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Holswilder, G.

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Chapter 5



Stroke progression and clinical outcome in ischemic stroke patients with a history of migraine

Inge A Mulder,* Ghislaine Holswilder*, Marianne AA van Walderveen, Irene C van der Schaaf, Edwin Bennink, Alexander D Horsch, L Jaap Kappelle, Birgitta K Velthuis, Jan Willem Dankbaar, Gisela M Terwindt, Wouter J Schonewille, Marieke C Visser, Michel D Ferrari, Ale Algra, Marieke JH Wermer; DUST investigators.

**authors contributed equally*

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Abstract

Background

Patients with migraine might be more susceptible of spreading depolarizations, which are known to affect vascular and neuronal function and penumbra recovery after stroke. We investigated whether these patients have more severe stroke progression and less favorable outcomes after recanalization therapy.

Methods

We included patients from a prospective multicenter ischemic stroke cohort. Lifetime migraine history was based on the International Classification of Headache Disorders II criteria. Patients without confirmed migraine diagnosis were excluded. Patients underwent CT angiography and CT perfusion <9 h of onset and follow-up CT after three days. On admission, presence of a perfusion deficit, infarct core and penumbra volume, and blood brain barrier permeability (BBBP) were assessed. At follow-up we assessed malignant edema, hemorrhagic transformation, and final infarct volume. Outcome at three months was evaluated with the modified Rankin Scale (mRS). We calculated adjusted relative risks (aRR) or difference of means (aB) with regression analyses.

Results

We included 600 patients of whom 43 had migraine. There were no differences between patients with or without migraine in presence of a perfusion deficit on admission (aRR: 0.98, 95%CI: 0.77–1.25), infarct core volume (aB: -10.8, 95%CI: -27.04–5.51), penumbra volume (aB: -11.6, 95%CI: -26.52–3.38), mean blood brain barrier permeability (aB: 0.08, 95%CI: -3.11–2.96), malignant edema (0% vs. 5%), hemorrhagic transformation (aRR: 0.26, 95%CI: 0.04–1.73), final infarct volume (aB: -14.8, 95%CI: 29.9–0.2) or outcome after recanalization therapy (mRS > 2, aRR: 0.50, 95%CI: 0.21–1.22).

Conclusion

Elderly patients with a history of migraine do not seem to have more severe stroke progression and have similar treatment outcomes compared with patients without migraine.

Introduction

Migraine patients, especially with aura, have an increased risk of ischemic stroke.¹ The association between ischemic stroke and migraine is complex and probably multifactorial.^{2,3} One interesting mechanism involved in the association is spreading depolarization (SD). SDs are waves of depolarizing neuronal and glia cells, spreading through brain tissue and are the presumed underlying neurovascular mechanism of a migraine aura. SDs have been linked directly to ischemia in pure migrainous infarction. Besides that, it has been shown in mice that micro-emboli can also trigger SDs, with or without causing microinfarctions^{4,5} and increased migraine with aura (MA) and stroke occurrence is reported in patients with patent foramen ovale.⁶ SDs in healthy brain tissue are probably a benign phenomenon but in ischemic tissue they may increase (secondary) tissue changes after stroke.^{2,7,8}

Within minutes after an ischemic event, cells contributing to the infarct core become necrotic with membrane breakdown, dysfunctional cellular metabolism and energy supply, disturbed ion homeostasis, and loss of cell integrity. The tissue surrounding the core (the penumbra) is “struggling to survive” due to collateral blood supply being borderline sufficient.^{9,10} Cells in the penumbra are metabolically still active for some time, until the disruption of the cellular homeostasis in these cells also leads to cell death. Within minutes after vessel occlusion, a first depolarization wave travels through the penumbra, triggered by loss of membrane integrity due to hypoxia and energy depletion. Multiple SDs can follow thereafter, resulting in an additional reduction of blood flow and increased ischemic damage with each wave.^{11–14} These peri-infarct polarizations have been found in patients with malignant middle cerebral artery (MCA) infarctions.¹² Also, SDs possibly affect blood brain barrier (BBB) permeability leading to increased secondary hemorrhagic changes, malignant edema, and faster penumbra turnover into infarct core.^{15–17}

Although SDs also occur in stroke patients without migraine, stroke patients with a history with migraine may be more susceptible for SDs. Mice carrying the familial hemiplegic migraine gene have a decreased cortical SD threshold and increased infarct sizes compared with wild-type mice.⁷ In a recent retrospective MRI study of 72 ischemic stroke patients, patients with migraine had a faster penumbra turnover than patients without migraine.^{18,19} This fast penumbra turnover might restrict the time window for revascularization therapies and decrease the chance of good functional recovery.³

We investigated with modern CT-stroke imaging techniques in a prospective clinical stroke cohort, whether stroke progression is more severe in patients with migraine

than in those without and whether migraine patients have poorer outcomes after intravenous thrombolysis or mechanical thrombectomy.

