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

Os, H.J.A. van; Verbaan, D.; Ruigrok, Y.M.; Dennesen, P.; Muller, M.C.A.; Coert, B.A.; ... ; Wermer, M.J.H.

BRIEF REPORT

Delayed Cerebral Ischemia After Aneurysmal Subarachnoid Hemorrhage in Young Patients With a History of Migraine

Hendrikus J.A. van Os , MD; Dagmar Verbaan , PhD; Ynte M. Ruigrok , MD, PhD; Paul Dennesen , MD, PhD; Marcella C.A. Müller , MD, PhD; Bert A. Coert, MD, PhD; Mervyn D.I. Vergouwen , MD, PhD; Marieke J.H. Wermer , MD, PhD

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

METHODS: In our prospective cohort study, we included patients with aSAH under 50 years of age from 3 hospitals in the Netherlands. We assessed lifetime migraine history with a short screener. Delayed cerebral ischemia was defined as neurological deterioration lasting >1 hour not attributable to other causes by diagnostic workup. Adjustments were made for possible confounders in multivariable Cox regression analyses, and adjusted hazard ratios 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 delayed cerebral ischemia compared with patients without migraine (25% versus 20%; adjusted hazard ratio, 1.16 [95% CI, 0.57–2.35]). Additionally, no increased risk was found in migraine patients with aura (adjusted hazard ratio, 0.85 [95% CI, 0.30–2.44]) or in women (adjusted hazard ratio, 1.24 [95% CI, 0.58–2.68]).

CONCLUSIONS: Patients with aSAH under the age of 50 years with a history of migraine are not at increased risk of delayed cerebral ischemia.

Key Words: epilepsy ■ hospitals ■ middle aged ■ migraine disorders ■ subarachnoid hemorrhage

Delayed cerebral ischemia (DCI) is a major contributor to the high morbidity and mortality in patients who survive subarachnoid hemorrhage from a ruptured aneurysm (aneurysmal subarachnoid hemorrhage [aSAH]). DCI occurs in around 30% of aSAH patients, mostly between days 4 and 14 after hemorrhage onset.[1] The mechanisms underlying DCI are still largely unknown, although cortical spreading depolarizations (CSDs) may play a role.[2] CSDs are likely to be the 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 is associated with an ≈2-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 hazard ratio [aHR], 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 of age were included in this cohort. In the current study, we assess the potential association between migraine

Table 1. Baseline Characteristics of the Participants

Characteristics	Migraine (n=44)	Migraine with aura (n=22)	No migraine (n=192)
Demographics			
Age, y; mean±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	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 on admission, n (%)‡			
Oral anticoagulation use	0 (0%)	0 (0%)	1 (1%)
Oral contraceptive use	6 (33%)	2 (18%)	13 (33%)
Platelet aggregation inhibitor use	2 (8%)	2 (13%)	1 (1%)
GCS on admission (IQR)	15 (13–15)	15 (13–15)	15 (13–15)
GCS on admission <13, n (%)	6 (20%)	3 (20%)	26 (21%)

GCS indicates Glasgow Coma Scale; HMC, Haaglanden Medical Center; IQR, interquartile range; SAH, subarachnoid hemorrhage; and UMCU, University Medical Center Utrecht.

*History of ischemic stroke, myocardial infarction, or peripheral artery disease.
†Current smoking: within 6 mo before admission.
‡Medication on admission was assessed in the UMCU and the HMC only.

history and development of DCI specifically in the cohort of aSAH patients under 50 years of age.

METHODS

In our prospective cohort study, we included patients under the age of 50 years admitted with aSAH between 2008 and 2021 to 2 university hospitals (the University Medical Center Utrecht and the Amsterdam University Medical Center, location Meibergdreef [Amsterdam UMC]) and 1 large teaching hospital (Haaglanden Medical Center). In all centers, baseline characteristics were collected, and outcome was assessed using the modified Rankin Scale 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 3 centers, medical ethical approval was waived. The authors declare that all supporting data are available within the article.

DCI was defined based on a previously published consensus statement as the occurrence of focal neurological impairment or a decrease of at least 2 points on the Glasgow Coma Scale. The symptoms had to last for at least 1 hour, were not present immediately after aneurysm occlusion, and could not be attributed to other causes. DCI was prospectively assessed during hospitalization by trained neurologists.

