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# Atrial fibrillation and migraine with aura in young adults with ischemic stroke

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## Abstract

**Background:** Migraine is associated with an increased risk of ischemic stroke. The associations are stronger in migraine with aura than in migraine without aura, in women than in men, and in younger subjects. However, the mechanisms by which migraine might increase the risk of ischemic stroke are debated.

**Methods:** We analysed the associations between migraine without aura and migraine with aura and the causes of ischemic stroke in patients aged 18–54 years treated consecutively in a university hospital stroke center.

**Results:** A total of 339 patients (mean/SD age 43.8/8.8 years, 62.83% male) were included. Migraine with aura was diagnosed in 58 patients, and migraine without aura in 54 patients. Patients with migraine with aura were younger and had fewer traditional cardiovascular risk factors than patients with no migraine. Migraine with aura was strongly associated with atrial fibrillation (odds ratio, 5.08; 95% confidence interval, 1.24–21.92;  $p = 0.011$ ) and negatively associated with atherosclerosis (odds ratio, 0.29; 95% confidence interval, 0.05–0.97;  $p = 0.033$ ) and small vessel disease (odds ratio, 0.13; 95% confidence interval, 0.00–0.87;  $p = 0.022$ ). No other cause of stroke was significantly associated with migraine. The most common cause of stroke was atherosclerosis in no-migraine patients, dissection in migraine without aura patients and patent foramen ovale in migraine with aura patients. Atrial fibrillation was, together with dissection, the second leading cause of stroke in migraine with aura patients, accounting for 10.34% of cases in this subgroup.

**Conclusion:** We showed that atrial fibrillation was a common cause of ischemic stroke in young adults with migraine with aura.

## Keywords

Stroke, migraine, ASCOD, atrial fibrillation

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## Introduction

Migraine is associated with an increased risk of ischemic stroke. The associations are stronger in migraine with aura (MWA) than in migraine without aura (MWOA), in women than in men, and in younger subjects (1).

The mechanisms by which migraine might increase the risk of ischemic stroke are debated and possibly multifactorial. Previous studies have shown associations of MWOA with dissection (2,3), MWA with patent foramen ovale (PFO) (4–6), especially PFO combined with atrial septal aneurysm (ASA) (7), and MWA with atrial fibrillation (8–10). However, because these studies focused on one particular cause of stroke, they do not allow for an assessment of the relative

importance of each potential cause of stroke in migraine sufferers. In elderly persons, MWA has been associated with atrial fibrillation in populations with (10) and without (8) ischemic stroke. In younger persons, MWA has been associated with atrial fibrillation (9), but the association of MWA and atrial fibrillation

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in a cohort of ischemic stroke patients has not been determined.

In a large series of young adults treated consecutively for acute ischemic stroke in a university hospital, we sought to determine associations between MwoA and MWA and the causes of ischemic stroke.

## Methods

This was a single-centre study conducted in a University Hospital stroke unit between January 2017 and June 2019, including patients aged 18–54 consecutively treated for first-ever acute ischemic stroke. Data were retrospectively reviewed using the electronic data base of our institution. Patients with cerebral venous thrombosis, subarachnoid hemorrhage with secondary brain ischemia, or transient ischemic attack as defined by transient neurological dysfunction without evidence of infarction on brain imaging were excluded. Non-inclusion criteria were death in the acute phase of stroke, persistent severe aphasia, psychiatric or cognitive disorders, language barrier, and missing data.

All patients were evaluated by the same headache specialist to determine the diagnosis of migraine with aura (MWA) and migraine without aura (MwoA) according to the International Classification of Headache Disorders, 3rd edition (ICHD-3) (11). Migraine assessment was performed during the initial hospitalisation or, in case of regressive aphasia, during the subsequent outpatient visit approximately 3 months later. Active migraine was defined by the occurrence of at least one migraine attack during the last year. Other collected migraine characteristics included the number of migraine attacks in the last year, the type and frequency of auras, the use of triptans and preventive treatments.