Methods

Patients

We included patients from a large prospective multicenter cohort study in the Netherlands (Dutch Acute Stroke Trial (DUST)²⁰). The main goal of the DUST study was to analyze the predictive value of computed tomography angiography (CTA) and perfusion (CTP) on clinical outcome in patients with ischemic stroke. Inclusion criteria were: age ≥ 18 years, stroke symptom onset at time of imaging < 9 h, National Institutes of Health Stroke Scale (NIHSS) ≥ 2 or ≥ 1 if intravenous thrombolysis (IVT) with rtPA was indicated, and known absence of renal failure or allergy to contrast agent. Patients with discharge diagnoses other than ischemic stroke (for example TIA without CT perfusion defect) were excluded from analysis. Non-contrast CT (NCCT), CTP, and CTA were performed on admission, with scan protocols standardized between centers. Study approval was received from the institutional medical ethics committee of all participating hospitals. Ethical approval was obtained from the medical ethics committee of the University Medical Center Utrecht (UMCU), the Netherlands, in addition to local approval from all participating hospitals. Written informed consent was obtained from patients or their legal representative. The medical ethics committee UMCU waived the need for informed consent for patients who died before informed consent could be obtained.

Follow-up NCCT was repeated around three days with (depending on the consent) additional CTP and CTA or MRI if clinically indicated. CT protocols were adjusted within centers according to the hardware used for comparable results, described in detail previously.²⁰

Migraine diagnosis

Migraine (past and present) was diagnosed upon admission with a 5-point questionnaire Migraine Screener for Stroke (MISS)²¹ by trained headache research nurses. Although this questionnaire has a high negative predictive value (0.99), the positive predictive value (0.80 overall and 0.38 for MA) is less accurate. To exclude false positive diagnoses, we approached all patients with a positive migraine screener (at least 1 question answered with “yes”) for an extensive telephone interview to verify the migraine diagnosis. Interview questions were based on International Classification of Headache Disorders II criteria (ICHD-II) migraine and aura criteria in a (semi-) structured manner. In case of ambiguity, a headache neurologist (GMT) was consulted. Patients were excluded when they were unable to answer screener

questions due to severe aphasia or decreased cognitive abilities and when migraine diagnosis could not be verified due to loss of follow-up or refusal to participate in the interview.

Clinical characteristics and outcome

We collected data about cardiovascular risk factors, NIHSS, and modified Rankin Scale (mRS) prior to stroke on admission. Stroke-to-imaging time and mode of treatment (intravenous treatment, mechanical thrombectomy or no revascularization therapy) were recorded. Stroke etiology was classified with the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification,²² and infarct localization was scored with the Oxfordshire classification²³ consisting of the subtypes partial anterior circulation infarct (PACI), total anterior circulation infarct (TACI), lacunar infarct (LACI), and posterior circulation infarct (POCI).

After a follow-up period of three months, the mRS was prospectively assessed by a telephone interview performed by a trained research nurse. An mRS > 2 was considered a poor clinical outcome.

Radiological characteristics

All radiological assessments were performed blinded for clinical diagnosis and migraine diagnosis (except for side of symptoms) by trained observers with at least five years of experience in neurovascular imaging. Upon admission, early ischemic changes were evaluated on NCCT with the Alberta Stroke Program Early CT score (ASPECTS) scale. The ASPECTS is a 10-point (0=all areas involved, 10=no areas of the MCA territory involved in the infarct) quantitative topographic CT scan score evaluated on two standardized levels.²⁴ The score was dichotomized ≤ 7 or > 7 which has previously been identified as a useful predictive cutoff point for clinical functional outcome.²⁵

Clot Burden Score was determined on CTA as the absence of opacification in the anterior circulation on a 10-point scale where a score of 10 indicates the contrast opacification of all vessel segments and 0 lack of opacification of any vessel segment and dichotomized in < 7 and ≥ 7 .²⁶ Collaterals were determined on CTA in patients with anterior circulation infarction (ACA and MCA) due to a large vessel occlusion. Subsequently collaterals were defined as poor when collateral filling was $\leq 50\%$ of the affected area.^{26–28}

The CTP parameters cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), and time to peak (TTP) were automatically calculated (using Extended Brilliance Workstation 4.5; Philips Healthcare software and in-

house developed perfusion software applying a bSVD algorithm) and displayed in color coded maps; MTT and CBV thresholds to define infarct core and penumbra were applied as described previously.²⁹ Our primary outcome variable presence of a perfusion deficit (yes or no) at entry was visually assessed using CBF, CBV, MTT, and TTP color coded maps. Infarct core and penumbra area at entry were classified into two levels by applying the ASPECTS to the MTT and CBV thresholds and again dichotomized in <8 and ≥ 8 .³⁰ Volumes of infarct core and penumbra were calculated within the whole scan range using in-house software, with: $T_{max} > 6$ s for total infarct area and a relative CBF threshold of 30% was used to differentiate between core and penumbra.^{31,32}

We calculated the BBB permeability surface area product with CTP data according to the nonlinear regression method described in detail previously.³³ A BBB permeability ratio >1 indicates that the BBB permeability of the ipsilateral hemisphere is higher compared with that in the contralateral hemisphere.

