right-to-left shunt (RLS) detected with TCD-BS served as a measure of PFO in patients and controls, acknowledging that some of the detected RLS may represent a shunt at other sites such a pulmonary vessels. TCD-BS was performed according to consensus guidelines,[27] with agitated 10 mL saline-blood or saline-only solution as a contrast, which was injected into the antecubital vein. The test was performed both at rest and with Valsalva maneuver, unless there was a severe RLS at rest. Highest degree of RLS was recorded and classified as small (1-9 bubbles), moderate (10-24 bubbles), or severe (≥25 bubbles or a curtain). Activity of PFO was classified as stable (RLS only with Valsalva) and active (RLS at rest).

Migraine screener

We developed a short version of migraine screener — aiming to be suitable for stroke patients in a multicenter study — based on a migraine screening questionnaire that has been validated in general population and proved to provide good discrimination between migraine subtypes.[28] The screener

was to follow the main criteria of the ICHD, 3rd edition,[19] with slight adaptations. For the short version, we selected nine questions, including three screening questions on headache attacks and attacks with visual aura as well as six specific questions on headache characteristics (Supplemental Table s3). During the interview, the questions were read to the participants by study personnel, who were aware of the participants' case-control status. In stroke patients, it was emphasized that possible headache or visual symptoms associated with the stroke itself should be disregarded.

If the response to all of the first three screening questions was negative, i.e. "Never", the participant was judged as not having migraine. The participant was assigned to have MA if their response to at least one the questions "Have you ever had a headache attack that was preceded by a disturbance in your vision (such as zigzag lines, shimmering or vibrating patches, blind spots, bright lights, or blobs for several minutes)?" or "Have you ever had one or more attacks with disturbance in your vision (such as zigzag lines, shimmering or vibrating patches, blind spots, bright lights, or blobs) lasting 10-30 minutes without headache?" was "Two times or more". Information on other types of aura symptoms was not asked. For the diagnosis of migraine without aura (MO), the participant had to answer "Five times or more" to question "Have you had repeated headache attacks anytime during your lifetime?" and "Yes" responses to questions on headache duration and the presence of nausea/vomiting or photo-/phonophobia, as well as at least two "Yes" responses on questions regarding headache moderate/severe intensity, pulsatility, unilaterality, and aggravation by physical activity, as outlined in Figure. If the participant experienced both MA and MO attacks, migraine subtype was coded as MA.

For the screener validation, an independent experienced senior headache-neurologist (V.A.) was considered the gold standard and established migraine diagnosis by a telephone interview of 50

randomly selected patients and 50 stroke-free control subjects enrolled at the Helsinki University Hospital, blinded to participants' status and clinical data. The diagnosis generated by the screener and the diagnosis made by the headache-neurologist were compared. Finally, the screener items were translated back and forth, and culturally adapted to local languages by a company experienced with translations of medical documents (TransPerfect Inc.) for the use in study centers.

Statistical analyses

We used Cohen's kappa statistics to measure agreement between the screener and gold standard,[29] with kappa-value over 0.75 considered as an excellent agreement.[30] Sensitivity and specificity were calculated and we applied the Clopper-Pearson exact method to calculate their 95% confidence intervals (CIs).[31] 95% CIs for PPVs and NPVs were calculated with the standard logit method.[32]

For a matched case-control analysis, assuming a 15% prevalence of migraine among controls[33] an alpha of 5% and power of 90%, a minimum sample of 272 case-control pairs would have been sufficient to demonstrate an association with an odds ratio (OR) of 2.0 or greater (allowing detection an effect size which is at least as strong as reported in case-control and cohort studies for any migraine and MA[9,10]). Assuming stronger than expected association, with an OR of 2.5 or greater, a total of 146 case-control pairs would be sufficient, respectively. For MO, a considerably weaker association could be assumed;[9,10] to show hypothesized association with an OR of 1.5, 872 case-control pairs would be needed.

