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

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

Stroke

CLINICAL AND POPULATION SCIENCES

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

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

BACKGROUND AND PURPOSE: Delayed cerebral ischemia (DCI) is a major contributor to the high morbidity in patients with aneurysmal subarachnoid hemorrhage (aSAH). Spreading depolarizations may play a role in DCI pathophysiology. Because patients with migraine are probably more susceptible to spreading depolarizations, we investigated whether patients with aneurysmal subarachnoid hemorrhage with migraine are at increased risk for DCI.

METHODS: We included patients with aneurysmal subarachnoid hemorrhage from 3 hospitals in the Netherlands. We assessed lifetime 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. We assessed the interaction effects of age and sex.

RESULTS: We included 582 patients (mean age 57 years, 71% women) mostly with mild to moderate aneurysmal subarachnoid hemorrhage of whom 108 (19%) had a history of migraine (57 with aura). Patients with migraine were not at increased risk of developing DCI compared with patients without migraine (22% versus 24%, aHR, 0.89 [95% CI, 0.56–1.43]). Additionally, no increased risk was found in patients with migraine with possible aura (aHR, 0.74 [95% CI, 0.39–1.43]), in women (aHR, 0.88 [95% CI, 0.53–1.45], $P_{interaction}$=0.859), or in young patients aged <50 years (aHR, 1.59 [95% CI, 0.72–3.49]), although numbers in these subgroups were limited. We found an interaction between migraine and age with an increased risk of DCI among young patients with migraine ($P_{interaction}$=0.075).

CONCLUSIONS: Patients with migraine are in general not at increased risk of DCI. Future studies should focus in particular on young SAH patients, in whom there might be an association between migraine history and development of DCI.

Key Words: aneurysm ■ brain ■ hemolysis ■ hemorrhage ■ hyperemia

Subarachnoid hemorrhage from a ruptured aneurysm (aSAH) results in death within 3 months of around one-third of all patients, and more than half of all survivors make an incomplete recovery.[1] A major contributor to the high morbidity in patients who survive is delayed cerebral ischemia (DCI). DCI occurs in around 30% of patients with SAH, mostly between day 4 and 10 after hemorrhage onset.[2] The mechanisms underlying DCI are still largely unknown.

Several animal experiments suggest that spreading depolarizations (SDs) play a role in the development of DCI, possibly induced by products of hemolysis.[3–6] SDs are the underlying mechanism of a migraine aura and are characterized by slowly spreading waves of intense neuroglial depolarizations followed by silencing of brain activity. Hemodynamically, SDs start with a short hyperemia which is followed by a prolonged period of oligemia. The normal hemodynamic response to SDs in metabolic

Correspondence to: Hendrikus J.A. van Os, Leiden University Medical Center, Albinusdreef 2, 2333 ZA, Leiden, the Netherlands. Email h.j.a.van_os@lumc.nl
This manuscript was sent to Jean-Claude Baron, Guest Editor, for review by expert referees, editorial decision, and final disposition.
For Sources of Funding and Disclosures, see page 3044.

Stroke is available at www.ahajournals.org/journal/str

Nonstandard Abbreviations and Acronyms

aHR	adjusted hazard ratio
aSAH	aneurysmatic subarachnoid hemorrhage
DCI	delayed cerebral ischemia
HR	hazard ratio
SAH	subarachnoid hemorrhage
SD	spreading depolarization

intact brain tissue is characterized by spreading hyperemia followed by (reversible) oligemia. However, in pathological situations—for example after aSAH—an inverse hemodynamic response can occur in which case spreading ischemia is followed by hyperemia.[7] In one study repetitively induced SDs resulted in neuronal death in the juvenile SAH rat brain, confirming that spreading oligemia following SDs can in certain circumstances progress to tissue ischemia.[8] Additionally, valproate—which is an SD inhibitor—prevented SD related delayed brain injury in rats after experimental SAH.[9] In a small pilot study of patients with aneurysmal subarachnoid hemorrhage with the aneurysms treated by clipping, SDs have been recorded directly with electrocorticography, and SD patterns seemed to be related to DCI development.[10,11]

Migraine with possible aura increases the risk of ischemic and hemorrhagic stroke ≈2-fold, especially in women.[12–14] 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 and only women were included.[5]

In this study, we investigated in a large prospectively collected cohort of patients with aneurysmal subarachnoid hemorrhage whether patients with migraine are at increased risk of developing DCI compared with patients without migraine.