On follow-up we assessed imaging markers of secondary brain damage including presence of malignant edema, defined as a midline shift ≥ 5 mm; hemorrhagic transformation, defined using the European Cooperative Acute Stroke Study criteria and included the presence of any subtype;³⁴ and final infarct volume (cc), quantified by manually delineating hypodense territory on NCCT.³⁵ Presence of a persistent occlusion was defined as no recanalization visible on follow-up CTA in the subgroup of patients with vessel occlusion at entry.

Data analysis

The primary outcome variable for our study was considered to be the presence of a perfusion deficit. A post-hoc power analysis was performed for this outcome, resulting in sufficient precision to detect a 15% difference in perfusion deficit presence (in 60% of the patients without migraine vs. 75% in those with migraine).

Poisson and linear regression (all univariable and multivariable) analyses with migraine as the determinant were used to calculate (adjusted) risk ratios (RR) or beta-coefficients (B) including 95% confidence intervals (95% CIs). Adjustments were made for age, sex, stroke-to-imaging time (STI), NIHSS on admission, smoking, and a history of hypertension. In addition, for outcome variables at follow-up, an adjustment for IVT and/or mechanical thrombectomy treatment was added. Three subgroup analyses were performed: (1) for patients with MA because patients with MA might be more susceptible for SDs, (2) for patients with large infarcts (based on Oxfordshire classification at discharge: excluding LACI and unknown) because secondary changes are likely to be dependent on infarct size, and (3) for

patients with proven vessel occlusions. Missing values were imputed with single imputation for multivariable analyses. Missing values were not imputed when comprising more than 20% of the data (in case of the BBB permeability ratio), when random imputation would lead to improbable results (“infarct locations” and “occlusion”) and when variables were not missing at random (follow-up imaging variables “malignant edema”, “hemorrhagic transformation”, “final infarct volume”, and “persistent occlusion”).

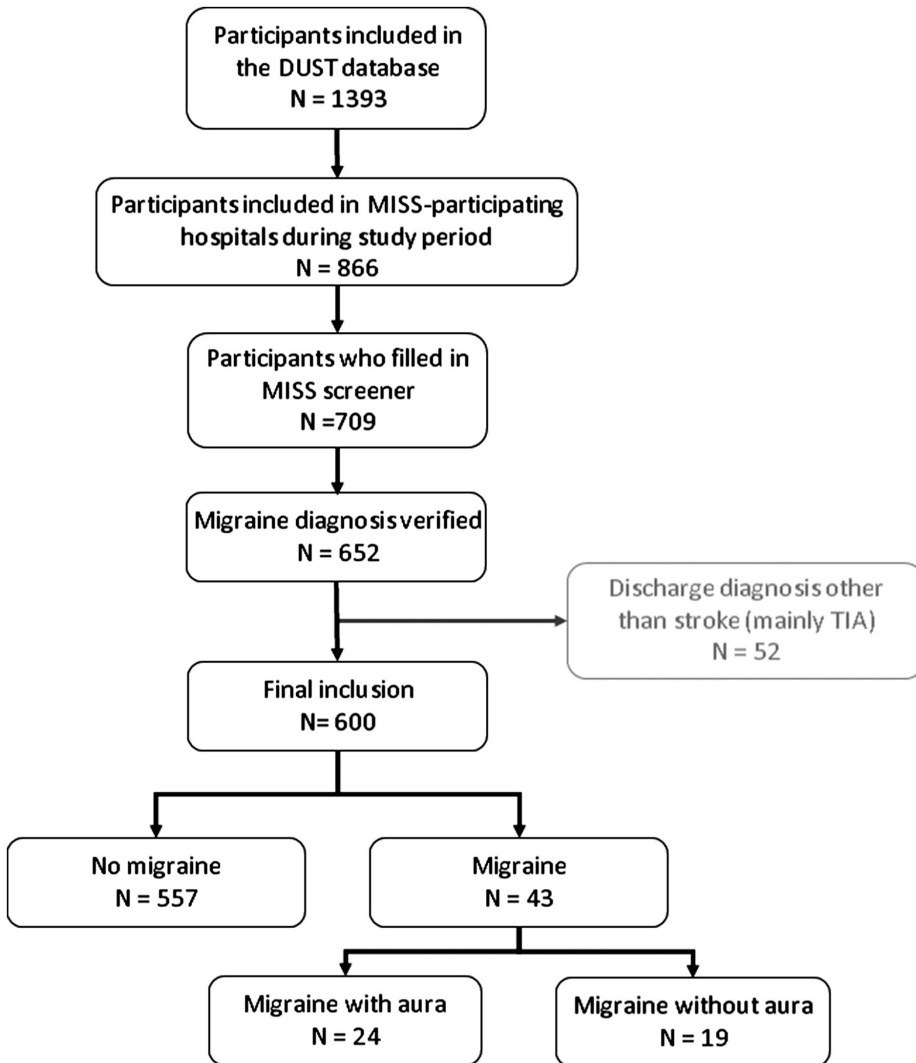


Figure 1. Inclusion flow chart. MISS: Migraine Screener for Stroke.