For univariate comparisons between cases and controls we used statistical testing appropriate for matched case-control studies: McNemar's test for dichotomized variables, Paired t-test for normally

distributed continuous variables (reported with mean ± standard deviation) and Wilcoxon signed rank test for non-normally distributed continuous variables (reported with median and interquartile range [IQR]). In analyses including patients or controls only, categorical variables were compared with the Chi square or Fisher's exact tests and ordinal variables with the Mantel-Haenzel test of trends.

To assess the association between migraine and CIS, we used conditional logistic regression to produce adjusted ORs and 95% CIs for the entire cohort and both sexes, with MA and MO compared to non-migraineur group. Covariates used for adjusting were selected based on differences between cases and controls, biological plausibility and existing evidence, including age, level of education, hypertension, diabetes mellitus, waist-to-hip ratio, physical inactivity, current tobacco smoking, heavy alcohol use, and use of oral estrogen. We created two models, the first adjusted for age and level of education and the second adjusted for demographics and vascular risk factors. Interaction between sex and MA was studied in the fully adjusted model of entire cohort.

Due to reduced statistical power in subgroup analyses and lacking association of MO with CIS, subsequent exploratory analyses were performed by comparing MA to non-migraineurs with unpaired data, using logistic regression. Sex-specific subgroup analyses included current smoking (no/yes), obesity (no/yes), heavy alcohol use (no/yes), and, in women, oral estrogen use (no/yes). Interaction terms (MA x risk factor) were applied in the fully adjusted models.

In PFO-specific analysis, participants undergoing TCD-BS were included and patients were compared with unmatched controls. Interaction between PFO and MA was studied in logistic regression adjusted for age, sex, level of education, and vascular risk factors by including the presence of PFO as a covariate and including an interaction term in the model.

We performed sensitivity analyses comparing performance of a limited set of screener questions using the first three questions only (Supplemental Table s3). Furthermore, we analyzed the association between migraine and CIS with comparing patients to controls who were identified strictly from population-based sources.Individual missing values were reported and since there were only few, participants with missing data in one of more of the covariates were excluded from the multivariable models. Statistical analyses used IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA) and R (http://www.r-project.org) version 3.4.3 "Kite-Eating Tree". A *P*-value of <0.05 was considered significant. Univariate *P*-values were adjusted for multiple comparisons with the Holm-Bonferroni method.[34]

Results

Validation and performance of the migraine screener

For the validation of the screener, we included 50 patients (median age 41 years; 23 women) and 50 control subjects (median age 42 years; 24 women) who provided a complete set of responses to the screener. Table 1 shows performance of the migraine screener against clinical diagnosis, including kappa values, sensitivity and specificity as well as positive and negative predictive values with their 95% CIs. The agreement was excellent for any migraine, MA, and MO, both in patients and controls. Screener sensitivity for any migraine and MA was lower for controls than for patients. Furthermore, screener sensitivity for MO was lower than for MA in both patients and controls.

Univariate comparison between patients and matched controls

To study associations, we included 347 patients with CIS (median age 40.6 years, IQR 34.1-45.7; 46.4% women) and 347 age- and sex-matched controls. Controls were slightly older than patients, with a mean difference of 0.6 years (95% CI 0.4-0.9). In patients, median delay from stroke to hospital admission was 0 (IQR 0-1) days and admission to study inclusion/interview 6 (IQR 3-9) days. Median NIHSS score on admission was 2 (IQR 0-4, range 0-17). There were 8 (2.3%) patients fulfilling the ICHD criteria for migrainous infarction.

Compared to controls, patients with CIS had a lower level of education, a higher waist-to-hip ratio, and they were more often current tobacco smokers and heavy alcohol users. Patients had more frequently any migraine and MA. Compared to female controls, female patients had a lower level of

education, a higher waist-to-hip ratio, and more frequently any migraine and MA. Female controls had no diabetes mellitus. Compared to male controls, male patients had a lower level of education, higher waist-to-hip ratio, and they were more often heavy alcohol users and current smokers. Also male patients had more frequently any migraine and MA compared to controls. Overall, there were very few participants with pre-existing cardiovascular disease (Table 2).

