Migraine and Stroke
Perspectives for Stroke Physicians
Tobias Kurth, MD, ScD; Hans-Christoph Diener, MD, PhD

Migraine and stroke have been linked by numerous individual studies1-4 and 3 meta-analyses5-7. Advances in pathophysiology have increased our knowledge about potential mechanisms linking migraine with cerebral vascular events.8,9 Overall, there is consistent evidence that individuals with migraine are approximately 2 times more likely to develop an ischemic stroke8,9 and in most studies this association is limited to patients with migraine with aura (MA) and stronger among younger women, particularly if they smoke or use oral contraceptives.4,6

It remains unclear, however, how important migraine is when a patient has a stroke. Because migraine is a very prevalent disease with approximately 20% of the general population being affected at least part of their lives,10 it is not surprising that many patients with a stroke have a history of migraine. However, often migraine is not directly linkable to the stroke event and uncertainties remain for the necessity of additional diagnostic workup and for potential therapeutic consequences. Moreover, the interrelationship between migraine and stroke is complicated by the fact that other distinct clinical conditions can trigger a migraine-like attack and that these conditions are stroke risk factors by themselves such as artery dissections.11

In this review, we summarize the evidence linking migraine with stroke, highlight new aspects of this association, and discuss potential mechanisms that are of interest for the management of patients with stroke who have a history of migraine.

Epidemiological Evidence Linking Migraine With Stroke

Ischemic Stroke
Results of 3 meta-analyses of observational studies5-7 show that individuals with migraine have a 2-fold increased risk of ischemic stroke. In 2,6,7 this increased risk is limited to patients with MA. The risk seems to increase with increasing migraine attack frequency12,13 and women and younger age groups are particularly affected.6 With regard to potential modifying factors, smoking and oral contraceptive use have been linked with further increased risk.6 The combination of smoking and oral contraceptives among young female patients with MA has been shown to increase stroke risk by a factor of approximately 9 when compared with women without migraine.6,6

Although migraine has been linked with increased prevalence of an unfavorable cardiovascular risk profile,12,15 the association between MA and ischemic stroke is independent of traditional cardiovascular risk factors.5,7 Furthermore, the risk of ischemic stroke is most pronounced among individuals with a low vascular risk profile,4,16-18 suggesting that other pathways play a role. With regard to functional outcome after ischemic stroke, a recent study showed that MA is only linked with ischemic strokes of good functional outcome.19

Hemorrhagic Stroke
Only very few studies have evaluated the role of migraine in hemorrhagic stroke occurrence. One case-control study found an increased risk of hemorrhagic stroke for subjects with a family history of migraine (OR, 2.30; 95% CI, 1.35–3.90).2 Another study showed increased risk of hemorrhagic stroke (OR, 1.8; 95% CI, 1.2–2.7) for migraineurs, which was most consistent for women with migraine who also took oral contraceptives.1

Results from a prospective cohort study among women indicate that the association between migraine and hemorrhagic stroke is limited to the subgroup of women with MA (relative risk, 2.25; 95% CI, 1.11–4.54).20 The risk was stronger for fatal hemorrhagic strokes and appeared to be limited to women aged ≥55 years. In a large, population-based inpatient sample, International Classification of Diseases, 9th Revision coding for migraine in the peripartum was associated with various vascular events, including intracerebral hemorrhage (OR, 9.1; 95% CI, 3.0–27.8).21

MRI Structural Brain Lesions
There is increasing evidence that migraine is associated with higher prevalence of white matter hyperintensities (Figure 1)22,23 and silent infarcts.24-25 These pathologies are also relevant for stroke physicians because they may be found in

Received March 9, 2012; final revision received April 20, 2012; accepted April 20, 2012.
From the Inserm Unit 708—Neuroepidemiology, Bordeaux, France (T.K.); the University of Bordeaux, Bordeaux, France (T.K.); the Division of Preventive Medicine, Brigham and Women’s Hospital, Boston, MA (T.K.); and the Department of Neurology, University Hospital Essen, Essen, Germany (H.C.D.).
Correspondence to Tobias Kurth, MD, ScD, Inserm Unit 708—Neuroepidemiology, Université Bordeaux Segalen, 146 rue Léo Saignat, case 11, 33076 Bordeaux, France. E-mail tobias.kurth@univ-bordeaux.fr
(Stroke. 2012;43:3421-3426.)
© 2012 American Heart Association, Inc.
Stroke is available at http://stroke.ahajournals.org
DOI: 10.1161/STROKEAHA.112.656603