Results

Patients

We included 600 patients; 43 (7%) with migraine (24 with aura and 19 without aura) and 557 patients without migraine (Figure 1). Baseline characteristics were comparable between patients with and without migraine, except that patients with migraine were in general younger at time of stroke onset, more often female and more often had lacunar or vertebrobasilar infarctions compared with patients without migraine (Table I).

Table I. Baseline characteristics of patients

	Migraine (all) N=43	Migraine with aura N=24	No migraine N=557
Clinical characteristics			
Women	22 (51%)	9 (38%)	209 (38%)
Age, mean years (SD)	60.0 (11.5)	57.9 (8.5)	67.2 (13.4)
Age < 50	10 (23%)	5 (21%)	70 (13%)
NIHSS (median, IQR)	5 (2–11)	5 (2–11)	5 (3–10)
mRS before stroke > 0	9 (21%)	7 (29%)	122 (22%)
STI, min (median, IQR)	116 (83–210)	120 (79–225)	113 (72–171)
<i>Oxfordshire-classification</i>			
TACI	6 (14%)	5 (21%)	82 (15%)
PACI	11 (26%)	6 (25%)	221 (40%)
POCI	9 (21%)	7 (29%)	82 (15%)
LACI	9 (21%)	5 (21%)	70 (13%)
Unclear	0	0	25 (4%)
Unknown	8 (19%)	1 (4%)	77 (14%)
<i>TOAST</i>			
LVD	12 (28%)	6 (25%)	165 (30%)
CE source	8 (19%)	3 (13%)	93 (17%)
SVD	7 (16%)	4 (17%)	75 (13%)
Other	3 (7%)	1 (4%)	42 (7%)
Unknown	13 (30%)	10 (42%)	182 (33%)
<i>Treatment</i>			
IVT alone	19 (44%)	9 (38%)	344 (62%)
IAT	5 (12%)	2 (8%)	32 (6%)
None	19 (44%)	13 (54%)	181 (32%)

Table 1. Baseline characteristics of patients (continued)

	Migraine (all) N=43	Migraine with aura N=24	No migraine N=557
Risk factors			
Smoking	19 (45%)	12 (50%)	160 (30%)
Hypertension	16 (37%)	7 (29%)	266 (48%)
Diabetes	5 (12%)	3 (13%)	81 (15%)
Myocardial infarction	4 (10%)	3 (13%)	68 (12%)
Previous stroke/TIA	9 (21%)	6 (25%)	123 (22%)
AF	5 (12%)	2 (8%)	63 (11%)
Hyperlipidemia	18 (42%)	12 (50%)	176 (33%)
Peripheral vessel disease	2 (5%)	2 (8%)	22 (4%)
≥2 risk factors	21 (51%)	12 (52%)	271 (50%)

IAT: IA treatment alone or IA as well as IV treatment; SD: standard deviation; smoking: current smoker or quit smoking less than six months before event; TIA: transient ischemic attack; AF: atrial fibrillation; NIHSS: National Institutes of Health Stroke Scale; IQR: interquartile range; mRS: modified Rankin Scale; STI: stroke-to-imaging; TACI: total anterior circulation infarct; PACI: partial anterior circulation infarct; POCI: posterior circulation infarct; LACI: lacunar infarct; TOAST: Trial of Org 10172 in Acute Stroke Treatment; LVD: large vessel disease; CE: cardio-embolism; SVD: small vessel disease; IV: intravenous; IA: intra-arterial.

Numbers might not add up due to missing values.

Stroke on admission and follow-up

No differences were found between patients with and without migraine history in presence of a perfusion defect on admission (adjusted relative risks (aRR): 0.98, 95% CI: 0.77–1.25), ASPECTS infarct core <8 (aRR: 0.95, 95%CI: 0.45–2.00), ASPECTS penumbra <8 (aRR: 0.90, 95%CI: 0.60–1.34), infarct core volume (aB: -10.8, 95%CI: -27.0–5.5), penumbra volume (aB: -11.6, 95%CI: -26.5–3.4), or BBB permeability ratio on CTP (aB: -0.08, 95%CI: -3.11–2.96; Table 2, upper part).

Follow-up imaging on average three days after stroke onset was performed in 522 (87%) patients. In 325 (54%) patients follow-up imaging included CTP. No difference was found between migraine versus non-migraine patients in prevalence of malignant edema (0/30 (0%) 16/327 (5%)) and hemorrhagic transformation (aRR: 0.26, 95%CI: 0.04–1.73) or final infarct volume (aB: -14.8, 95%CI: -29.9–0.2; Table 2, lower part). Subgroup analysis including only migraine patients with aura or patients with large infarcts or patients with proven vessel occlusions showed essentially similar results (Supplementary Tables 1 and 2).