Association between migraine and CIS

Adjusted for demographic factors, conditional logistic regression demonstrated an association between any migraine and MA with CIS both in women and men. After further adjustment for vascular risk factors, these associations remained robust (Table 3). Although the point estimate was higher in women, there was no formal interaction between MA and sex (P=0.496).

In the exploratory subgroup analysis among women, we found no interaction between MA and estrogen use, current smoking, obesity, and heavy alcohol use. Subgroup analyses suggested a lower stroke risk with MA in men with current smoking and heavy alcohol use (Table 4).

Subgroup analysis in participants screened for PFO

TCD-BS was performed in 187 (53.9%) patients and 155 (44.7%) controls, with PFO found in 122 (65.2%) patients and 55 (35.5%) controls, respectively (P<0.001). There was neither sex difference in the prevalence of PFO among patients (women 67.0% vs. men 63.5%; P=0.647) nor controls (women 41.7% vs. men 30.1%; P=0.356).

Compared to patients without PFO, those with PFO trended to have a higher prevalence of MA (45.9% vs. 29.2%; *P*=0.054). The prevalence of MA increased with increasing volume of RLS (29.2% for no RLS, 37.9% for small RLS, 46.7% for moderate RLS, and 49.4% for severe RLS; *P*=0.042). The frequency of stable vs. active PFO was not different in patients with MA (40.4% vs. 50.7%; *P*=0.272).

Comparing controls with and without PFO, no difference in the prevalence of MA (13.0% vs. 8.0%; *P*=0.644) was observed. In controls, there was no obvious trend in the prevalence of MA with volume of RLS (8.0% for no RLS, 10.7% for small, 9.1% for moderate, 20.0% for severe RLS; *P*=0.570). The frequencies of stable and active PFO were not different in controls with MA (12.1% vs. 14.1%; *P*=1.000).

Logistic regression analysis adjusted for demographics and vascular risk factors demonstrated a significant association between MA and CIS irrespective of PFO (Table 5).

Sensitivity analyses

Sensitivity analyses showed a poorer performance of the migraine screener if the first three questions were used. Cohen's kappa values for MA and MO were 0.80 and 0.64 for patients, along with 0.88 and 0.75 for controls, respectively (Supplemental Table s4).

When selecting case-control pairs with strictly population-based controls (n=214 pairs), any migraine (OR 3.09, 95% CI 1.74-5.50) and MA (OR 4.60, 95% CI 2.34-9.08) remained associated with CIS in

fully adjusted matched conditional logistic regression. The associations were significant regardless of sex (Supplemental Table s5).

Discussion

We demonstrated a robust independent association between MA with CIS in young adults even after adjusting for multiple well-known confounders. This association seemed not to be affected essentially by sex and concomitant habitual risk factors. Furthermore, we found that the increased risk of CIS with MA occurred irrespective of the presence of PFO.

In the most recent meta-analyses, pooled adjusted OR for ischemic stroke in patients with MA was 2.25 (95% CI 1.53-3.33) in case-control and cohort studies together[9] whereas relative risk was 2.14 (95% CI 1.33-3.43) in cohort studies.[10] Neither of these meta-analyses demonstrated elevated risk of ischemic stroke for MO. Similar magnitude of heightened risk was observed in a recent population-based cohort study for both MA and MO,[35] yet acknowledging that risk estimates and methods to ascertain migraine diagnosis in case-control and longitudinal studies are not fully comparable. In our study, the association between MA and CIS was stronger than that reported for non-selected ischemic strokes in prior studies, which indicates that MA is a more profound risk factor particularly for early-onset CIS than for ischemic strokes of defined etiologies at younger ages or in general. Our study found no association with MO and CIS, but was underpowered to detect a weak effect, and thus firm conclusion on this question cannot be drawn.

