Hacking stroke in women: towards aetiology-driven precision prevention

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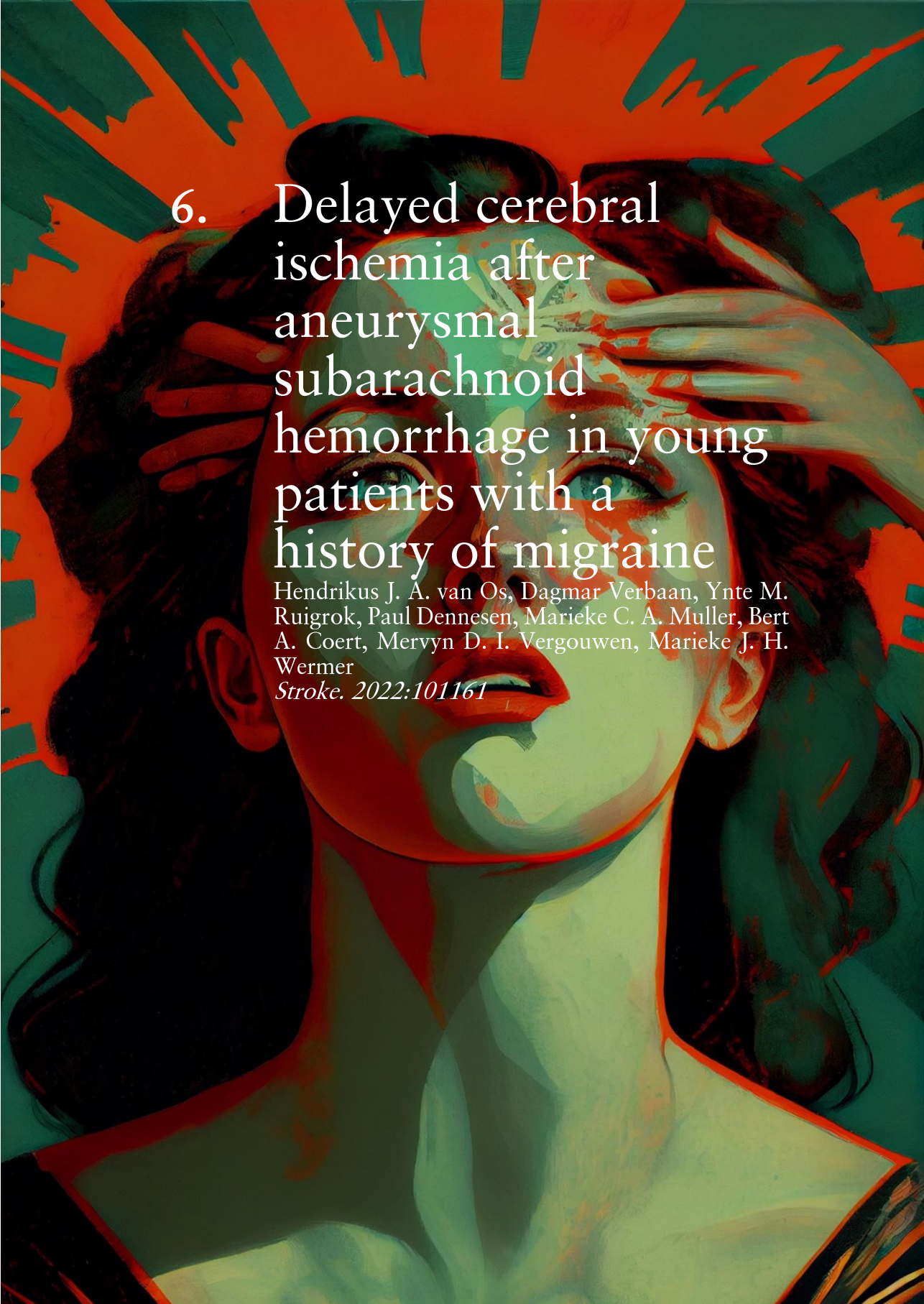

6. Delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage in young patients with a history of migraine

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Stroke. 2022:101161

Abstract

Background and purpose: Young patients with aneurysmal subarachnoid hemorrhage (aSAH) and a history of migraine may have an increased risk of delayed cerebral ischemia (DCI). We investigated this potential association in a prospective cohort of aSAH patients under 50 years of age.

Methods: We included patients with aSAH under 50 years from three hospitals in the Netherlands. We assessed life-time migraine history with a short screener. DCI was defined as neurological deterioration lasting >1 hour not attributable to other causes by diagnostic work-up. Adjustments were made for possible confounders in multivariable Cox regression analyses and adjusted hazard ratios (aHR) were calculated.