Table 2. Radiological characteristics upon admission and follow-up

	Migraine (all) N=43	No migraine N=557	RR (95%CI)	aRR (95%CI)
Admission				
Infarct location				
ACA	1/42 (2%)	22/534 (4%)	0.58 (0.08–4.18)	
MCA	29/42 (69%)	414/533 (78%)	0.89 (0.72–1.09)	
PCA	1/42 (2%)	31/533 (6%)	0.41 (0.06–2.93)	
VBA	10/41 (24%)	64/534 (12%)	2.04 (1.13–3.66)	
Border zone	0/41 (0%)	6/533 (1%)	–	
Large vessel occlusion	17/42 (40%)	271/550 (49%)	0.82 (0.56–1.20)	
Clot Burden Score <7	6/43 (14%)	70/557 (13%)	1.11 (0.51–2.41)	
Poor collaterals ≤50%*	1/13 (8%)	42/228 (18%)	0.42 (0.06–2.80)	
Stroke progression on admission				
ASPECTS—NCCT <8	4/43 (9%)	43/557 (8%)	1.21 (0.45–3.20)	1.12 (0.38–3.28)
Perfusion defect present	26/43 (61%)	342/557 (61%)	0.99 (0.77–1.27)	0.98 (0.77–1.25)
ASPECTS infarct core <8	6/43 (14%)	89/557 (16%)	0.87 (0.41–1.88)	0.95 (0.45–2.00)
ASPECTS penumbra <8	14/43 (33%)	203/557 (36%)	0.89 (0.57–1.39)	0.90 (0.60–1.34)
Volume infarct core (cc) [†]	32.2 (28.9)	43.4 (47.8)	-11.2 (-27.5–5.1) [‡]	-10.8 (-27.0–5.5) [‡]
Volume penumbra (cc) [†]	28.6 (31.7)	40.8 (46.2)	-12.2 (28.0–3.7) [‡]	-11.6 (-26.5–3.4) [‡]
Volume mismatch ratio [†]	1.64 (1.30–2.03)	1.71 (1.32–2.58)	-0.11 (-0.77–0.54) [‡]	-0.13 (-0.77–0.52) [‡]
BBBP ratio [‡]	1.41 (0.89–2.56)	1.58 (0.95–3.04)	-0.25 (-3.25–2.76) [‡]	-0.08 (-3.11–2.96) [‡]
Follow-up				
Stroke progression on follow-up				
Malignant edema	0/30 (0%)	16/327 (5%)	–	–
Hemorrhagic transformation	1/38 (3%)	45/484 (9%)	0.28 (0.04–2.00)	0.26 (0.04–1.73)
Final infarct volume (cc) [§]	11.4 (21.2)	22.7 (51.8)	-11.3 (-28.2–5.5) [‡]	-14.8 (-29.9–0.2) [‡]

RR: risk ratio; ACA: anterior cerebral artery; MCA: middle cerebral artery; PCA: posterior cerebral artery; VBA: vertebrobasilar arteries; ASPECTS: Alberta Stroke Program Early CT score; NCCT: non-contrast CT; BBBP ratio: blood-brain-barrier permeability ratio ipsilateral/contralateral; SD: standard deviation.

* Population of patients with occlusion and anterior circulation infarction, N=13 migraine and 228 no migraine patients.

[†] Within scan range; N=34 migraine and 456 no migraine patients.

[‡] N=30 migraine and 442 no migraine patients.

[§] N=37 migraine and 474 no migraine patients.

^{||} Numbers are displayed as difference of the means (B) or adjusted difference of the means (aB).

Missing values were imputed except for variables Infarct location, perfusion defect present, BBBP ratio, and follow-up variables. Adjustments for admission variables were made for age, sex, stroke-to-imaging time, NIHSS on admission, smoking and a history of hypertension. Additional adjustment for treatment was performed concerning the follow-up variables. Volumes (cc) are listed as mean (standard deviation), ratios as median (IQR).

Treatment outcome

Overall, the proportion of patients with a poor outcome (mRS > 2) after three months did not differ between migraineurs and non-migraineurs (aRR: 0.60, 95%CI: 0.30–1.20). In the patients who were treated with IVT or mechanical thrombectomy no difference was found in the number of persistent occlusions (aRR: 0.92, 95%CI: 0.41–2.04) or mRS > 2 at three months (aRR: 0.50, 95%CI: 0.21–1.22; Table 3).