The three case-control studies specifically reporting association between migraine and CIS (Supplemental Table s1)[16-18] did not show significant associations when adjusted for vascular comorbidities. One of these studies found a relatively weak association (OR 1.6, 95% CI 1.1-2.3) between probable migraine with visual aura and CIS in women aged <50 years when adjusted for age, race, and geographic region, but this association diminished after further adjustment.[17] In contrast

to our findings, a recent population-based study comparing patients with cryptogenic transient ischemic attack (TIA) and ischemic stroke to those with known etiologies found migraine diagnosis to be significantly associated with the event only at older age (≥65 years, OR 1.8, 95% CI 1.4-2.4) but not at younger age (≤55 years, OR 1.1, 95% CI 0.6-2.2).[18] However, number of patients in the youngest age group was limited (n=89) in that study.

We observed a strong association between MA and CIS in both sexes, the point estimate being more profound in women. This finding is in accordance with findings from studies assessing non-selected ischemic stroke cases, however, the association in male sex has remained inconclusive.[9] Potential reasons for the sex difference include interaction with sex-specific risk factors, such as estrogen use, as well as habitual risk factors such as smoking. However, we did not find significant interaction between MA and female sex, or between MA andestrogen use and smoking in women, as previously documented.[38] That occurred possibly because of lower estrogen doses in the present time compared to that some decades ago and because relatively few women were smoking in our cohort. Interestingly, though, we found an interaction between MA and smoking and heavy alcohol use in men, but these interactions indicated no additive effect from these risk factors. Although our subgroup analyses were exploratory only, these findings strengthens the view that MA is an independent risk factor for CIS also in men and irrespective of habitual risk factors.

Potential mechanisms explaining the increased risk of ischemic stroke with MA are complex and include cerebral microcirculatory vasoconstriction induced by cortical spreading depression, vasospasm in the larger intracerebral arteries, increased platelet aggregation, increased concentrations of procoagulant factors, endothelial dysfunction, as well as paradoxical embolism via PFO.[36,37] One of the factors explaining the strong association between MA with CIS particularly in young adults

could be their high frequency of PFO.[13,14] Paradoxical embolism, serotonin-induced platelet activation, and transient hypoxemia leading to increased expression of plasminogen activator-1 and suppression of fibrinolysis have been suggested to be specific factors linking ischemic stroke, PFO, and migraine, with substantial uncertainty, however.[36, 37] Our study, with the increasing prevalence of MA with increasing RLS magnitude, supports the theory that PFO and MA are interconnected in the pathogenesis of CIS. We observed no clear relationship between RLS magnitude and prevalence of MA in stroke-free controls, raising a novel hypothesis: is the pathophysiology of MA in PFO patients suffering a CIS distinct, favoring e.g. development of thrombosis in the venous system as paradoxical embolism would require a venous thrombosis in the legs or pelvis? Supporting the hypothesis of paradoxical embolism as a common mechanism for both MA and PFO-related CIS in the young is the relatively new finding of the increased risk of venous thromboembolism in young patients with MA.[35,39]

Nevertheless, since we ound that the association between MA and CIS was independent of the presence of PFO, there likely are other profound factors explaining the heightened risk of stroke in patients with MA. Such factors include common genetic precipitants linking migraine to more generalized cardiovascular and endothelial involvement, as suggested by observational[35] and genome-wide association studies.[40]

The previously reported MISS screener, which was assessed in patients with ischemic or hemorrhagic stroke, or TIA, had a sensitivity of 0.47 (95% CI 0.31-0.62) and a specificity of 0.97 (95% CI 0.93-0.99) and performed poorly in identifying MA.[35] Our migraine screener appeared to perform reasonably well against an experienced blinded headache specialist. Sensitivity analyses showed that by using a more limited set of screener questions the accuracy was lower, stressing the importance of

including questions on ancillary headache characteristics in the screener. In addition to screener properties, also population characteristics (young vs. elderly, differing risk factors and etiologic spectrum, degree of neurological deficits) may explain the differences in the performance of our screener compared to MISS screener. It is notable, that we required only two questions for the diagnosis of MA and included those experiencing migraine auras without headache as having MA. Furthermore, the performance of our screener was more modest for MO and it does not characterize the proportion of MO attacks among patients with both types of attacks. Therefore, we may underestimate the prevalence of MO to some degree. Additional limitations of our screener include that it considers only visual aura and does not gather details on visual aura symptoms or other types of aura symptoms.

