Stroke and migraine: Translational studies into a complex relationship

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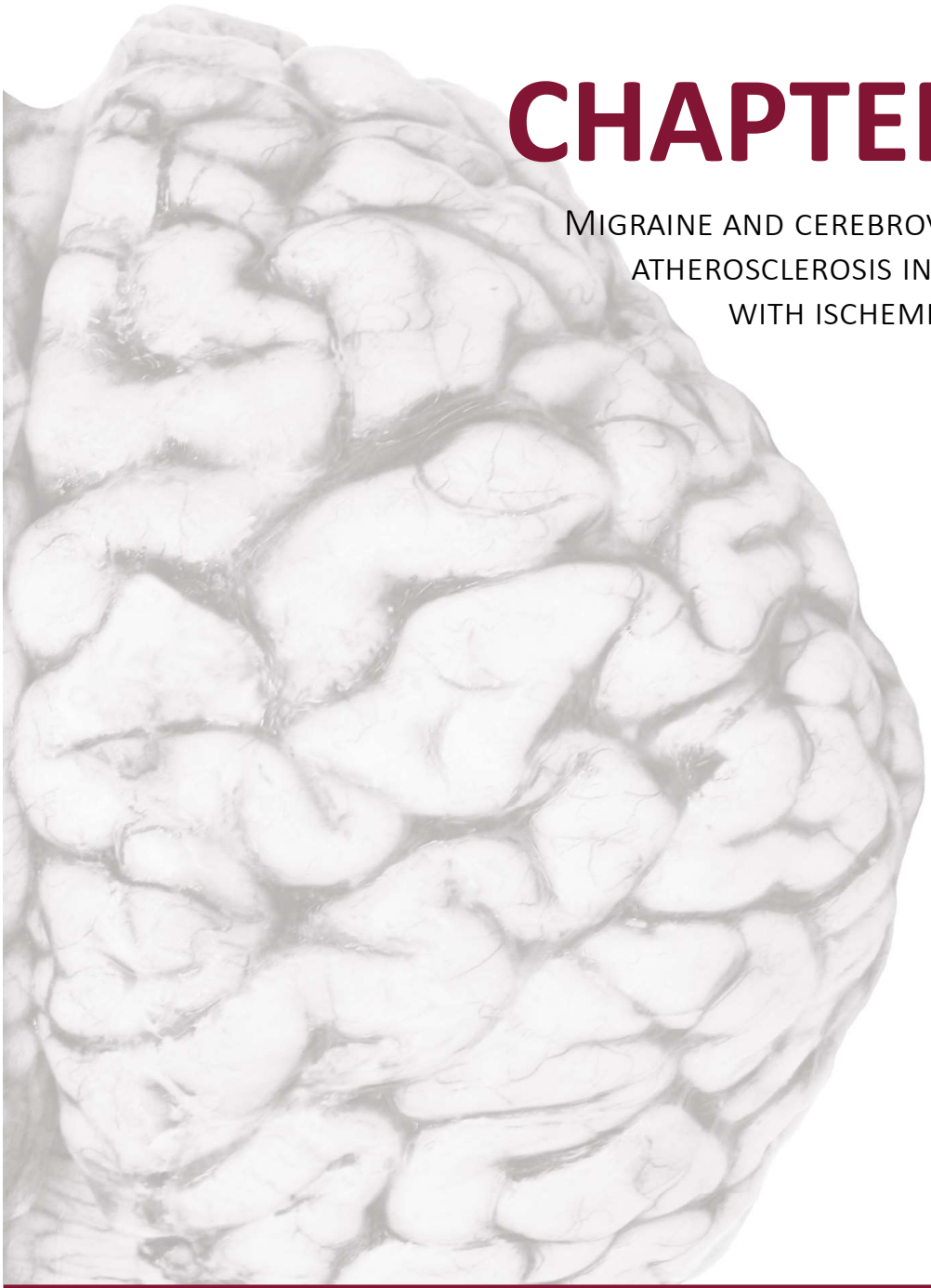

CHAPTER 8

Migraine and cerebrovascular atherosclerosis in patients with ischemic stroke

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ABSTRACT

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.

We retrieved data on patients with ischemic stroke from the DUST (Dutch Acute Stroke Study). Migraine history was assessed with a migraine screener and confirmed by telephone interview based on the ICHD criteria (International Classification of Headache Disorders). We assessed intra- and extracranial atherosclerotic changes and quantified intracranial internal carotid artery calcifications as measure of atherosclerotic burden on noncontrast computed tomography and computed tomographic angiography. We calculated risk ratios with adjustments for possible confounders with multivariable Poisson regression analyses.

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% *vs* 74%; adjusted risk ratio, 0.82; 95% confidence interval, 0.64–1.05) or extracranial vessels (62% *vs* 79%; adjusted risk ratio, 0.93; 95% confidence interval, 0.77–1.12) than patients without migraine and had comparable internal carotid artery calcification volumes (largest *vs* medium and smallest volume tertile, 23% versus 35%; adjusted risk ratio, 0.93; 95% confidence interval, 0.57–1.52).