Table 3. Outcome in patients including sub-analyses for patients treated with intravenous thrombolysis or mechanical thrombectomy for patients with or without migraine (top); patients with or without migraine with aura (middle) and large infarcts, with or without migraine (bottom)

	Migraine	No migraine	RR (95%CI)	aRR (95%CI)
All	N=43	N=557		
Persistent occlusion*	4/12 (33%)	92/175 (53%)	0.63 (0.28–1.43)	0.75 (0.32–1.72)
FU3 mRS > 2	7/43 (16%)	160/557 (29%)	0.57 (0.28–1.13)	0.60 (0.30–1.20)
Treated patients	N=24	N=376		
Persistent occlusion*	4/11 (36%)	53/125 (42%)	0.86 (0.38–1.92)	0.92 (0.41–2.04)
FU3 mRS > 2	4/24 (17%)	117/376 (31%)	0.54 (0.22–1.33)	0.50 (0.21–1.22)
	Migraine with aura	No migraine	RR (95%CI)	aRR (95%CI)
All	N=24	N=557		
Persistent occlusion*	2/8 (25%)	92/175 (53%)	0.48 (0.14–1.59)	0.52 (0.15–1.85)
FU3 mRS > 2	3/24 (13%)	160/557 (29%)	0.44 (0.15–1.26)	0.47 (0.15–1.48)
Treated patients	N=11	N=376		
Persistent occlusion*	2/7 (29%)	53/125 (42%)	0.67 (0.21–2.21)	0.66 (0.20–2.17)
FU3 mRS > 2	0/11 (0%)	117/376 (31%)	–	–
Only large infarcts	Migraine	No migraine	RR (95%CI)	aRR (95%CI)
All	N=26	N=385		
Persistent occlusion*	3/11 (27%)	82/156 (53%)	0.52 (0.20–1.38)	0.60 (0.22–1.64)
FU3 mRS > 2	6/26 (23%)	122/385 (32%)	0.73 (0.36–1.49)	0.73 (0.36–1.49)
Treated patients	N=14	N=273		
Persistent occlusion*	3/10 (30%)	50/113 (44%)	0.68 (0.26–1.79)	0.74 (0.28–1.94)
FU3 mRS > 2	3/14 (21%)	91/273 (33%)	0.64 (0.23–1.78)	0.52 (0.20–1.39)

FU3: follow-up after three months; mRS: modified Rankin Scale.

* Persistent occlusion of total patients with occlusion present at admission and available follow-up imaging.

Adjustments were made for age, sex, stroke-to-imaging time, NIHSS on admission, smoking, a history of hypertension, and treatment. In the sub-analysis of the treated patients, the same adjustments were made, however without adjusting for treatment.

Discussion

Elderly patients with a history of migraine did not have more severe stroke progression or poorer outcome compared with patients without migraine. Also, no difference in outcome after recanalization treatment was present. If anything, brain injury seemed smaller in patients with migraine although these differences were not statistically significant.

Our findings seem to contradict previous findings in animal studies. Mice carrying the familial hemiplegic migraine type I (FHM1) mutation developed faster and had a larger infarct volume after MCA occlusion compared with control mice.⁷ This was most likely caused by the lower threshold for occurrence of SDs.^{11,36,37} However, in these animal studies, MCA occlusion was performed in a standardized way which always resulted in an infarct at the same location. In our study, reflecting clinical practice, we compared patients with infarcts at very heterogeneous locations and including lacunar infarcts. Unfortunately, we were not able to assess penumbra turnover in our patients because follow-up CTP scans were not available in almost half of the patients and volumes of the perfusion deficits were surrounded by wide CIs. In one retrospective study, a non-mismatch pattern was more often seen in migraineurs with aura within 72 h of stroke onset, based on diffusion and perfusion weighted MRI.¹⁹ Although we could not confirm or refute this finding, we found no differences in the extent of early ischemic changes on NCCT, presence of a perfusion deficit or extent of infarct core, and penumbra on admission (CTP) between patients with and without migraine. A possible explanation for the tendency of even less secondary damage in migraineurs is the hypothesis that migraine attacks could be of homeostatic and neuroprotective response to oxidative stress in the brain.³⁸

Our findings are important for clinical practice, as we found no diminished treatment effect of IVT or mechanical thrombectomy in patients with migraine. Clinical outcome in general was comparable in patients with and without migraine. This finding is in line with the Women's Health study where no difference was found in functional outcome after TIA or stroke in women with a history of migraine, but no treatment effect was assessed.³⁹ Based on our data there seems to be no reason to restrict the time window for revascularization treatment in migraineurs.

Strengths of our study are the large number of included ischemic stroke patients in a prospective manner in combination with the extensive standardized CT imaging in the acute phase of ischemic stroke. All life-time migraine diagnoses were confirmed by telephone interview with questions based on the formerly ICHD-II criteria but for migraine diagnoses comparable with the new ICHD-III criteria, which decreased

the chance of misclassification bias.

Our study also has limitations. For the primary analyses, we combined migraine with and without aura, which could have diluted the effect of MA on stroke characteristics. Spreading depolarization is a mechanism that is in particular related to MA although some studies suggest that it also occurs in migraine without aura.⁴⁰ In a secondary analysis, we compared migraine patients with aura with patients without migraine. The effect estimates obtained pointed in the same direction as our main results.