Overweight was defined as body mass index  $> 25$ . Hypertension was defined as persistent systolic blood pressure  $> 130$  mm Hg or diastolic blood pressure  $> 80$  mm Hg documented before stroke, or treatment with antihypertensive drugs before stroke (12). Diabetes was defined as previous diagnosis of type 1 or type 2 diabetes. Tobacco use was recorded in patients currently smoking. Hyperlipidemia was defined as elevated low-density lipoprotein cholesterol  $> 1.6$  g/L or hypertriglyceridemia  $> 2.0$  g/L.

The cause of stroke was diagnosed using a progressive diagnostic algorithm (13). The initial work-up, performed in all patients, included brain MRI or CT when MRI was contraindicated, ECG, routine blood studies (complete blood cell count, prothrombin time, activated partial thromboplastin time, fibrinogen, D-dimer, C-reactive protein, serum creatinine, glucose, cholesterol, and triglyceride concentrations) and angiography of cerebral and cervical vessels using magnetic

resonance and/or CT angiography. We used axial T1-weighted MRI scans with fat saturation for the diagnosis of arterial dissection. Carotid atherosclerosis was further evaluated with carotid ultrasound duplex. ECG monitoring using inpatient telemetry for 72 h was performed in all patients without definite cause of stroke on initial workup. Transesophageal echocardiography (TEE) and transthoracic echocardiography were also performed in patients without definite cause of stroke on initial workup. Patent foramen ovale (PFO) was assessed at rest and during provocative manoeuvres using IV injection of agitated saline. PFO and atrial septal aneurysm (ASA) were diagnosed using criteria published previously (14,15). Searching for atrial fibrillation was completed by a 24-h Holter ECG and, in selected patients, by prolonged non-invasive or invasive ECG-monitoring. Further investigations (e.g. testing for acquired or genetic thrombophilia, CSF analysis, searching for active malignancy, testing for genetic leukoencephalopathies) were performed in patients with suggestive medical history or clinical findings and in patients without potential cause of stroke on initial workup and cardiac evaluation.

All individual data were reviewed by a senior vascular neurologist and the causes of stroke were classified using the ASCOD (A: atherosclerosis; S: small-vessel disease; C: cardiac pathology; O: other causes) classification system (16). A potential cause of stroke was defined as an ASCOD grade 1 cause of stroke. We also identified patients with PFO among those with no grade 1 cause of stroke. PFO with ASA (PFO-ASA) and large PFO ( $> 30$  bubbles) were classified as high-risk PFO (17).

## Data analysis

Data are reported as mean with standard deviation or number and percentage. MwoA and MWA patients were compared to patients with no migraine (NM patients). Quantitative variables were compared with Student's *t*-test and qualitative variables with Fisher's exact test and using unadjusted odds ratios (OR) with their 95% confidence intervals (CI). All tests were bilateral. Significance was set at  $p < 0.05$ . Statistics were performed using R statistical software v4.0.0.

## Ethics

The study conformed to the principles outlined in the Declaration of Helsinki. All patients were informed that clinical data collected during their hospitalisation could be used for research purpose and gave their consent. The study was approved by our Institutional Review Board (internal reference RnIPH 2020-28).

## Data availability

Anonymised data not published within this article will be made available by request from any qualified investigator.

## Results

### Population

A total of 376 patients aged 18–54 years (mean age [SD] 43.88 [8.89] years, 62.83% male) were treated for first-ever ischemic stroke at our institution during the study period. Thirty-seven patients were not included. Reasons for non-inclusion were: Fatal stroke (7), persistent severe aphasia (9), language barrier (9), cognitive or psychiatric disorder (6), and missing data (6). Among the 339 included patients, 58 had MWA (16.81%) and 54 had MWoA (16.22%) (Figure 1).