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MR imaging of patients with stroke with a history of migraine. In 2 studies the infarct lesions among patients with migraine are located in the posterior circulation territory (Figure 2), which is consistent with the location of strokes among young patients with migraine. In a study of individuals aged ≥65 years, infarct lesions were more likely outside the brain stem and cerebellum. A recent study of 34 patients with migraine and 35 matched control subjects suggested that the cerebellar predilection of ischemic lesions in migraine with aura might be a combination of altered autoregulation and additional factors such as the end artery cerebellar angioarchitecture.

Despite the association between MA and structural brain lesions, the mechanisms and practical consequences remain unclear. In particular, it remains unclear whether presence of these lesions increases the likelihood of a subsequent stroke event among patients with MA. Thus, there is currently no evidence that the presence of these lesions would require different treatment or prophylactic strategies for patients with migraine and stroke.

Role of Migraine-Specific Medication on Stroke Risk
Two effective migraine acute treatments, ergot alkaloids and triptans, have vasoconstrictive effects raising concerns about potential cardiovascular side effects including stroke. Although ergotamine overuse has been linked with increased risk of vascular disease, results of a large population-based study do not suggest a link of triptans with stroke. In addition, the fact that the migraine–stroke association is limited to MA argues against a strong influence of migraine treatment in stroke occurrence as all patients with migraine receive treatment not just patients with MA.

Absolute Importance of Migraine Among Patients With Stroke
Despite clear evidence from epidemiological studies that MA increase the risk of ischemic stroke by approximately 2-fold, one has to take into consideration that a stroke is still a rare event among patients with MA. Data from the Women’s Health Study, which included women aged ≥45 years, suggest that there are 4 additional ischemic stroke cases per 10 000 women per year attributable to MA, when it is assumed that MA causes stroke.

More relevant data about the role of migraine among patients with stroke may come from stroke registries. Of 3502 patients with first ischemic stroke from the Lausanne Stroke Registry, 130 (3.7%) had active migraine. In patients with ischemic stroke who were aged <45 years, active migraine was seen in 23% of women and 8.2% of men, which is consistent with the prevalence of active migraine in that age group in the general population. Although in these patients common causes for stroke (ie, large artery disease, embolic
stroke, patent foramen ovale) was noted in approximately half of the cases, 35 of 66 (53%) had other, mostly undetermined causes. In 24 patients the migraine attack was present at the time of the stroke event and 11 had rare causes such as venous cerebral thrombosis, dolichoectasia, or fibromuscular dysplasia. In the population-based stroke registry of the city of Dijon, which included 2389 patients with stroke, only 49 (2%) had a history of migraine. With regard to the distribution of stroke subtypes, there was a suggestion of higher migraine prevalence among hemorrhagic stroke cases compared with other subtypes.

In the Italian Project on Stroke in Young Adults, 981 patients <45 years old with migraine and stroke were identified. Within this group, the risk of having MA increased with decreasing number of cardiovascular risk factors, increasing number of thrombophilic variants, and the presence of a right-to-left shunt as compared with patients with stroke without migraine.

Specific Clinical Aspects

Migrainous Stroke

The criteria for a migrainous stroke have been established by the International Headache Society. They require that a patient with a history of MA has, for that patient, typical aura, persisting for >60 minutes and with neuroimaging signs of an infarct in a relevant area and provided that the stroke is not attributed to another disorder. Applying these criteria makes a migrainous infarct a very rare event. In the Lausanne Stroke Registry, 9 of 3502 (0.3%) ischemic strokes were classified as migrainous stroke; in the Dijon Stroke Registry, there were 12 of 2389 (0.5%) cases. The presence of a prolonged aura in a patient with MA, however, does not necessarily mean this patient has a manifest stroke event.