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

We included patients from the DUST (Dutch Acute Stroke Study), 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 hours, and National Institutes of Health Stroke Scale score of ≥2 or ≥1 if intravenous thrombolysis with rtPA (recombinant tissue plasminogen activator) 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 noncontrast computed tomography, computed tomographic angiography, and computed tomography perfusion on admission with standardized scan protocols (Methods in the Supplemental Material). Radiological parameters were assessed by trained neuroradiologists with good interobserver variability.[3]

At baseline, we collected data on cardiovascular risk factors and medical history. Stroke subtype was classified according to the TOAST criteria (Trial of ORG 10172 in Acute Stroke Treatment). The DUST research nurses recorded the Migraine in Stroke Screener, a 5-item

Characteristics	Migraine (n=53)	No Migraine (n=603)
Demographics		
Age, mean y (±SD)	59.9±11.0	67.0±13.4
Age <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

Table 1. Clinical Characteristics of the Participants. NIHSS indicates National Institutes of Health Stroke Scale; and TIA, transient ischemic attack. *Current smokers and smokers who stopped smoking >6 months ago.

migraine screener that retrospectively assesses migraine history and was validated previously in a stroke cohort. Migraine in Stroke Screener data were obtained when the patient entered the DUST study.

The Migraine in Stroke Screener has a very high negative predictive value (0.99), but a moderate positive predictive value especially for aura symptoms.[4] In case of ≥1 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 (International Classification of Headache Disorders) 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 computed tomographic angiography. We measured intracranial internal carotid artery 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 noncontrast computed tomography using dedicated software (Methods in the Supplemental Material).
We performed multivariable Poisson regression analyses (Methods in the Supplemental Material). Risk ratios and adjusted risk ratio with 95% confidence intervals 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,

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 volume‡	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)

Table 2. Prevalence of atherosclerotic changes according to presence or absence of migraine. aRR indicates adjusted risk ratio; CI, confidence interval; ICA, internal carotid artery; and RR, risk ratio. * Age and sex adjusted. †Anterior and posterior circulation combined. ‡ Tertile largest *vs* tertiles medium and smallest volume of internal carotid artery calcifications.

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 2x per month (n=22). The baseline characteristics are shown in Table 1.

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 internal carotid artery 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 cause (Tables 1 and 2 in the Supplemental Material).

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 mellitus, and hyperlipidemia. Compared with these traditional risk factors, the contribution of the possible migrainerelated 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 the 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 Migraine in Stroke Screener 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.

AUTHORS CONTRIBUTION

H.J.A. van Os contributed to analysis and interpretation, critical revision of the article, study concept design, and is a lead author; I.A. Mulder contributed to data acquisition, analysis and interpretation, and critical revision of the article; Drs van der Schaaf, Kappelle, Velthuis, Visser, and Schonewille contributed to data acquisition and critical revision of the article; Dr Broersen contributed to critical revision of the article and provided and supported use of software for data analysis; Dr Algra contributed to analysis and interpretation and critical revision of the article; Drs Terwindt and Ferrari contributed to critical revision of the article and study concept design; Dr van Walderveen contributed to data acquisition, analysis and interpretation, critical revision of the article, and study concept design; and Dr Wermer contributed to data acquisition, analysis and interpretation, critical revision of the article, study concept design, and acts as a supervisor of lead author.

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Supplemental Material

Methods

Standardized scan protocol

All patients underwent non-contrast CT (NCCT), CTA and CTP on admission with standardized scan protocols. Scan parameters of the NCCT were: 120 kV, 300-375 mAs and 1 mm reconstructed slice thickness. For CTA 50–70 mL of contrast agent (300 mg I/mL) was injected into the antecubital vein (18-gauge needle) at a rate of 6 mL/s followed by a 40-mL saline flush at a rate of 6 mL/s. The scan parameters for the CTA were: 120 kV, 150 mAs and 5 mm reconstructed slice thickness. Radiologic parameters were assessed by trained neuroradiologists with good inter observer variability.[1]

MISS screener

The MISS consisted of five items: 1. Did you ever or do you still have migraine attacks? 2. Were you ever diagnosed with migraine by a physician? 3. Did you ever suffer from attacks of severe headache that lasted for several hours to days, with concomitant nausea and possible vomiting? 4. Did you ever suffer from attacks of severe headache that lasted several hours to days during which you had very low tolerance of light and noise? 5. Did you ever experience attacks that lasted between 5 to 60 minutes during which your sight was diminished or blurry at one side with possible flashes or glitters in the visual field, followed by headache?[2]

Radiological assessment of atherosclerosis

We assessed patients with any sign of atherosclerosis in intra- and extracranial vessels of the anterior and posterior circulation on CTA. Signs of atherosclerosis in extracranial vessels were defined as presence of soft plaque, calcified changes or mixed plaque. Intracranial vessels were divided into segments: the anterior cerebral (A1, A2), middle cerebral (M1, M2), posterior cerebral (P1, P2), vertebral (V1, V2), the internal carotid arteries up to and past the clinoid process and the basilar artery. Extracranial vessels were divided into the posterior (vertebral arteries) and anterior circulation (internal carotid arteries). Stenosis was classified in intracranial vessel segments as any sign of stenosis and additionally in extracranial vessels as stenosis ≥70%.[3]