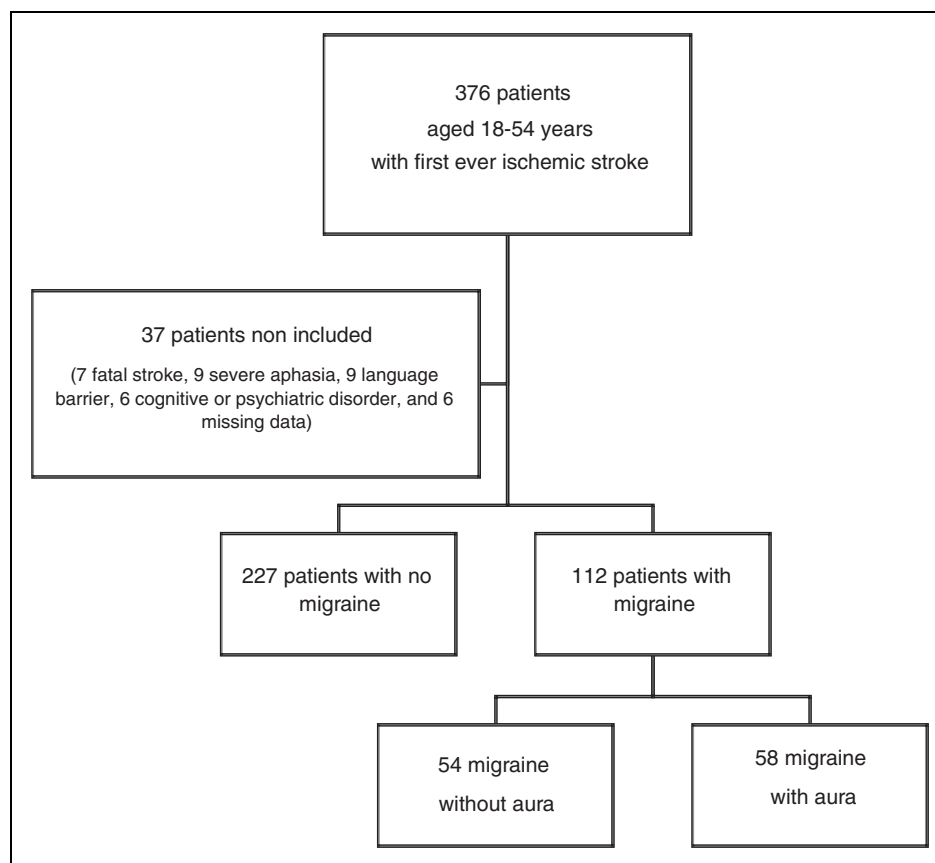
Patient characteristics are presented in Table 1. Migraine sufferers were younger than NM patients and there were more women among them. Hypertension in MWA and overweight in MWoA were less common than in NM patients. Diabetes,

hyperlipidemia, tobacco and oestrogen use were of similar prevalence in the three subgroups.

Characteristics of migraine are presented in Table 2. Among migraineurs, one patient suffered from chronic migraine, and nine patients had an inactive migraine defined by the absence of any migraine attack during the last year. Three MWoA patients were on preventive treatment (aspirin in one patient, a beta-blocker in two patients). Nine patients (four MWoA and five MWA) used a triptan for the treatment of their migraine attack. Only one MWoA patient, whose stroke was attributed to atherosclerosis, had taken a triptan the day of stroke. The aura was visual in 56 (96.55%) patients, sensory in eight (13.79%) patients and dysphasic in three (5.17%) patients.

### ASCOD grade I causes of stroke

There were no differences in the causes of stroke between MWoA patients and NM patients. In contrast, atherosclerosis (OR, 0.29; 95% CI [0.05–0.97];  $p=0.033$ ) and small vessel disease (OR, 0.13; 95% CI [0.00–0.87];  $p=0.022$ ) were significantly less common in MWA patients than in NM patients. The prevalence