As secondary tissue changes after stroke are dependent on infarct size at admission we also performed an additional analysis including only large infarcts. This analysis again showed comparable results with the main analyses. However, because of the limited group sizes these additional analyses should be interpreted with great caution and replication in future studies with larger number of MA patients is warranted.

Our population was in general about 65 years old at time of their stroke. Because migraine is most active at younger age recall bias might have occurred. We also did not take into account the (possible) use of prophylactic migraine medications which may have influenced occurrence of SDs. Unfortunately, we had no data on the date of the last migraine attack or the presence of active migraine. The higher susceptibility for SDs in migraineurs might be associated with current status of migraine activity. In another study of our group on the effect of migraine history on delayed cerebral ischemia (DCI) after subarachnoid hemorrhage (SAH) we found a statistically significant interaction of the effect with age.⁴¹ Only in young SAH patients migraine history was related to DCI.⁴¹ As the proportion of young stroke patients in our present study is low we feel more data are needed before the current reassuring results can be generalized to patients under the age of 50 years.

Declaration of conflicting interests

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Supplementary materials



Scan the QR code to view the supplementary materials of chapter 5.

References

1. Schurks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T. Migraine and cardiovascular disease: systematic review and meta-analysis. *BMJ* 2009; 339: b3914.
2. Dreier JP, Reiffurth C. The stroke-migraine depolarization continuum. *Neuron* 2015; 86: 902–922.
3. Milhaud D, Bogousslavsky J, van Melle G, Liot P. Ischemic stroke and active migraine. *Neurology* 2001; 57: 1805–1811.
4. Donmez-Demir B, Yemisci M, Kilic K, et al. Microembolism of single cortical arterioles can induce spreading depression and ischemic injury: a potential trigger for migraine and related MRI lesions. *Brain Res* 2018; 1679: 84–90.
5. Nozari A, Dilekoz E, Sukhotinsky I, et al. Microemboli may link spreading depression, migraine aura, and patent foramen ovale. *Ann Neurol* 2010; 67: 221–229.
6. Del Sette M, Angeli S, Leandri M, et al. Migraine with aura and right-to-left shunt on transcranial Doppler: a case-control study. *Cerebrovasc Dis* 1998; 8: 327–330.
7. Eikermann-Haerter K, Lee JH, Yuzawa I, et al. Migraine mutations increase stroke vulnerability by facilitating ischemic depolarizations. *Circulation* 2012; 125: 335–345.
8. Hamming AM, Wermer MJ, Umesh Rudrapatna S, et al. Spreading depolarizations increase delayed brain injury in a rat model of subarachnoid hemorrhage. *J Cereb Blood Flow Metab* 2016; 36: 1224–1231.
9. Astrup J, Siesjö BK, Symon L. Thresholds in cerebral ischemia – the ischemic penumbra. *Stroke* 1981; 12: 723–725.
10. Ebinger M, De Silva DA, Christensen S, et al. Imaging the penumbra – strategies to detect tissue at risk after ischemic stroke. *J Clin Neurosci* 2009; 16: 178–187.
11. Dijkhuizen RM, Beekwilder JP, van der Worp HB, Berkelbach van der Sprenkel JW, Tulleken KA, Nicolay K. Correlation between tissue depolarizations and damage in focal ischemic rat brain. *Brain Res* 1999; 840: 194–205.
12. Dohmen C, Sakowitz OW, Fabricius M, et al. Spreading depolarizations occur in human ischemic stroke with high incidence. *Ann Neurol* 2008; 63: 720–728.
13. Nakamura H, Strong AJ, Dohmen C, et al. Spreading depolarizations cycle around and enlarge focal ischaemic brain lesions. *Brain* 2010; 133: 1994–2006.
14. Woitzik J, Hecht N, Pinczolis A, et al. Propagation of cortical spreading depolarization in the human cortex after malignant stroke. *Neurology* 2013; 80: 1095–1102.
15. Gursay-Ozdemir Y, Qiu J, Matsuoka N, et al. Cortical spreading depression activates and upregulates MMP-9. *J Clin Invest* 2004; 113: 1447–1455.
16. Leira R, Sobrino T, Rodriguez-Yanez M, Blanco M, Arias S, Castillo J. Mmp-9 immunoreactivity in acute migraine. *Headache* 2007; 47: 698–702.
17. Jung JE, Kim GS, Chen H, et al. Reperfusion and neurovascular dysfunction in stroke: from basic mechanisms to potential strategies for neuroprotection. *Mol Neurobiol* 2010; 41: 172–179.
18. Dreier JP. The role of spreading depression, spreading depolarization and spreading ischemia in neurological disease. *Nat Med* 2011; 17: 439–447.
19. Mawet J, Eikermann-Haerter K, Park KY, et al. Sensitivity to acute cerebral ischemic injury in migraineurs: a retrospective case-control study. *Neurology* 2015; 85: 1945–1949.
20. van Seeters T, Biessels GJ, van der Schaaf IC, et al. Prediction of outcome in patients with suspected acute ischaemic stroke with CT perfusion and CT angiography: the Dutch acute stroke trial