METHODS

Patients

We included patients from 2 University hospitals (the University Medical Center Utrecht [UMCU] and the Amsterdam University Medical Center, University of Amsterdam [Amsterdam UMC]) and 1 large teaching hospital (Haaglanden Medical Center [HMC]). In the UMCU, we included consecutive patients admitted for aSAH in the period from 2008 to 2018. In the HMC, we consecutively included patients admitted for aSAH from 2014 to 2016. In all centers the following baseline characteristics were collected during admission: modified Rankin Scale score before admission, age, sex, cardiovascular risk factors, history of cardiovascular disease, Glasgow Coma Scale score at admission, location of aneurysm, and aneurysm treatment modality. Outcome was assessed via modified Rankin Scale score at discharge and after 3 (UMCU and HMC) or 6 months (Amsterdam UMC). The authors declare that all supporting data are available within the article.

Standard Protocol Approvals, Registrations, and Patient Consents

In the UMCU, data for this study were collected within the context of the String of Pearls study. This study was approved by the Medical Ethical Committee, and informed consent was obtained from all patients for use of the data. In the Amsterdam UMC and the HMC data were collected in the context of the NIASH registration. Medical ethical approval was not required for this registration.

Migraine Questionnaire

In all 3 participating centers research nurses recorded a migraine screener.[15] From this screener, the following questions were used for this study: (1) "Did you ever or do you still have migraine attacks?" (2) "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?" (3) "Did you ever experience periods that lasted between 5 and 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?" A history of migraine was considered to be present when answers to both question 1 and 2 were positive. If answers to all 3 questions were positive, patients were classified as having migraine with possible aura. The migraine screener has been validated previously in a stroke population. For the combination of questions we used in our study, the positive predictive value for migraine was 0.78, and the negative predictive value was 0.97. For migraine with aura, the negative predictive value was 0.97, but the positive predictive value was only 0.38. Therefore, we decided to use the term migraine with possible aura in this study.[15]

Assessment of Delayed Cerebral Ischemia

DCI was defined as the occurrence of focal neurological impairment (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect) 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 after clinical assessment, computed tomography or magnetic resonance imaging scanning of the brain, and appropriate laboratory studies. DCI was assessed during hospitalization.[16]

Sample Size Calculation

To calculate the sample size needed we choose an alpha of 5% and a power of 80%. We expected DCI to occur in around 30% of unexposed patients.[2] Migraine prevalence was found to be around 17% in patients with aneurysmal SAH,[17] and one-third of patients with migraine were expected to have migraine with aura.[18] For our calculation, we used the odds ratio from a previous observational study investigating the risk of developing DCI in patients with migraine versus those without (odds ratio, 2.68).[5] Based on these parameters, a total sample size of 228 patients was needed to detect an association with overall migraine, and 551 to detect an association with migraine with aura.[19]

Statistical Analysis

Because the development of DCI is time-dependent, we performed a 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 a multivariable Cox regression analysis, and hazard ratios (HR) and adjusted HR (aHR) with 95% CI were calculated. Because migraine is more often active in young patients and in women, we stratified for age <50 years and sex, and we included the interaction terms age×migraine and sex×migraine in the analyses.[18] Statistical testing for interactions was done using an a priori α=0.10.[20] In addition, we constructed a Kaplan-Meier curve showing DCI-free survival of patients with and without a history of migraine. We calculated adjusted relative risks for outcome with Poisson regression.

RESULTS

Patients

In total, 879 patients were eligible for the study. Of these patients, 582 had complete data on both migraine and DCI and were included. Most patients who were included had mild and moderate aSAH. Baseline characteristics of excluded patients were comparable with those of included patients (data not shown). Mean age of the included patients was 57±13 (SD) years and 415 (71%) were women (Table 1). A history of migraine was reported in 108 (19%) patients, and 57 (10%) patients had migraine with possible aura. Patients with migraine were more often female. Clinical outcome at 3 months was available for 294 of 382 patients (77%) from the UMCU and HMC, and clinical outcome at 6 months for 185 of 200 patients (93%) from the Amsterdam UMC.

Delayed Cerebral Ischemia

Patients with a history of migraine were not at increased risk for developing DCI compared to patients without migraine (22% versus 24%, aHR, 0.88 [95% CI, 0.53–1.45]). In addition, no increased DCI risk was found in patients with migraine with possible aura compared with patients with SAH without migraine (20% versus 24%, aHR, 0.74 [95% CI, 0.39–1.43]).