**Figure 1.** Study flow chart.

**Table 1.** Patient characteristics. *p*-values are given for MWoA and MWA vs. no migraine.

	No migraine (n = 227)	MWoA (n = 54)	<i>p</i> -value	MWA (n = 58)	<i>p</i> -value
Women (%)	60 (26.43)	36 (66.67)	<0.0001	30 (51.72)	0.0004
Age, mean (sd), years	45.07 (8.31)	42.17 (9.39)	0.040	40.85 (9.73)	0.003
BMI, mean (sd), kg/m <sup>2</sup>	26.42 (4.99)	24.84 (5.73)	0.069	25.23 (5.19)	0.122
Overweight (%)	118 (51.98)	18 (33.33)	0.013	26 (44.83)	0.298
Hypertension (%)	81 (35.68)	14 (25.93)	0.201	9 (15.52)	0.002
Diabetes (%)	15 (6.61)	5 (9.26)	0.551	4 (6.90)	1
Hyperlipidemia (%)	48 (21.15)	8 (14.81)	0.347	9 (15.52)	0.461
Tobacco use (%)	117 (51.54)	29 (53.70)	0.879	23 (39.66)	0.140
Use of oestrogen (%)	9 (15.00)	9 (25.00)	0.168	5 (16.66)	1

**Table 2.** Characteristics of migraine.

Characteristics of migraine, mean (SD)	MWoA (n = 54)	MWA (n = 58)
Age at first migraine attack, years	21.58 (11.33)	22.34 (10.42)
Duration of migraine, years	20.92 (12.43)	18.81 (11.48)
Annual frequency of migraine attacks, years	15.36 (14.76)	15.84 (17.28)
Age at first MWA attack, years	–	25.70 (11.68)
Duration of MWA since the first aura, years	–	15.17 (12.30)
Percentage of MWA attacks (%)	–	71.98

**Table 3.** ASCOD Grade I causes of stroke in MWoA patients and MWA patients compared to NM patients.

	NM (n = 227)	MWoA (n = 54)	OR [95% CI]	MWA (n = 58)	OR [95% CI]
Atherosclerosis, n (%)	36 (15.86)	5 (9.26)	0.54 [0.15–1.49]	3 (5.17)	0.29 [0.05–0.97]*
Small vessel disease, n (%)	26 (11.45)	4 (7.41)	0.62 [0.15–1.90]	1 (1.75)	0.13 [0.003–0.87]†
Cardiac pathology, n (%)	16 (7.04)	3 (5.56)	0.77 [0.13–2.86]	9 (15.51)	2.41 [0.88–6.21]
Other cause, n (%)	15 (6.61)	7 (12.96)	2.09 [0.68–5.84]	5 (8.62)	1.33 [0.36–4.08]
Dissection, n (%)	23 (10.13)	8 (14.81)	1.54 [0.55–3.85]	6 (10.34)	1.02 [0.32–2.76]

NM: no migraine, MWoA: migraine without aura, MWA: migraine with aura.

\**p* = 0.033; †*p* = 0.022.

of grade 1 cardiac pathology was not statistically different between MWA and NM patients (Table 3).

The most common grade 1 cardiac pathology was atrial fibrillation (five NM, six MWA), followed by dilated cardiomyopathy (two NM, one MWA), left ventricular mural thrombus (three NM), heart failure with left ventricular ejection fraction < 35% (two NM), mechanical valve (two NM), infectious endocarditis (one NM, one MWA), papillary fibroelastoma (one MWoA, one MWA), left atrial myxoma (one MWoA), left ventricular aneurysm (one NM), left ventricular non-compaction cardiomyopathy (one MWoA).

Atrial fibrillation was significantly more frequent in MWA patients (10.34%) than in NM patients (2.20%), (OR, 5.08; 95% CI [1.24–21.92]; *p* = 0.011) (Table 4). This result could not be explained by differences in the

duration of ECG monitoring, which was similar in the three subgroups (Table 5). Atrial fibrillation was paroxysmal in the six MWA patients and in 3/5 NM patients. It was unknown before stroke in the six MWA patients and in 3/5 NM patients.

### PFO

No grade 1 cause of stroke was found in 174 (51.33%) patients, including 111 (48.89%) NM patients, 27 (50%) MWoA patients, and 34 (58.62%) MWA patients. Assessment of PFO and ASA with TEE was performed in 104/113 (93.69%) NM patients, 25/27 (92.59%) MWoA patients and 30/34 (88.23%) MWA patients. There were no significant differences in the prevalence of PFO, PFO-ASA and high-risk PFO between subgroups (Table 4).