Treatment aspects in patients with CIS and MA deserve a comment. Aspirin seems a reasonable first-line option for antithrombotic medication in secondary prevention after CIS, as evidence from randomized controlled trials suggests aspirin can reduce the frequency of migraine attacks.[41] However, optimal dosage is unclear. It is unknown, whether reducing the frequency of migraine attacks can prevent from recurrent strokes in patients with CIS, but especially in hypertensive patients with CIS and frequent or severe attacks, it may be reasonable to consider candesartan or beta-blockers as first-line options due to their favorable effects on migraine frequency.[42] However, these and other measures of migraine prevention specifically in post-stroke setting should be further investigated.

The most notable overall strengths of our study include the robustness of the study protocol, prospective design, an extensive and timely diagnostic work-up, inclusion of only imaging-verified ischemic strokes, as well as structured data collection. All participants were examined in a standardized manner, with only few missing data, and migraine was defined according to ICHD,

reducing misclassification bias. Moreover, we were able to consider multiple relevant confounders in our multivariable analyses.

Our study does not go without limitations. Shortcomings inherent to any other case-control study apply also to our study. While the aim was to enroll consecutive patients, we cannot fully exclude the possibility of some selection. Patients included had relatively mild strokes while some patients with more severe symptoms may have been left out from the study. As we interviewed our patients relatively soon after their stroke with all their deficits, there might be some inaccuracies among the interviewed study items, including questions on migraine, which might have led to misclassification. The prevalence of migraine in our control subjects was higher than that in the general population, which may indicate that controls with suspected migraine might have been more willing to participate in this kind of study, as observed also previously.[17] However, this should have led to underestimation, rather than overestimation of the effect size in our study and when restricting the analysis strictly to population-based controls, our key findings remained robust and nearly unchanged. Finally, we used TCD-BS to define PFO instead of echocardiography as TCD-BS was obtainable from a substantial number of stroke-free controls. TCD-BS is a sensitive method to detect RLS, but cannot characterize the anatomic site of RLS. It is likely that RLS occurring at other sites than PFO might be present in our participants, as also control subjects had a relatively high proportion of RLS (35.5%). However, that proportion is only slightly higher than the 31.3% estimated with TCD-BS in the population.[43]

Conclusions

To the best of our knowledge, our study is the first to conclusively demonstrate that MA is a vigorous player underlying CIS among young adults, regardless of sex, and independent of vascular risk factors. Furthermore, the association remained robust independent of PFO, albeit in patients with PFO the prevalence of MA increased with increasing magnitude of RLS. Future studies should explore in depth the mechanisms and associated features increasing the risk of CIS in patients with MA, such as activity, recent onset, and lifetime burden of migraine attacks, specific cardiovascular structural and functional properties, coagulation abnormalities, and shared genetic underpinnings.

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Figure legend

Figure. Decision algorithm to reach migraine diagnosis in the study based on 3 screening and 6 ancillary questions.

Table Legends

Table 1. Comparison of performance of migraine screener with an independent experienced senior headache-neurologist blinded to participant clinical data.

Table 2. Characteristics of young cryptogenic ischemic stroke patients and stroke-free control subjects included in the study.

Table 3. Odds ratios and 95% confidence intervals from conditional logistic regression on the association between migraine and cryptogenic ischemic stroke.

Table 4. Exploratory subgroup analyses on the association between migraine with aura (MA) and cryptogenic ischemic stroke.

Table 5. Logistic regression analyses on the association between migraine with aura (MA) and cryptogenic ischemic stroke in participants screened for patent foramen ovale (PFO).