Ischemic Stroke Triggering a Migraine

The association between migraine and ischemic stroke is complicated by the fact that an ischemic cerebral event can trigger a migraine-like attack, which may lead to misinterpretation of the stroke event as “complicated migraine.” Many patients with stroke report having a headache. In a study of >2000 patients with stroke, 27% reported a headache at the time of stroke onset.

Distinct Clinical Conditions Linked to Migraine and Stroke

There are several clinical conditions that have been linked to migraine and by themselves increase the likelihood of stroke. The identification of this group of patients may be the most important aspect for stroke clinicians because it involves a somewhat different diagnostic workup and therapeutic considerations (Table).

Cervical Artery Dissection

A recent meta-analysis summarized the association between migraine and cervical artery dissection. In pooled analysis, migraine doubled the risk of cervical artery dissection (OR, 2.06; 95% CI, 1.33–3.19). The risk further...
increased for multiple dissections. Although the association was somewhat stronger for MA, there was no significant difference according to aura status. The reason for this link remains unclear. Shared genetic susceptibility and increased serum elastase in migraine might be involved. Cases of carotid artery dissections triggering migraine attacks have also been described.

**Patent Foramen Ovale**

The association between migraine and patent foramen ovale (PFO) has gained enormous attention over the past years. Initial evidence from case–control studies showed that PFO is more prevalent among patients with migraine and migraine more prevalent among patients with a PFO. The negative results of the Migraine Intervention With STARFlex Technology (MIST) trial have put unrealistic hopes that migraine can be cured by PFO closure in perspective. The lack of association between migraine and PFO in a large population-based study among elderly individuals and in a hospital-based case–control study further question whether PFO plays a causal part in patients with migraine in general. However, because it has been shown that small particles and air bubbles can trigger cortical spreading depression, the likely pathophysiological correlate of the migraine aura, it is plausible that PFO can trigger migraine aura in some patients.

For young patients with a stroke of unknown origin, an examination of an existing PFO is part of routine causative diagnostics. The decision of PFO closure, however, should be based on stroke prevention and not on potential beneficial effects on migraine.

**Markers of Hypercoagulability and Inflammation**

Migraine has been associated with endothelial dysfunction of which hypercoagulability is a well-established consequence. In a young, relatively healthy cohort of women, strong associations between biomarkers of endothelial activation and migraine were found. These include von Willebrand factor activity, C-reactive protein, tissue-type plasminogen activator antigen, and total nitrite/nitrate concentration and the association was generally stronger for MA. Particularly the role of von Willebrand factor in the migraine–stroke association has been investigated. In a study of 63 patients with migraine, 11 patients with a history of migraine and stroke, and 35 control subjects, von Willebrand factor antigen and activity was highest in the group of patients with migraine and stroke. In another study, carriers of factor V Leiden mutation, the G20210A mutation in the prothrombin gene, or both of the prothrombotic genotypes had 2-fold increased risk for MA (OR, 2.21; 95% CI, 1.05–4.68) as compared with patients with stroke without migraine.

**Rare Clinical Syndromes**

There are very rare and clinically distinct syndromes and vascular pathologies that have been linked with MA. These include cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), arteriovenous malformations, leptomeningeal angiomatosis, Sneddon syndrome, Moyamoya syndrome, right-to-left shunts, antiphospholipid antibody syndrome, cardiac myxoma, essential thrombocythemia, and mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS).

**Genetic Factors**

Migraine is determined by the interplay of environmental and genetic factors. However, only few studies could evaluate whether specific genetic factors further increase stroke risk among patients with MA. The strongest evidence links a polymorphism in the methylenetetrahydrofolate reductase gene with further increased ischemic stroke risk. However, practical consequences remain uncertain because patients with migraine do not have increased levels of homocysteine.

Results of a recent genomewide association study suggest that 2 single nucleotide polymorphisms are involved in the MA–ischemic stroke association, but further studies are needed to unveil involved mechanisms. Thus, genetic testing among patients with stroke and migraine is currently not indicated.

**The Clinical Challenge: Migraine Aura Versus Transient Ischemic Attack**

Even for experienced neurologists, a differentiation between migraine aura and transient ischemic attacks is often challenging. This is particularly true for patients aged ≥60 years among whom transient ischemic attack occurrence increases, whereas attacks of MA are more likely to become more atypical because they are not always followed by a migraine headache. The sudden onset of transient ischemic attack symptoms paired with the presence of vascular risk factors is the strongest difference from MA, which has a more gradual-progressing occurrence of symptoms. The presence of a headache after transient neurological symptoms does not necessarily mean that these symptoms are consistent with a diagnosis of MA, because a migraine-like attack can be triggered by ischemic vascular events.