**Table 4.** Cardiac pathology. High risk PFO was defined as PFO + ASA or large PFO.

	NM (n = 227)	MWoA (n = 54)	OR [95% CI]	MWA (n = 58)	OR [95% CI]
Atrial fibrillation, n (%)	5 (2.20)	0 (0.00)	–	6 (10.34)	5.08 [1.24–21.92]*
Other ASCOD grade I cardiac pathology, n (%)	11 (4.84)	3 (5.56)	1.15 [0.19–4.58]	3 (5.17)	1.07 [0.18–4.24]
PFO, n (%)	40 (17.62)	9 (16.67)	0.93 [0.37–2.14]	13 (24.14)	1.34 [0.60–2.84]
PFO + ASA, n (%)	21 (9.25)	6 (11.11)	1.22 [0.38–3.36]	7 (12.07)	1.34 [0.45–3.51]
High risk PFO, n (%)	28 (12.33)	7 (12.96)	1.05 [0.36–2.67]	10 (17.24)	1.47 [0.59–3.40]

PFO: patent foramen ovale; ASA: atrial septal aneurysm; NM: no migraine; MWoA: migraine without aura; MWA: migraine with aura.

\* $p = 0.011$ .

**Table 5.** Duration of ECG monitoring by subgroups in patients without ASCOD grade I on initial workup.

	Controls (n = 117)	MWoA (n = 27)	MWA (n = 41)	<i>p</i>
72h ECG monitoring by in-patient telemetry, n (%)	115 (98.29)	27 (100)	40 (97.56)	1
Holter 24 h, n (%)	84 (71.79)	17 (62.96)	29 (70.73)	0.654
Holter 3–7 days, n (%)	24 (20.51)	9 (33.33)	13 (32.70)	0.184
Cardiac insertable device, n (%)	14 (11.96)	3 (11.11)	6 (14.63)	0.946

### Most common causes of stroke by subgroups

Major causes of stroke by subgroups are depicted in Figure 2. The four most common causes of stroke were: High-risk PFO, atrial fibrillation, dissection and atherosclerosis in MWA; dissection, high-risk PFO, atherosclerosis and small vessel disease in MWoA; atherosclerosis, high-risk PFO, small vessel disease, and dissection in NM.

Only one stroke was classified as migrainous infarction as defined by the ICHD-3.

