Hacking stroke in women: towards aetiology-driven precision prevention

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Part I.
Pathophysiology of stroke in women

2. Migraine and cerebrovascular atherosclerosis in patients with ischemic stroke

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Abstract

Background and purpose: Migraine is a well-established risk factor for ischemic stroke, but migraine is also related to other vascular diseases. This study aims to investigate the association between migraine and cerebrovascular atherosclerosis in patients with acute ischemic stroke.

Methods: We retrieved data on patients with ischemic stroke from the Dutch acute stroke study. Migraine history was assessed with a migraine screener and confirmed by telephone interview based on the ICHD criteria. We assessed intra- and extracranial atherosclerotic changes and quantified intracranial internal carotid artery (ICA) calcifications as measure of atherosclerotic burden on non-contrast CT and CT-angiography. We calculated risk ratios (RR) with adjustments for possible confounders (aRR) with multivariable Poisson regression analyses.

Results: We included 656 patients, aged 18 to 99 years, of whom 53 had a history of migraine (29 with aura). Patients with migraine did not have more frequent atherosclerotic changes in intracranial (51% versus 74%; aRR: 0.82; 95%CI: 0.64–1.05) or extracranial vessels (62% versus 79%; aRR: 0.93; 95%CI: 0.77–1.12) than patients without migraine and had comparable ICA calcification volumes (largest versus medium and smallest volume tertile, 23% versus 35%, aRR: 0.93; 95%CI: 0.57–1.52).

Conclusion: Migraine is not associated with excess atherosclerosis in large vessels in patients with acute ischemic stroke. Our findings suggest that the biological mechanisms by which migraine results in ischemic stroke are not related to macrovascular cerebral atherosclerosis.

Introduction

Migraine, especially with aura, is a risk factor for ischemic stroke.[1] Migraine patients also have an increased risk for cardiovascular disease in the systemic circulation such as myocardial infarction and peripheral artery disease.[2] The connection between migraine and cardiovascular disease is complex and probably multifactorial. One of the possible mediating mechanisms is enhanced atherosclerosis. The aim of our study was to investigate the association between migraine and cerebrovascular atherosclerosis in a large cohort of patients with acute ischemic stroke.

Methods

Patients

We included patients from the Dutch acute stroke study (DUST), a large prospective multicenter cohort study performed between May 2009 and August 2013.[3] Inclusion criteria for DUST were: age ≥18 years, onset of stroke symptoms <9 h and NIHSS ≥2 or ≥1 if intravenous thrombolysis with rtPA was indicated. Exclusion criteria were known renal failure and contrast agent allergy.[3] DUST was approved by the Medical Ethical Committee of the participating hospitals. Informed consent was obtained from all patients for use of the data. All patients underwent non-contrast CT (NCCT), CTA and CTP on admission with standardized scan protocols (Supplementary Methods). Radiologic parameters were assessed by trained neuroradiologists with good inter observer variability.[3] At baseline we collected data on cardiovascular risk factors and medical history. Stroke subtype was classified according to the TOAST criteria. The DUST research nurses recorded the MISS (Migraine In Stroke Screener), a five-item migraine screener that retrospectively assesses migraine history and was validated previously in a stroke cohort. MISS data were obtained when the patient entered the DUST study. The MISS has a very high negative predictive value (0.99), but a moderate positive predictive value especially for aura symptoms.[4] In case of one or more positive answers to the screener the participants were contacted by telephone by a migraine research nurse. This semi-structured telephone interview consisted of detailed questions on headache and aura characteristics, including ICHD-II migraine and aura criteria. Patients were excluded when there was suspicion of migraine based on the screener but the migraine diagnosis could not be confirmed by telephone because patients were lost to follow-up or refused participation.

We assessed patients with any sign of atherosclerosis in intra- and extracranial vessels of the anterior and posterior circulation on CTA. We measured intracranial internal carotid artery (ICA) calcification volume, using calcium as a measure for

atherosclerosis. Calcium volumes were measured from the petrous part to the top of the intracranial carotid arteries on NCCT using dedicated software (Supplementary Methods). We performed multivariable Poisson regression analyses (Supplementary Methods). Risk ratios (RR) and adjusted RR (aRR) with 95% confidence intervals (CI) were calculated.

Results

In total, 707 DUST participants (82%) filled in the screener. Fifty-one patients were lost to follow-up or refused to participate in the telephone interview and were excluded. Therefore, 656 patients were included in this study of whom 53 had a confirmed migraine diagnosis (29 with aura) by telephone interview and 603 had no history of migraine. The median of time since the last attack was 1 year (n=47) and 38% of patients reported to have active migraine. Median attack frequency was 2 times per month (n=22). The baseline characteristics are shown in Table 1.