After stratification for sex, we did not find an association between migraine and DCI development in women (aHR, 0.88 [95% CI, 0.53–1.45]), and interaction between migraine and sex was not statistically significant ($P_{interaction=}$0.859). After stratification for age, we also did not find an association between migraine and DCI development in patients <50 years (aHR, 1.59 [95% CI, 0.72–3.49]). However, the point estimate of the association changed from 0.70 in patients ≥50 to 1.59 in patients <50 years old, and we found an interaction between migraine and age ($P_{interaction}$=0.075; Table 2).

Table 1. Baseline Characteristics of the Participants

Characteristics	Migraine (n=108)	MA (n=57)	No Migraine (n=474)
Demographics			
Age, mean years±SD	56±12	58±13	58±13
Women, n (%)	90 (83%)	49 (86%)	325 (69%)
History, n (%)			
Hypertension	42 (40%)	22 (39%)	185 (40%)
Diabetes mellitus	4 (4%)	3 (5%)	20 (4%)
Hyperlipidemia	20 (19%)	14 (25%)	87 (19%)
Cardiovascular disease*	10 (9%)	6 (11%)	56 (12%)
SAH	4 (4%)	2 (4%)	13 (2%)
SAH in family history	2 (4%)	2 (6%)	5 (3%)
Intracranial hemorrhage	1 (1%)	0 (0%)	3 (1%)
Smoking: current†	54 (52%)	12 (20%)	217 (48%)
Smoking: past†	20 (19%)	30 (51%)	100 (22%)
Alcohol use†	51 (49%)	30 (55%)	277 (62%)
Medication on admission, n (%)†			
Oral anticoagulation use	1 (2%)	1 (3%)	12 (5%)
Oral contraceptive use	7 (14%)	3 (10%)	17 (11%)
Platelet aggregation inhibitor use	9 (15%)	6 (16%)	29 (12%)
GCS at admission (IQ range)	15 (13–15)	15 (13–15)	15 (13-15)
GCS at admission <13, n (%)	17 (18%)	7 (13%)	102 (23%)

GCS indicates Glasgow Coma Scale; HMC, Haaglanden Medical Center; IQ, intelligence quotient; MA, migraine with possible aura; SAH, subarachnoid hemorrhage; and UMCU, University Medical Center Utrecht.

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

†Current smoking: within 6 months before admission; past smoking: quit smoking >6 months before admission; alcohol use: any use of alcohol.

‡Medication at admission was assessed in the UMCU and the HMC only.

The Kaplan-Meier curve (Figure) showed no difference in time to DCI between patients with and without a history of migraine (log-rank test *P*=0.474).

Clinical outcome was comparable between patients with and without a history of migraine. At 3-month follow-up after SAH, 83% patients with migraine versus 74% of patients without migraine had an modified Rankin Scale score ≤2 (adjusted relative risk, 1.02 [95% CI, 0.90–1.17]; data from UMCU, HMC), and at 6-month follow-up, 68% patients with migraine versus 79% patients without migraine had an modified Rankin Scale score ≤2 (adjusted relative risk, 0.82 [95% CI, 0.65–1.05]; data from Amsterdam UMC).

DISCUSSION

This study shows that patients with a history of migraine are in general not at increased risk of developing DCI. However, a possible association could not be excluded in the subgroup of patients <50 years because a statistically significant interaction was found between migraine and age. The subgroup of patients <50 years had a limited sample size leading to larger confidence intervals.

Table 2. Risk for Delayed Cerebral Ischemia in Patients With and Without Migraine, Stratified by Age and Sex