### Discussion

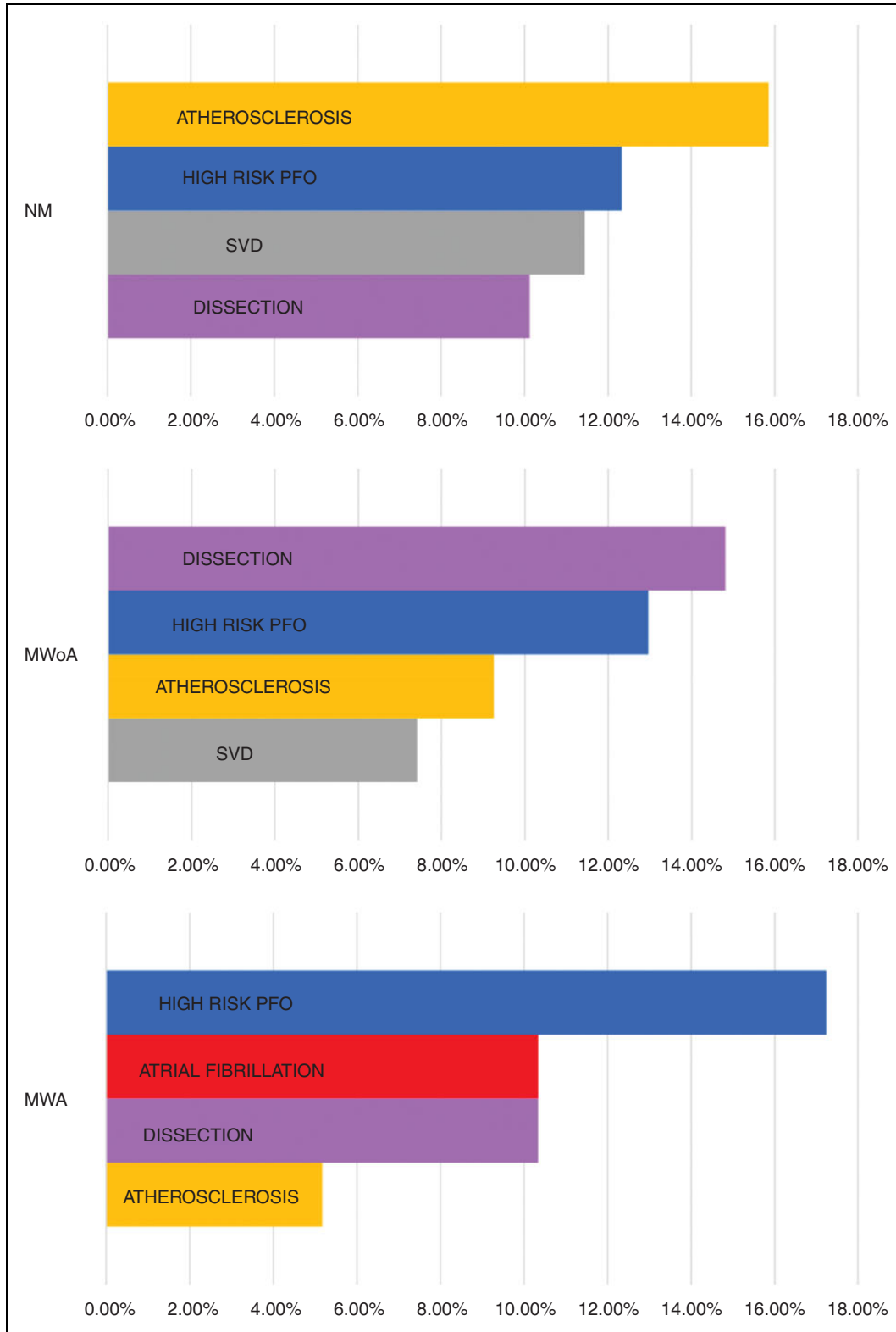
This study in young ischemic stroke patients showed a strong association of MWA with atrial fibrillation, as well as negative associations of MWA with atherosclerosis and small vessel disease.

A link between MWA and atrial fibrillation was reported in two previous studies. A Danish nationwide population-based cohort study showed an increased incidence of atrial fibrillation in people with MWA. This study also confirmed the increased incidence of ischemic stroke in MWA but the association of MWA and atrial fibrillation in the ischemic stroke cohort was not reported. In the Atherosclerosis Risk in Communities study, an increased risk of cardioembolic stroke was observed in elderly (mean age, 73.7 years) patients with MWA (10). The vast majority (87%) of cardioembolic strokes were attributed to atrial fibrillation (8). In contrast, a recent study using Mendelian randomisation and genome-wide

association studies showed no association between migraine and atrial fibrillation. However, results regarding the association of MWA with atrial fibrillation have not been reported (18). The present study is the first to our knowledge to demonstrate an association between MWA and atrial fibrillation in young ischemic stroke patients. Atrial fibrillation and dissection were the second leading causes of stroke in MWA patients, each accounting for 10.34% of strokes in this subgroup, whereas it was uncommon in NM and MWoA patients.

This association was not explained by differences in the duration of ECG monitoring, which was similar in all subgroups. In addition, patients with MWA were younger than NM patients, and other traditional risk factors for atrial fibrillation were less frequent (hypertension) in MWA than in NM patients or of similar prevalence (diabetes, overweight). Current use of non-steroidal anti-inflammatory drugs has been associated with atrial fibrillation (19). However, an impact of these drugs was unlikely in the present study because there was no case of atrial fibrillation among MWoA patients and because the risk of AF is associated to new use and not to long-term use, as is the case with migraine patients.