Table 1. Clinical characteristics of the participants

Characteristics	Migraine (n=53)	No migraine (n=603)
Demographics		
Age, mean years (±SD)	59.9 ± 11.0	67.0 ± 13.4
Age under 50, n(%)	10 (19%)	76 (13%)
Women, n(%)	29 (55%)	223 (37%)
History, n(%)		
Hypertension	21 (40%)	289 (49%)
Diabetes mellitus	7 (13%)	92 (15%)
Hyperlipidemia	21 (40%)	200 (34%)
Previous stroke or TIA	14 (26%)	139 (23%)
Myocardial infarction	5 (10%)	77 (13%)
Atrial fibrillation	6 (11%)	70 (12%)
Peripheral artery disease	3 (6%)	24 (4%)
Smoking: current	23 (44%)	170 (30%)
Smoking: lifetime*	34 (65%)	372 (65%)
Alcohol use	27 (73%)	267 (62%)
Baseline NIHSS**, median	5	5

**Current smokers and smokers who stopped smoking >6 months ago; **NIHSS: NIH Stroke Scale*

Atherosclerosis in intracranial vessel segments was as frequent in migraine patients as in patients without migraine (Table 2). This was the same for extracranial vessels and was also true for both the anterior and posterior circulation. High intracranial ICA calcification volumes were as frequent in migraine patients as in patients without migraine. We found no differences in atherosclerotic changes in migraine patients with and without aura, although group sizes were small. Our results remained consistent after stratification for age and stroke etiology (Supplementary Table I and II).

Table 2. Prevalence of atherosclerotic changes according to presence or absence of migraine

Atherosclerotic changes	Migraine (n=53)	No migraine (n=603)	RR (95% CI)	aRR (95% CI)†
Intracranial circulation				
Any sign of atherosclerosis*	27 (51%)	445 (74%)	0.69 (0.53–0.90)	0.82 (0.64–1.05)
Any sign of stenosis	4 (8%)	80 (13%)	0.57 (0.22–1.49)	0.77 (0.29–2.02)
Tertile largest ICA calcification vol.**	12 (23%)	211 (35%)	0.65 (0.39–1.08)	0.93 (0.57–1.52)
Extracranial circulation				
Any sign of atherosclerosis*	33 (62%)	476 (79%)	0.79 (0.64–0.98)	0.93 (0.77–1.12)
Atherosclerosis anterior circulation	32 (60%)	465 (77%)	0.78 (0.63–0.98)	0.92 (0.76–1.13)
Atherosclerosis posterior circulation	12 (23%)	225 (37%)	0.61 (0.36–1.01)	0.86 (0.54–1.37)
Any sign of stenosis	18 (34%)	260 (43%)	0.79 (0.53–1.16)	0.97 (0.67–1.41)
Stenosis ≥70%	10 (19%)	139 (23%)	0.82 (0.46–1.46)	0.91 (0.51–1.62)

**Anterior and posterior circulation combined*

***Tertile largest versus tertiles medium and smallest volume of internal carotid artery calcifications*

†Age and sex adjusted

Discussion

Our findings argue against the hypothesis that migraine patients are at higher risk for ischemic stroke because of higher atherosclerotic load in the cerebral vasculature. If anything, our data suggest that the prevalence of atherosclerotic changes was lower in stroke patients with migraine. This confirms previous findings in the literature where the risk for ischemic stroke was apparent for migraine patients without vascular risk factors (except for use of oral contraceptives and

smoking) and low Framingham risk scores.[5] Strong points of our study include the large number of participants and the state-of-the-art imaging methods enabling detailed assessment of the radiological characteristics of atherosclerosis. All migraine diagnoses were confirmed by an extensive telephone interview according to the ICHD-II criteria which are comparable with the recent updated ICHD-III criteria.

Our study also has limitations. First, the study is performed in a stroke population with highly prevalent traditional risk factors such as older age, history of hypertension, diabetes and hyperlipidemia. Compared with these traditional risk factors, the contribution of the possible migraine-related atherosclerosis may be too small to be detected. Second, our study did not include a control group without stroke. One could hypothesize that migraine patients might show enhanced atherosclerosis at younger ages resulting in earlier strokes but with comparable atherosclerotic changes than patients without migraine at time of the stroke. However, although migraine patients were indeed younger at time of their stroke, our results were consistent in different age categories. Third, not all patients filled in the MISS and not all screen positives could be confirmed by telephone interview. Patients with possible migraine but without confirmation were excluded from the study to avoid misclassification bias. Therefore, the exact prevalence of migraine in our stroke population cannot be derived from our study. Also, patients who were moribund or severely aphasic were less likely to have filled in the screener. We cannot rule out that this affected the generalizability or the internal validity of the results.

Our study does not provide information on other possible mechanisms underlying the increased ischemic stroke risk in migraine patients. Endothelial dysfunction has been related to early development of atherosclerosis but also to activation of the coagulation pathway, enhanced inflammatory responses and impaired vascular reactivity.[6] Although we found no excess atherosclerosis in migraine patients, future studies should investigate the possible impact of endothelial dysfunction on stroke risk via other mechanisms.

References

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