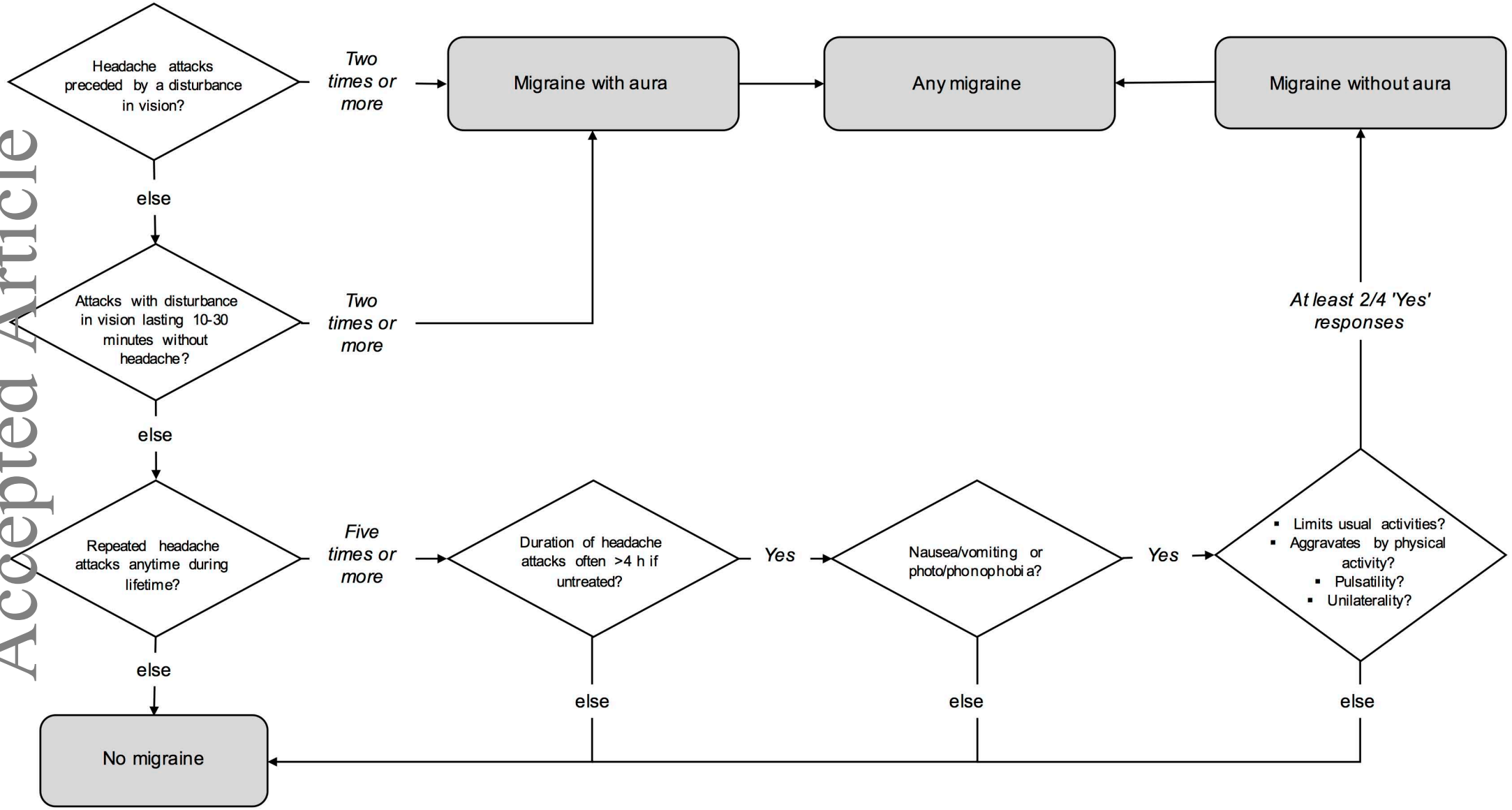

Table 1. Comparison of performance of migraine screener with an independent experienced senior headache-neurologist blinded to participant clinical data.