Presence of DCI (n/N [%])	Migraine	MA	No Migraine	Migraine vs No Migraine aHR (95% CI)	MA vs No Migraine aHR (95% CI)
All patients (n=582)	24/108 (22%)	11/55 (20%)	115/474 (24%)	0.89 (0.56–1.43)*	0.74 (0.39–1.43)*
Women (n=415)†	21/90 (23%)	10/47 (21%)	86/325 (27%)	0.88 (0.53–1.45)‡	0.73 (0.37–1.46)‡
Men (n=167)	3/18 (17%)	1/8 (13%)	29/149 (20%)	1.00 (0.30–3.36)‡	0.81 (0.11–6.03)‡
Age <50 y (n=151)	10/31 (32%)	4/13 (31%)	24/120 (20%)	1.59 (0.72–3.49)§	1.55 (0.53–4.57)§
Age ≥50 y (n=431)	14/77 (18%)	7/42 (17%)	91/353 (26%)	0.70 (0.39–1.26)§	0.56 (0.24–1.29)§

aHR indicates adjusted hazard ratio; DCI, delayed cerebral ischemia; GCS, Glasgow Coma Scale; and MA, migraine with possible aura.
*Hazard ratio adjusted for age, sex, and GCS at admission,
†Interaction between migraine and sex: 0.89 (0.24–3.26), *P*=0.859; interaction between migraine and age (continuous): 0.93 (0.94–1.00), *P*=0.075.
‡Hazard ratio adjusted for age and GCS at admission.
§Hazard ratio adjusted for sex and GCS at admission.

In one other study, the association between DCI and migraine in patients with aneurysmal subarachnoid hemorrhage was investigated. In that study, patients with migraine more often developed DCI (odds ratio, 2.68 [95% CI, 0.99–7.29]).[5] The study differed from our study on several important points. First, the study had a case-control design and included 36 young, female patients with aneurysmal subarachnoid hemorrhage who had developed DCI as cases and 36 age-matched female patients with aneurysmal subarachnoid hemorrhage without DCI as controls. The women were younger (mean age 42 years) and more patients had a history of migraine (36%) than the participants of our study. Additionally, assessment of migraine was different (open questionnaire based on ICHD-criteria versus our migraine screener). Both studies used the same definition of DCI. Although we found no association between migraine and risk of DCI in our entire population, the interaction between migraine and age suggests that young patients with migraine may have an increased risk of DCI, supporting the conclusion of the previous case-control study.[5]

SDs are considered to play an important role in the development of DCI after SAH. SDs are abrupt and sustained mass neuronal depolarizations initiating cytotoxic edema (water uptake by neurons) in the cerebral gray matter. SDs occur in various neurological diseases including all strokes that involve the cerebral cortex. They can be induced by several triggers, not only by trauma or ischemia but also by spasm of arteries or arterioles or various chemical factors induced by clotting or hemolysis. SDs and their pathomorphological correlate, cytotoxic edema, represent in principle a reversible process and in metabolic intact brain tissue they are mostly harmless. It is, for example, assumed that short-lasting SDs occur in patients with a migraine attack when they experience an aura. In this circumstance, there is a normal hemodynamic response to SDs characterized by spreading hyperemia followed by mild reversible oligemia after neuronal repolarization and edema recovery. Only if SDs and the associated cytotoxic edema are long-lasting, permanent neuronal damage develops. In such pathological situations, for example after stroke, an inverse hemodynamic response occurs where the depolarization

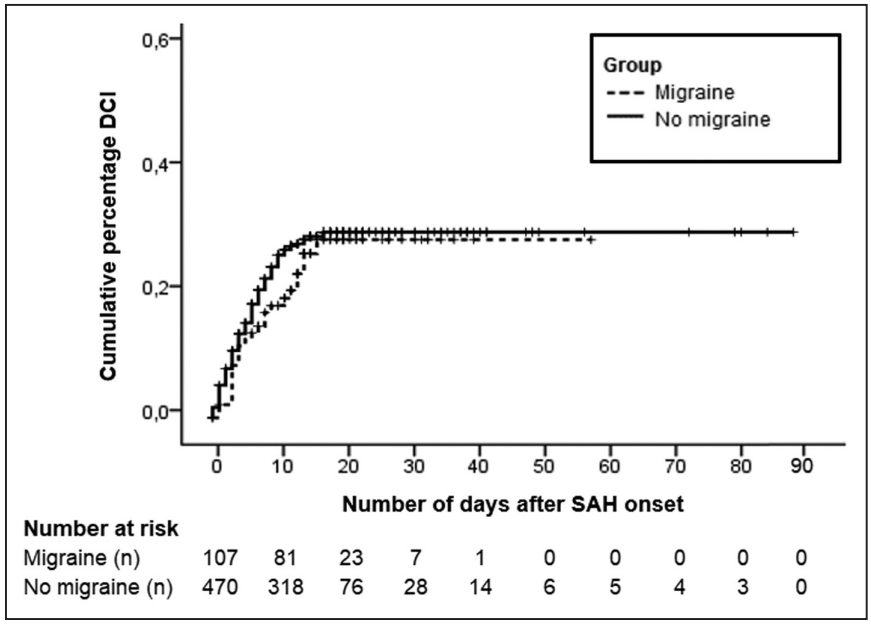

Figure. Delayed cerebral ischemia (DCI) rate over time in patients with and without migraine.
SAH indicates subarachnoid hemorrhage.