We also assessed atherosclerotic changes by measuring intracranial internal carotid artery (ICA) calcification volume, using calcium as a measure for atherosclerosis since these two parameters are highly correlated.[4] Calcium volumes were measured from the petrous part to the top of the intracranial carotid arteries on NCCT using dedicated software (customized research version of CalcScore V11.1 by Medis Specials bv, The Netherlands). Regions of interest were drawn to discern intracranial ICA calcifications from the skull base using a threshold. A small pilot study was performed to find the optimal threshold for visually discerning ICA calcifications from the skull base. Since DUST was a multicenter study with CT data from different vendors, we tested several thresholds on 10 randomly selected data sets per center. We found the optimal threshold to be 160 Hounsfield units, which resulted in a spread of ICA calcification volume data that did not notably vary between centers. Continuous intracranial ICA calcification volume data were subsequently divided into tertiles (small, medium and large ICA calcification volumes).

Statistical analysis

We performed multivariable Poisson regression analyses to identify possible relationships between history of migraine and radiological characteristics of atherosclerosis. Adjustments were made for age and sex. Adjustments for hypertension and smoking had only a minimal effect on the results and were therefore not performed in the final analyses. Additionally, we stratified for age and stroke etiology according to the TOAST criteria. Risk ratios (RR) and adjusted RR (aRR) with 95% confidence intervals (CI) were calculated.

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TABLES

	MA (n=29)	MO (n=24)	RR (95% CI)	aRR (95% CI)†
Intracranial circulation				
Any sign of atherosclerosis*	14 (48%)	13 (54%)	0.89 (0.53 – 1.51)	1.41 (0.80 – 2.45)
Any sign of stenosis	2 (7%)	2 (8%)	0.83 (0.13 – 5.45)	1.05 (0.36 – 3.04)
Tertile largest ICA calcification volume**	6 (21%)	6 (25%)	0.83 (0.31 – 2.24)	1.11 (0.28 – 4.44)
Extracranial circulation				
Any sign of atherosclerosis*	19 (66%)	14 (58%)	1.12 (0.73 – 1.73)	1.40 (0.87 – 2.25)
Any sign of stenosis	9 (31%)	9 (38%)	0.83 (0.39 – 1.75)	0.86 (0.41 – 1.83)
Stenosis ≥70%	7 (24%)	3 (13%)	1.93 (0.56 – 6.67)	1.84 (0.54 – 6.26)

Supplemental Table 1. Prevalence of atherosclerotic changes in the 53 migraine patients according to presence or absence of aura. *Anterior and posterior circulation combined. **Tertile largest volume versus tertiles medium and smallest volume of internal carotid artery (ICA) calcifications. † Adjusted for age and sex

Stratification factor	Any sign of atherosclerosis	Migraine	No migraine	RR (95% CI)	aRR (95% CI)†
Age group, n (%)					
<50	Intracranial	0 (0%)	18 (24%)	–	–
(86, 14%)	Extracranial	0 (0%)	25 (33%)	–	–
50-69	Intracranial	19 (56%)	190 (73%)	0.77 (0.56 – 1.04)	0.77 (0.56 – 1.05)
(294, 45%)	Extracranial	25 (74%)	210 (81%)	0.91 (0.74 – 1.12)	0.94 (0.77 – 1.16)
≥70	Intracranial	8 (89%)	237 (89%)	1.00 (0.79 – 1.27)	1.00 (0.79 – 1.28)
(276, 42%)	Extracranial	8 (89%)	241 (90%)	0.99 (0.78 – 1.25)	0.99 (0.79 – 1.24)
Stroke etiology group, n (%)*					
Large vessel disease	Intracranial	8 (62%)	145 (85%)	0.73 (0.47 – 1.12)	0.85 (0.55 – 1.33)
(184, 43%)	Extracranial	10 (77%)	150 (88%)	0.88 (0.65 – 1.19)	0.96 (0.72 – 1.29)
Cardioembolism	Intracranial	7 (88%)	70 (72%)	1.21 (0.91 – 1.62)	1.27 (0.95 – 1.69)
(105, 25%)	Extracranial	6 (75%)	77 (79%)	0.95 (0.63 – 1.43)	0.98 (0.69 – 1.40)
Small vessel disease	Intracranial	3 (43%)	58 (72%)	0.60 (0.25 – 1.42)	0.66 (0.27 – 1.61)
(88, 21%)	Extracranial	5 (71%)	60 (74%)	0.96 (0.59 – 1.57)	1.06 (0.76 – 1.47)

Supplemental Table 2. Any sign of atherosclerotic changes according to presence or absence of migraine, stratified for age or stroke etiology. † Adjusted for age and sex. * Stroke etiology according to the TOAST criteria.