	Patients (n=50)	**Controls (n=50)**
Any migraine		
Screener	26 (52)	14 (28)
Headache-neurologist	28 (56)	17 (34)
Cohen's Kappa	0.84	0.77
Sensitivity	89.3 (71.2-97.7)	76.5 (50.1-93.2)
Specificity	95.5 (77.2-99.2)	97.0 (84.2-99.9)
Positive predictive value	96.2 (78.6-99.4)	92.9 (64.9-98.9)
Negative predictive value	87.5 (70.5-95.3)	88.9 (77.2-95.0)
Migraine with aura		
Screener	22 (44)	5 (10)
Headache-neurologist	22 (44)	7 (14)
Cohen's Kappa	0.84	0.81
Sensitivity	90.9 (70.8-98.9)	71.4 (29.0-96.3)
Specificity	92.9 (76.5-99.1)	98.5 (91.8-99.3)
Positive predictive value	90.9 (72.3-97.5)	100 (91.6-100)
Negative predictive value	92.9 (77.6-98.0)	95.6 (86.9-98.6)
Migraine without aura		
Screener	4 (8)	9 (18)
Headache-neurologist	6 (12)	10 (20)
Cohen's Kappa	0.78	0.81
Sensitivity	66.7 (22.3-95.7)	80.0 (44.4-97.5)
Specificity	100 (91.9-100)	97.5 (86.8-99.9)
Positive predictive value	100 (92.3-100)	88.9 (52.9-98.3)
Negative predictive value	95.7 (87.7-98.6)	95.1 (84.9-98.5)

Data are n (%) or % and 95% confidence interval.

Table 2. Characteristics of young cryptogenic ischemic stroke patients and stroke-free control subjects included in the study.

	All		Women		Men	
Characteristic (no. of participants with missing data)	**Patients (n=347)**	**Controls (n=347)**	**Patients (n=161)**	**Controls (n=161)**	**Patients (n=186)**	**Controls (n=186)**
Level of education (6)						
Primary or lower secondary	38 (11.0)	9 (2.6)	12 (7.5)	2 (1.3)	26 (14.0)	7 (3.8)
Upper secondary	153 (44.2)	110 (32.2)	67 (41.9)	52 (32.7)	86 (46.2)	58 (31.7)
Post-secondary or tertiary	155 (44.8)	223 (65.2)*	81 (50.6)	105 (66.0)*	74 (39.8)	118 (64.5)*
Hypertension (1)	115 (33.1)	92 (26.6)	47 (29.2)	38 (23.8)	68 (36.6)	54 (29.0)
Diabetes mellitus (1)	13 (3.7)	6 (1.7)	6 (3.7)	0	7 (3.8)	6 (3.2)
Cardiovascular disease (1)	1 (0.3)	1 (0.3)	1 (0.6)	0	0	1 (0.5)
History of VTE (1)	11 (3.2)	3 (0.9)	6 (3.7)	1 (0.6)	5 (2.7)	2 (1.1)
Current tobacco smoking (3)	114 (32.9)	66 (19.1)*	40 (25.0)	32 (19.9)	74 (39.8)	34 (18.5)*
Use of oral estrogen (0)	NA	NA	36 (22.4)	24 (14.9)	NA	NA
Physical inactivity (0)	49 (14.1)	40 (11.5)	21 (13.2)	17 (10.7)	28 (15.2)	23 (12.6)
Waist-to-hip ratio (4)	0.90 (0.10)	0.87 (0.09)*	0.85 (0.11)	0.81 (0.07)*	0.94 (0.07)	0.92 (0.08)*
Obesity‡	202 (58.7)	156 (45.1)*	67 (42.1)	41 (25.6)*	135 (73.0)	115 (61.8)
Heavy alcohol use (1)	74 (21.3)	45 (13.0)*	31 (19.3)	22 (13.8)	43 (23.1)	23 (12.4)*
Migraine status (3)						
No migraine	191 (55.2)	257 (74.5)	69 (43.1)	109 (68.6)	122 (65.6)	148 (79.6)
Migraine with aura	140 (40.5)	56 (16.2)*	82 (51.2)	29 (18.2)*	58 (31.2)	27 (14.5)*
Migraine without aura	15 (4.3)	32 (9.3)	9 (5.6)	21 (13.2)	6 (3.2)	11 (5.9)
Any migraine (3)	155 (44.8)	88 (25.5)*	91 (56.9)	50 (31.4)*	64 (34.4)	38 (20.4)*

Data are n (%) or mean (standard deviation).