 Stroke. 2020;51:3039–3044. DOI: 10.1161/STROKEAHA.120.030118

phase can directly induce severe vasoconstriction and hypoperfusion subsequently followed by hyperemia.[5]

The possible increased risk of DCI in young patients with migraine—especially those with aura—might be mediated partly by increased susceptibility to SDs. Migraine aura is part of the so-called stroke-migraine depolarization continuums.[5] Migraine aura is only one of the numerous manifestations of the SD continuum. Although SDs are expected to accompany every cortical stroke, the occurrence of a migraine aura during stroke is rarely reported. Probably SDs do not easily cross the border between pathological and normal brain tissue. In addition, not all stroke patients might be able to report or perceive aura symptoms for example when their consciousness or self-awareness is impaired. Recently, a study reported one patient with aneurysmal subarachnoid hemorrhage who experienced a migraine aura while an SD was recorded on electrocorticography. The majority of awake patients with aneurysmal subarachnoid hemorrhage, however, did not report migraine auras during the recording of isolated SDs and patients with aneurysmal subarachnoid hemorrhage undergoing clusters of recurrent SDs often were or became unconscious.[13]"

Given the SD hypothesis underlying the association between DCI and migraine, it is also possible to explain why this association is strongest in a younger population. Younger patients with migraine are known to have a higher attack frequency and therefore more active migraine status in young patients.[18] Migraine activity may be related to an increased susceptibility to SDs, which could lead to increased risk of DCI development. A study in mice with the mutation for familial hemiplegic migraine showed that development of ischemia may be facilitated by an increased susceptibility to SDs. These mice were studied between an age of 2 to 6 months, which is biologically equivalent to human young adult age.[21] The risk increase of ischemic stroke risk in patients with migraine is also highest in patients under 45 years and has clearly been associated with a high attack frequency. These findings may also be related to an increased susceptibility to SDs in these patient subgroups.[14,22]

However, also other pathophysiological processes may be underlying the relation between migraine and risk of DCI. Migraine has been linked with endothelial dysfunction, an association that appears to be particularly strong in young women.[23] In patients with aneurysmal subarachnoid hemorrhage endothelial dysfunction also plays an important role in the development of DCI, thus patients with aneurysmal subarachnoid hemorrhage with migraine—especially those of younger age—may be more susceptible for the pathophysiological cascade of events leading up to DCI.[24]

Several shortcomings of our study must be considered. First, our study population had a better clinical outcome than the average SAH patient population. This reflects the problem that 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 SAH population. Second, our migraine screener had several limitations. In a validation study, the negative predictive value was found to be high and the positive predictive value moderate. For migraine with aura, the negative predictive value was high but positive predictive value was low; hence, we used the term possible aura.[15] The potential misclassification bias in migraine diagnosis and aura symptoms might have diluted the effect sizes we found in our study. Patients who answered "yes" to only one of the first 2 questions of the screener could have incorrectly been classified as nonmigraineurs. However, the proportion of patients who answered "yes" to only one question was low (7%), and the analyses excluding these patients or adding them to the migraine group showed essentially the same results (data not shown). Furthermore, because the questionnaire relates to history of migraine, patients who did not experience attacks for a long time may have forgotten information leading to recall bias. However, the migraine prevalence of 19% in our cohort was in line with the prevalence of 17% found by a previous study in patients with aneurysmal SAH.[17] Additionally, the majority of our study population consists of women, and migraine prevalence in women in the general population is found to be around 17%.[18] Unfortunately, we did not have information about current attack frequency of patients with migraine. Lastly, the diagnose of DCI is challenging, as it is simultaneously based on clinical assessment and the elimination of other possible causes via neuroimaging among.[14] Ideally, in patients with aneurysmal subarachnoid hemorrhage suspected of DCI, more often (preferably serial) brain MRI scans should be performed, increasing the certainty of the DCI diagnosis and therefore quality of research on this topic.