The mechanisms underlying the association of MWA with atrial fibrillation cannot be determined from our study. An autonomic dysfunction previously reported in migraine patients may play a role, as both vagal and sympathetic stimulation can promote atrial fibrillation (20,21). Conversely, it has been



**Figure 2.** Four leading causes of stroke in patients without migraine (NM), patients with migraine without aura (MWoA) and patients with migraine with aura (MWA).

SVD: small vessel disease; PFO: patent foramen ovale.

hypothesised that cardiogenic microemboli may be responsible for cortical spreading depression and migrainous aura (22).

The negative associations of MWA with atherosclerosis and small vessel disease were possibly explained by a lower prevalence of cardiovascular risk factors in patients with MWA. The relatively small numbers of patients with atherosclerosis or small vessel disease did not permit multivariate analysis to determine whether these associations remained significant in models adjusting for traditional risk factors.

Previous studies have shown the association of MWA with PFO-ASA and MWoA with dissection (2–7). In the current study, high-risk PFO and dissection were among the most common causes of stroke in all three subgroups. There were more high-risk PFOs in MWA patients and more dissections in MWoA patients than in NM patients, but these trends were not statistically significant. Nevertheless, high-risk PFO and dissection were the leading causes of stroke in MWA and MWoA patients, respectively.

According to the ICHD3, migrainous infarction is defined as one or more symptoms of migraine aura occurring in association with ischemic brain injury in the appropriate territory, as demonstrated by neuroimaging, with onset during a typical MWA attack. Thus defined, migrainous infarction can be viewed as a consequence of the mechanisms underlying the migrainous aura or as an MWA attack induced by acute brain ischemia. Migrainous infarction was observed in only 1/58 (1.7%) MWA patients from the present study and was also rarely reported in previous studies (23,24).

The goal of our study was to classify the causes of ischemic stroke associated with migraine in an unselected population of young adults. This approach allowed us to determine the relative importance of each cause of stroke according to migraine status. The results are therefore useful to guide diagnosis in clinical practice. We noted that atrial fibrillation associated with MWA was paroxysmal and unknown prior to stroke in all cases. This result suggests that a thorough search for paroxysmal atrial fibrillation may be warranted in

patients with MWA in the absence of an apparent cause of stroke.

Strengths of this study include its monocentric nature and short inclusion period, as well as the evaluation of migraine by the same headache specialist in all patients, which allowed a homogeneous assessment of the patients. The etiology of ischemic stroke was analysed using modified ASCOD criteria, allowing an accurate analysis of migraine by etiologic subgroups including high-risk PFO.

While we consider our results to be valid, there are certain limitations that need to be recognised. First, the relatively small number of patients in some subgroups did not allow for multivariate analysis. However, as mentioned above, the prevalence of traditional cardiovascular risk factors in MWA patients was lower or similar to that of NM patients. Second, due to a wide confidence interval, the strength of the association between atrial fibrillation and MWA needs to be confirmed on a larger sample size. Third, the prevalence of atrial fibrillation may have been underestimated because ECG monitoring >72 h was not performed in all patients without a potential cause of stroke. There was no predefined algorithm for searching for atrial fibrillation and the duration of the recordings was left to the discretion of the treating neurologist, which may have induced an unrecognised bias. However, the low prevalence of atrial fibrillation in the overall sample was consistent with those reported in recent series of young adults with ischemic stroke, making it unlikely that atrial fibrillation was underdetected in our study (25–27). Finally, the assessment of migraine was performed with knowledge of the cause of the stroke in some patients. However, migraine was assessed prior to the demonstration of atrial fibrillation in all patients with MWA.

## Conclusion

In conclusion, we showed that atrial fibrillation was a common cause of ischemic stroke in young adults with MWA.

### Clinical implications

- Migraine with aura is strongly associated with atrial fibrillation in young adults with ischemic stroke.
- In these patients, atrial fibrillation and dissection were the second leading causes of stroke, behind high risk patent foramen ovale.
- Intensive searching for paroxysmal atrial fibrillation is warranted in young adults with migraine with aura and no definite cause of stroke.




### Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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