VTE, venous thromboembolism; NA, not applicable.

*P<0.05.

‡>0.85 in women, >0.90 in men.

Table 3. Odds ratios and 95% confidence intervals from conditional logistic regression on the association between migraine and cryptogenic ischemic stroke.

	Model adjusted for age and level of education	**Model adjusted for demographics and vascular risk factors***
All		
Migraine status		
No migraine	Reference	Reference
Migraine with aura	3.40 (2.20-5.25)	3.50 (2.19-5.61)
Migraine without aura	0.66 (0.31-1.39)	0.60 (0.27-1.31)
Any migraine vs. no migraine	2.48 (1.68-3.65)	2.48 (1.63-3.76)
Women		
Migraine status		
No migraine	Reference	Reference
Migraine with aura	4.14 (2.22-7.73)	4.32 (2.16-8.65)
Migraine without aura	0.66 (0.31-1.39)	0.63 (0.22-1.82)
Any migraine vs. no migraine	3.04 (1.73-5.34)	2.97 (1.61-5.47)
Men		
Migraine status		
No migraine	Reference	Reference
Migraine with aura	2.89 (1.54-5.41)	3.61 (1.75-7.45)
Migraine without aura	0.52 (0.16-5.41)	0.56 (1.15-2.14)
Any migraine vs. no migraine	2.04 (1.19-3.49)	2.47 (1.32-4.61)

*Adjusted for age, level of education, hypertension, diabetes, current tobacco smoking, physical inactivity, heavy alcohol use, and waist-to-hip ratio. In women, models were further adjusted for oral estrogen use but not for diabetes due to its low frequency.

Table 4. Exploratory subgroup analyses on the association between migraine with aura (MA) and cryptogenic ischemic stroke.

	Participants with MA **No. patients/ No. controls**	**Participants without migraine** **No. patients/ No. controls**	**Unadjusted odds ratio (95% confidence interval)**	***P* for interaction***
Women				
Current smoking				0.524
No	61/22	51/88	4.78 (2.63-8.69)	
Yes	20/7	17/21	3.53 (1.21-10.31)	
Obesity				0.921
No	46/21	40/84	4.60 (2.43-8.71)	
Yes	36/8	26/24	4.15 (1.61-10.70)	
Heavy alcohol use				0.251
No	66/27	56/92	4.02 (2.30-7.01)	
Yes	16/2	12/17	11.33 (2.19-58.73)	
Oral estrogen use				0.618
No	68/25	51/92	4.91 (2.77-8.69)	
Yes	14/4	17/17	3.50 (0.96-12.83)	
Men				
Current smoking				<0.001
No	43/17	67/123	4.64 (2.46-8.77)	
Yes	15/10	54/23	0.64 (0.25-1.63)	
Obesity				0.389
No	17/9	31/58	3.53 (1.41-8.85)	
Yes	40/18	90/90	2.22 (1.19-4.17)	
Heavy alcohol use				0.049
No	46/21	92/131	3.12 (1.75-5.58)	
Yes	12/6	29/17	1.17 (0.37-3.70)	

**P*-value from adjusted logistic regression with interaction term. In women, covariates included age, hypertension, current tobacco smoking, physical inactivity, heavy alcohol use, obesity, and oral estrogen use. In men, covariates included age, hypertension, diabetes, current tobacco smoking, physical inactivity, heavy alcohol use, and obesity.

Table 5. Logistic regression analyses on the association between migraine with aura (MA) and cryptogenic ischemic stroke in participants screened for patent foramen ovale (PFO).

	Participants with MA **No. patients/ No. controls**	**Participants without migraine** **No. patients/ No. controls**	**Unadjusted odds ratio (95% confidence interval)**	***P* for interaction***
PFO status				0.883
Absent	19/8	36/78	5.15 (2.06-12.86)	
Present*	56/7	62/42	5.42 (2.25-13.04)	

**P*-value from model adjusted for age, sex, level of education, hypertension, diabetes, current tobacco smoking, physical inactivity, heavy alcohol use, waist-to-hip ratio, and oral estrogen use.