Strong points of this study include the relatively large sample size and the detailed and uniform assessment of DCI. The multicenter design including 2 academic and 1 large teaching hospital and the inclusion of men and women of all ages increases the generalizability of our study.

CONCLUSIONS

In the overall SAH population, we found no association between DCI development and history of migraine. However, we found an interaction between migraine and age suggesting that young patients with migraine may have an increased risk of DCI. Future studies with a larger number of young patients with SAH are needed to further study the association between migraine and DCI in this particular subgroup.

ARTICLE INFORMATION

Received April 8, 2020; final revision received June 24, 2020; accepted July 20, 2020.

Affiliations

Department of Neurology, Leiden University Medical Center, the Netherlands (H.J.A.v.O., M.J.H.W.). Department of Neurology and Neurosurgery (Y.M.R., A.A., M.D.I.V.) and Julius Center for Health Sciences and Primary Care, UMC Utrecht Brain Center, University Medical Center Utrecht and Utrecht University, the Netherlands. Department of Neurosurgery, Amsterdam University Medical Center, the Netherlands (D.V., B.A.C.). 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.).

Sources of Funding

Dr Wermer was supported by a personal Veni and Vidi grant from ZonMw, a Dekker Junior Staff Member Grant from the Dutch Heart Foundation (2011T055), and a Fellowship Grant from the Dutch Brain Foundation (F2014(1)-22). Dr Van Os was supported by a personal Dekker Junior Clinical Scientist Grant from the Dutch Heart Foundation (2018T082).

Disclosures

None.