- (DUST) study protocol. *BMC Neurol* 2014; 14: 37.
21. van der Willik D, Pelzer N, Algra A, Terwindt GM, Wermer MJ. Assessment of migraine history in patients with a transient ischemic attack or stroke: validation of a migraine screener for stroke. *Eur Neurol* 2017; 77: 16–22.
 22. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993; 24: 35–41.
 23. Bamford J, Sandercock P, Dennis M, et al. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet* 1991; 337: 1521–1526.
 24. Barber PA, Demchuk AM, Zhang J, Burn J, Warlow C. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. *Lancet* 2000; 355: 1670–1674.
 25. Hill MD, Demchuk AM, Goyal M, et al. Alberta Stroke Program early computed tomography score to select patients for endovascular treatment: Interventional Management of Stroke (IMS)-III Trial. *Stroke* 2014; 45: 444–449.
 26. Tan IY, Demchuk AM, Hopyan J, et al. CT angiography clot burden score and collateral score: correlation with clinical and radiologic outcomes in acute middle cerebral artery infarct. *AJNR Am J Neuroradiol* 2009; 30: 525–531.
 27. Tan JC, Dillon WP, Liu S, Adler F, Smith WS, Wintermark M. Systematic comparison of perfusion-CT and CT-angiography in acute stroke patients. *Ann Neurol* 2007; 61: 533–543.
 28. Aoki J, Tateishi Y, Cummings CL, et al. Collateral flow and brain changes on computed tomography angiography predict infarct volume on early diffusion-weighted imaging. *J Stroke Cerebrovasc Dis* 2014; 23: 2845–2850.
 29. Wintermark M, Flanders AE, Velthuis B, et al. Perfusion-CT assessment of infarct core and penumbra: receiver operating characteristic curve analysis in 130 patients suspected of acute hemispheric stroke. *Stroke* 2006; 37: 979–985.
 30. van Seeters T, Biessels GJ, Niesten JM, et al. Reliability of visual assessment of non-contrast CT, CT angiography source images and CT perfusion in patients with suspected ischemic stroke. *PLoS One* 2013; 8: e75615.
 31. Campbell BC, Christensen S, Levi CR, et al. Cerebral blood flow is the optimal CT perfusion parameter for assessing infarct core. *Stroke* 2011; 42: 3435–3440.
 32. Olivot JM, Mlynash M, Thijs VN, et al. Optimal Tmax threshold for predicting penumbral tissue in acute stroke. *Stroke* 2009; 40: 469–475.
 33. Bennink E, Horsch AD, Dankbaar JW, Velthuis BK, Viergever MA, de Jong HW. CT perfusion analysis by nonlinear regression for predicting hemorrhagic transformation in ischemic stroke. *Med Phys* 2015; 42: 4610–4618.
 34. Berger C, Fiorelli M, Steiner T, et al. Hemorrhagic transformation of ischemic brain tissue: asymptomatic or symptomatic? *Stroke* 2001; 32: 1330–1335.
 35. van Seeters T, Biessels GJ, Kappelle LJ, et al. CT angiography and CT perfusion improve prediction of infarct volume in patients with anterior circulation stroke. *Neuroradiology* 2016; 58: 327–337.
 36. Back T, Ginsberg MD, Dietrich WD, Watson BD. Induction of spreading depression in the ischemic hemisphere following experimental middle cerebral artery occlusion: effect on infarct morphology. *J Cereb Blood Flow Metab* 1996; 16: 202–213.
 37. Busch E, Gyngell ML, Eis M, Hoehn-Berlage M, Hossmann KA. Potassium-induced cortical spreading depressions during focal cerebral ischemia in rats: contribution to lesion growth assessed by

- diffusion-weighted NMR and biochemical imaging. *J Cereb Blood Flow Metab* 1996; 16: 1090–1099.
38. Borkum JM. The migraine attack as a homeostatic, neuroprotective response to brain oxidative stress: preliminary evidence for a theory. *Headache* 2018; 58: 118–135.
 39. Rist PM, Buring JE, Kase CS, Schürks M, Kurth T. Migraine and functional outcome from ischemic cerebral events in women. *Circulation* 2010; 122: 2551–2557.
 40. Woods RP, Iacoboni M, Mazziotta JC. Brief report: bilateral spreading cerebral hypoperfusion during spontaneous migraine headache. *N Engl J Med* 1994; 331: 1689–1692.
 41. van Os HJA, Ruigrok YM, Verbaan D, et al. Delayed cerebral ischaemia after subarachnoid haemorrhage in patients with a history of migraine. *Eur stroke J* 2018; 3(1S): 3–586.