We determined that the required sample size was 228 based on an alpha of 5%, a power of 80%, and the odds ratio (OR) 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 the occurrence of DCI. Adjustments were made for possible confounders (age, sex, and Glasgow Coma Scale on admission) in multivariable Cox regression analysis, and hazard ratios and aHRs with 95% CIs were calculated. In addition, 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 of age (mean age, 41 years; 64% women) with complete data on both migraine and DCI were included. Forty-four (19%) patients had a history of migraine of whom 22 (9%) had migraine with possible aura (Table 1).

Patients with a history of migraine were not at increased risk for developing DCI compared with 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 with 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]; Table 2). 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).

DISCUSSION

This study shows that patients under 50 years of age with a history of migraine are not at increased risk of

Table 2. Risk for DCI in Patients With and Without Migraine, Stratified by Sex

Presence of DCI, n (%)	Migraine	MA	No migraine	Migraine versus no migraine, HR (95% CI)	Migraine versus no migraine, aHR (95% CI)	MA versus 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)*	0.85 (0.30–2.44)*
Women (n=150)	10/36 (28%)	5/18 (22%)	27/114 (24%)	1.16 (0.56–2.39)	1.24 (0.58–2.68)†	1.01 (0.35–2.90)†
Men (n=86)	1/8 (13%)	0/4 (0%)	11/78 (14%)	0.81 (0.10–6.26)	0.65 (0.08–5.15)†	NA†

aHR indicates adjusted hazard ratio; DCI, delayed cerebral ischemia; GCS, Glasgow Coma Scale; HR, hazard ratio; MA, migraine with aura; and NA, not available.
*HR adjusted for age, sex, and GCS on admission.
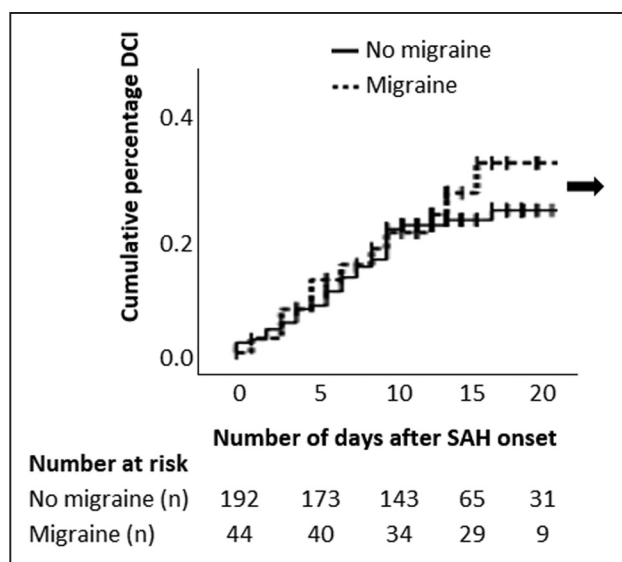†HR adjusted for age and GCS on admission.

Figure. Delayed cerebral ischemia (DCI) rate over time in patients with and without a history of migraine.
SAH indicates subarachnoid hemorrhage. *The Kaplan-Meier curve has been cut off at 20 d, as after this time no more DCI occurred.

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 of age 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 data set of matched pairs.[9] Although in our study no association between migraine and DCI was found, we still cannot completely exclude an effect size that is smaller than the OR of 2.68 but statistically significant when assessed in a larger cohort. However, based on our results, it is unlikely that the association between migraine and DCI would be 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.

ARTICLE INFORMATION

Affiliations

Department of Neurology, Leiden University Medical Center, the Netherlands (H.J.A.v.O., M.J.H.W.). Department of Neurosurgery and Amsterdam Neuroscience, Amsterdam UMC (D.V., B.A.C.). Department of Neurology and Neurosurgery, UMC Utrecht Brain Center, University Medical Center Utrecht and Utrecht University, the Netherlands (Y.M.R., M.D.I.V.). Department of Intensive Care, Haaglanden Medical Center, The Hague, the Netherlands (P.D.). Department of Intensive Care, Amsterdam UMC, University of Amsterdam, the Netherlands (M.C.A.M.).

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Disclosures

None.

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