REFERENCES

1. Macdonald RL, Schweizer TA. Spontaneous subarachnoid haemorrhage. *Lancet*. 2017;389:655–666. doi: 10.1016/S0140-6736(16)30668-7
2. Roos YB, de Haan RJ, Beenen LF, Groen RJ, Albrecht KW, Vermeulen M. Complications and outcome in patients with aneurysmal subarachnoid haemorrhage: a prospective hospital based cohort study in the Netherlands. *J Neurol Neurosurg Psychiatry*. 2000;68:337–341. doi: 10.1136/jnnp.68.3.337
3. Dreier JP, Ebert N, Priller J, Megow D, Lindauer U, Klee R, Reuter U, Imai Y, Einhäupl KM, Victorov I, et al. Products of hemolysis in the subarachnoid space inducing spreading ischemia in the cortex and focal necrosis in rats: a model for delayed ischemic neurological deficits after subarachnoid hemorrhage? *J Neurosurg*. 2000;93:658–666. doi: 10.3171/jns.2000.93.4.0658
4. Dreier JP, Körner K, Ebert N, Görner A, Rubin I, Back T, Lindauer U, Wolf T, Villringer A, Einhäupl KM, et al. Nitric oxide scavenging by hemoglobin or nitric oxide synthase inhibition by N-nitro-L-arginine induces cortical spreading ischemia when K+ is increased in the subarachnoid space. *J Cereb Blood Flow Metab*. 1998;18:978–990. doi: 10.1097/00004647-199809000-00007
5. Dreier JP, Kremer C, Lammers G, Lohmann F, Hansen HC, Valdueza JM. Migraine and delayed ischaemic neurological deficit after subarachnoid haemorrhage in women: a case-control study. *Eur J Neurol*. 2007;14:1363–1368. doi: 10.1111/j.1468-1331.2007.01980.x
6. Dreier JP, Petzold G, Tille K, Lindauer U, Arnold G, Heinemann U, Einhäupl KM, Dirnagl U. Ischaemia triggered by spreading neuronal activation is inhibited by vasodilators in rats. *J Physiol*. 2001;531(pt 2):515–526. doi: 10.1111/j.1469-7793.2001.0515i.x
7. Dreier JP, Reiffurth C. The stroke-migraine depolarization continuum. *Neuron*. 2015;86:902–922. doi: 10.1016/j.neuron.2015.04.004
8. Hamming AM, Wermer MJH, Umesh Rudrapatna S, Lanier C, van Os HJA, van den Bergh WM, Ferrari MD, van der Toorn A, van den Maagdenberg AMJM, Stowe AM, et al. Spreading depolarizations increase delayed brain injury in a rat model of subarachnoid hemorrhage. *J Cereb Blood Flow Metab*. 2016;36:1224–1231. doi: 10.1177/0271678X15619189
9. Hamming AM, van der Toorn A, Rudrapatna US, Ma L, van Os HJ, Ferrari MD, van den Maagdenberg AM, van Zwet E, Poinsatte K, Stowe AM, et al. Valproate reduces delayed brain injury in a rat model of subarachnoid hemorrhage. *Stroke*. 2017;48:452–458. doi: 10.1161/STROKEAHA.116.014738
10. Hartings JA, Wilson JA, Look AC, Vagal A, Shutter LA, Dreier JP, Ringer A, Zuccarello M. Full-band electrocorticography of spreading depolarizations in patients with aneurysmal subarachnoid hemorrhage. *Acta Neurochir Suppl*. 2013;115:131–141. doi: 10.1007/978-3-7091-1192-5_27
11. Dreier JP, Fabricius M, Ayata C, Sakowitz OW, Shuttleworth CW, Dohmen C, Graf R, Vajkoczy P, Helbok R, Suzuki M, et al. Recording, analysis, and interpretation of spreading depolarizations in neurointensive care: review and recommendations of the COSBID research group. *J Cereb Blood Flow Metab*. 2017;37:1595–1625. doi: 10.1177/0271678X16654496
12. Adelborg K, Szépligeti SK, Holland-Bill L, Ehrenstein V, Horváth-Puhó E, Henderson VW, Sørensen HT. Migraine and risk of cardiovascular diseases: Danish population based matched cohort study. *BMJ*. 2018;360:k96. doi: 10.1136/bmj.k96
13. Kurth T, Gaziano JM, Cook NR, Logroscino G, Diener HC, Buring JE. Migraine and risk of cardiovascular disease in women. *JAMA*. 2006;296:283–291. doi: 10.1001/jama.296.3.283
14. Schürks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T. Migraine and cardiovascular disease: systematic review and meta-analysis. *BMJ*. 2009;339:b3914. doi: 10.1136/bmj.b3914
15. 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. doi: 10.1159/000449425
16. Vergouwen MD, Vermeulen M, van Gijn J, Rinkel GJ, Wijdicks EF, Muizelaar JP, Mendelow AD, Juvela S, Yonas H, Terbrugge KG, et al. Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies: proposal of a multidisciplinary research group. *Stroke*. 2010;41:2391–2395. doi: 10.1161/STROKEAHA.110.589275
17. Vlak MH, Rinkel GJ, Greebe P, Algra A. Independent risk factors for intracranial aneurysms and their joint effect: a case-control study. *Stroke*. 2013;44:984–987. doi: 10.1161/STROKEAHA.111.000329
18. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF; AMPP Advisory Group. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology*. 2007;68:343–349. doi: 10.1212/01.wnl.0000252808.97649.21
19. Kelsey JL, Whittemore AS, Evans AS, Thompson WD. *Methods in Observational Epidemiology*. 2nd ed. New York: Oxford University Press; 1996.
20. Major S, Huo S, Lemale CL, Siebert E, Milakara D, Woitzik J, Gertz K, Dreier JP. Direct electrophysiological evidence that spreading depolarization-induced spreading depression is the pathophysiological correlate of the migraine aura and a review of the spreading depolarization continuum of acute neuronal mass injury. *Geroscience*. 2020;42:57–80. doi: 10.1007/s11357-019-00142-7
21. Eikermann-Haerter K, Lee JH, Yuzawa I, Liu CH, Zhou Z, Shin HK, Zheng Y, Qin T, Kurth T, Waeber C, et al. Migraine mutations increase stroke vulnerability by facilitating ischemic depolarizations. *Circulation*. 2012;125:335–345. doi: 10.1161/CIRCULATIONAHA.111.045096
22. Kurth T, Schürks M, Logroscino G, Gaziano JM, Buring JE. Migraine, vascular risk, and cardiovascular events in women: prospective cohort study. *BMJ*. 2008;337:a636. doi: 10.1136/bmj.a636
23. Tietjen GE, Herial NA, White L, Utley C, Kosmyna JM, Khuder SA. Migraine and biomarkers of endothelial activation in young women. *Stroke*. 2009;40:2977–2982. doi: 10.1161/STROKEAHA.109.547901
24. Francoeur CL, Mayer SA. Management of delayed cerebral ischemia after subarachnoid hemorrhage. *Crit Care*. 2016;20:277. doi: 10.1186/s13054-016-1447-6