Results: We included 236 young aSAH patients (mean age 41 years, 64% women) of whom 44 (19%) had a history of migraine (16 with aura). Patients with aSAH and a history of migraine were not at increased risk of developing DCI compared with patients without migraine (25% versus 20%, aHR: 1.16; 95% CI: 0.57–2.35). Additionally, no increased risk was found in migraine patients with aura (aHR: 0.85; 95% CI: 0.30–2.44) or in women (aHR: 1.24; 95% CI: 0.58–2.68).

Conclusion: Patients with aSAH under the age of 50 years with a history of migraine are not at increased risk of DCI.

Introduction

Delayed cerebral ischemia (DCI) is a major contributor to the high morbidity and mortality in patients who survive subarachnoid hemorrhage from a ruptured aneurysm (aSAH). DCI occurs in around 30% of aSAH patients, mostly between days four and fourteen after hemorrhage onset.[1] The mechanisms underlying DCI are still largely unknown, although cortical spreading depolarizations (CSDs) may play a role.[2] CSDs are the presumed underlying mechanism of a migraine aura and are characterized by slowly spreading waves of intense neuroglial depolarizations followed by silencing of brain activity. Migraine with aura (MA) is associated with an approximately two-fold increased risk of ischemic and hemorrhagic stroke, especially in women.[3] One case-control study suggested that women with migraine might have an increased risk of developing DCI after aSAH compared with women without migraine. However, sample size was limited to 72 patients and only women were included.[4] Recently we found in a large prospective cohort (n=582) that adult aSAH patients with migraine were not at increased risk of DCI (adjusted hazards ratio: 1.55;95%CI:0.53–4.57). However, we found a statistically significant interaction between migraine history and age, indicating a potential association between risk of DCI and history of migraine in young patients.[5] Since then, additional patients under 50 years were included in this cohort. In the current study we assess the potential association between migraine history and development of DCI specifically in the cohort of aSAH patients under 50 years of age.

Methods

We included patients under the age of 50 admitted with aSAH between 2008-2021 to two University hospitals (the University Medical Center Utrecht [UMCU] and the Amsterdam University Medical Center, location Meibergdreef [Amsterdam UMC]) and one large teaching hospital (Haaglanden Medical Center [HMC]). In all centers baseline characteristics were collected, and outcome was assessed using the mRS score. Data on migraine were collected via a validated questionnaire.[6] Since for migraine with aura the positive predictive value is relatively low, we decided to use the term migraine with possible aura.[5, 6] For data collection on patients with aSAH, in the three centers medical ethical approval was waived.

DCI was defined based on a previously published consensus statement as the occurrence of focal neurological impairment or a decrease of at least two points on the Glasgow Coma Scale. The symptoms had to last for at least one hour, were not present immediately after aneurysm occlusion, and could not be attributed to other causes. DCI was prospectively assessed during hospitalization by neurologists, neurosurgeons, or neurology or neurosurgery residents.

We determined that the required sample size was 228 based on an alpha of 5%, a power of 80%, and the odds ratio from a previous observational study (OR: 2.68).[4] We performed survival analysis to investigate whether migraine (with and without possible aura combined or with possible aura only) is associated with occurrence of DCI. Adjustments were made for possible confounders (age, sex, GCS at admission) in multivariable Cox regression analyses, and hazard ratios (HR) and adjusted HR (aHR) with 95% confidence intervals (CI) were calculated. We constructed a Kaplan-Meier curve showing the cumulative incidence of DCI for patients with and without a history of migraine.

Results

In total, 236 patients under 50 years (mean age 41 years, 64% women) with complete data on both migraine and DCI were included (Table 1). Forty-four (19%) patients had a history of migraine of whom 22 (9%) had migraine with possible aura. Patients with a history of migraine were not at increased risk for developing DCI compared to patients without migraine (25% versus 20%, aHR: 1.16; 95% CI: 0.57–2.35). In addition, no increased DCI risk was found in patients with migraine with possible aura compared to SAH patients without migraine (18% versus 20%, aHR: 0.85; 95% CI: 0.30–2.44). After stratification for sex, we did not find an association between migraine and DCI development in women (aHR: 1.24; 95% CI: 0.58–2.68). The Kaplan-Meier curve (Figure) showed no difference in cumulative incidence of DCI between patients with and without a history of migraine (Log-rank test p = 0.52).

Table 1. Baseline characteristics of the participants

Characteristics	Migraine (n=44)	Migraine with aura (n=22)	No migraine (n=192)
Demographics			
Age, *mean years ± SD*	42±6	41±7	41±7
Women, *n (%)*	36 (82%)	18 (82%)	114 (59%)
History, *n (%)*			
Hypertension	13 (30%)	7 (33%)	47 (26%)
Diabetes mellitus	1 (2%)	1 (5%)	1 (1%)
Hyperlipidemia	4 (9%)	3 (14%)	11 (6%)
Cardiovascular disease*	2 (5%)	1 (5%)	8 (4%)
SAH	2 (5%)	0 (0%)	4 (2%)
SAH in family history	1 (5%)	0 (0%)	2 (3%)
Intracranial hemorrhage	1 (2%)	0 (0%)	0 (0%)
Smoking: current**	25 (57%)	14 (64%)	93 (50%)
Alcohol use: any**	16 (40%)	7 (37%)	120 (66%)
Medication use on admission, *n (%)***			
Oral anticoagulation	0 (0%)	0 (0%)	1 (1%)
Oral contraceptive	6 (33%)	2 (18%)	13 (33%)
Platelet aggregation inhibitor	2 (8%)	2 (13%)	1 (1%)
GCS on admission *(IQ range)*	15 (13–15)	15 (13–15)	15 (13–15)
GCS on admission < 13, *n (%)*	6 (20%)	3 (20%)	26 (21%)

**History of ischemic stroke, myocardial infarction or peripheral artery disease*

***Within 6 months before admission*

****Assessed in the UMCU and the HMC only*

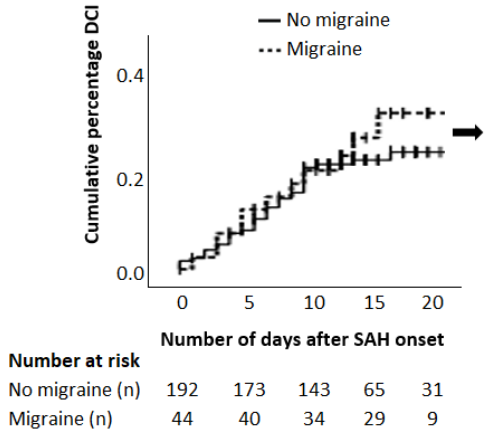
Table 2. Risk for delayed cerebral ischemia in patients with and without migraine, stratified by sex

Presence of DCI (n/N (%))	Migraine	MA	No migraine	Migraine vs. no migraine HR (95% CI)	Migraine vs. no migraine aHR (95% CI)	MA vs. no migraine aHR (95% CI)
All patients (n=236)	11/44 (25%)	4/22 (18%)	38/192 (20%)	1.25 (0.63–2.44)	1.16 (0.57–2.35)[1]	0.85 (0.30–2.44)[1]
Women (n=150)	10/36 (28%)	5/18 (22%)	27/114 (24%)	1.16 (0.56–2.39)	1.24 (0.58–2.68)[2]	1.01 (0.35–2.90)[2]
Men (n=86)	1/8 (13%)	0/4 (0%)	11/78 (14%)	0.81 (0.10–6.26)	0.65 (0.08–5.15)[2]	NA[2]

MA: Migraine with MA: Migraine with aura

Adjusted for age, sex and GCS at admission[1], for age and GCS at admission[2], and for sex and GCS at admission[3]

Figure. DCI rate over time in patients with and without a history of migraine



**The Kaplan-Meier curve has been cut off at 20 days, because after this time no more DCI occurred.*

Discussion

This study shows that patients under 50 years with a history of migraine are not at increased risk of developing DCI. Since migraine patients have a relatively more active form of migraine in young age, they may be more susceptible for CSDs compared with older patients in whom the last migraine attack is often many years before the aSAH.[7] In contrast with our hypothesis, we do not find an association between patients who were presumed to be more sensitive to CSDs and risk of DCI. This could indicate that the contribution of CSDs is relatively weak compared with other pathophysiological processes that may play a role in the development of DCI, such as microthrombosis or impaired cerebral autoregulation.[8]

For the current study, we expanded the number of young aSAH patients to increase our power. Our sample size calculations were based on a case-control study that included 72 age-matched women under 60 years and found an OR of 2.68 for the association between DCI and history of migraine.[4] However, as the authors of that study already acknowledged, this OR may have been an overestimation since it was based on a small dataset of matched pairs.[9] Although in our study no association between migraine and DCI was found, we still cannot completely exclude an effect size smaller than the odds ratio of 2.68 that could reach statistical significance when assessed in a larger cohort. However, based on our results it is unlikely that the association between migraine and DCI is substantial and clinically relevant.

Several shortcomings of our study must be considered. First, the migraine screener could only be assessed in patients in a well enough condition to answer the questions during admission. Therefore, we cannot generalize our results to a more severe aSAH population. Second, there are limitations on use of our migraine screener which have been described in the previous publication on this cohort.[5] Strong points of our study are the prospectively collected large sample of young patients with aSAH, and the detailed and uniform assessment of DCI. We conclude that a positive history of migraine is not a factor to take into account in treating patients with aSAH at risk of DCI.

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