Another problem may occur if a patient with known MA has a rapid onset of transient neurological symptoms, because the diagnosis of an ischemic cerebral event, or risk factors for it such as artery dissection, may be missed by discounting these symptoms as MA. A more detailed clinical workup is recommended for patients with known MA in whom their aura symptoms differ, are atypical, or are accompanied with clinical signs of involvement of the basilar artery.

**Practical Consequences**

**Treatment and Secondary Prevention**

In general, the acute treatment and secondary prevention of a patient with stroke who has a history of migraine does not differ from other patients with stroke (Table). Some aspects should be considered, however. Use of dipyridamole in the secondary prevention of recurrent stroke can lead to headache, which can be severe and patients may need to be switched to another antithrombotic treatment. There is some initial evidence that aspirin or clopidogrel have beneficial effects on migraine.

Recommendations to reduce the presence of cardiovascular risk factors such as hypertension, hyperlipidemia, or obesity...
also apply to patients with migraine who have a stroke. Patients with MA should strongly be advised to quit smoking and among women, oral contraceptives or postmenopausal hormone intake should be stopped.

**Migraine Treatment After Stroke**

The treatment of acute migraine attacks (with or without aura) may have to be adjusted after an ischemic vascular event, including transient ischemic attack. Ergotamine or triptan use is contraindicated in patients who had any ischemic vascular event because of their potential to narrow arteries.

There is currently no direct evidence to support that a migraine prophylactic treatment will reduce future stroke risk. If a patient has hypertension, some antihypertensive medications have migraine prophylactic characteristics. These include particularly β-blockers (propranolol, metoprolol, atenolol, bisoprolol) and angiotensin-converting enzyme or angiotensin receptor blockers.16

**Summary**

Although MA has been consistently linked with increased risk of stroke, MA plays only a small role when managing and treating patients with stroke. In very few cases migraine can be directly linked to a stroke event. Even if a patient has no other risk factors for a stroke than MA, this does not necessarily imply that the migraine caused the stroke because the mechanisms of such a link are still unclear. Distinguishing MA from a transient ischemic attack remains challenging in some patients and migraine-like attacks can be triggered by ischemic events. The role of migraine-like attacks that are secondary to comorbidities that increase stroke risk such as cervical artery dissection should be considered in the clinical management. The acute treatment of patients with stroke who have a migraine does not differ from any other patient with stroke but secondary prevention and migraine acute treatment may need to be adjusted.

**Disclosures**

Dr Kurth has received investigator-initiated research funding from the French National Research Agency (ANR), the US National Institutes of Health, the Migraine Research Foundation, and the Parkinson’s Research Foundation. He has received honoraria from Allergan, the American Academy of Neurology and Merck for educational lectures, the BMJ for editorial work, and from MAP Pharmaceutical for contributing to a scientific advisory panel. Dr Diener has received honoraria for participation in clinical trials and contribution to advisory boards or oral presentations from: Addex Pharma, Allergan, Almirall, AstraZeneca, Bayer Vital, Berlin Chemie, Coherex, CoLucid, Böhringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Grünenthal, Janssen-Cilag, Lilly, La Roche, 3M Medica, MAP Pharmaceuticals, Medtronic, Minster, MSD, Novartis, Johnson & Johnson, Pierre Fabre, Pfizer, Schaper and Brümmel, SanofiAventis, and Weber & Weber. Financial support for research projects was provided by Allergan, Almirall, AstraZeneca, Bayer, GSK, Janssen-Cilag, and Pfizer. Headache research at the Department of Neurology in Essen is supported by the German Research Council (DFG), the German Ministry of Education and Research (BMBF), and the European Union. He has no ownership interest and does not own stocks of any pharmaceutical company.

**References**


Key Words: migraine ■ stroke
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Stroke. 2012;43:3421-3426; originally published online September 20, 2012;
doi: 10.1161/STROKEAHA.112.656603
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/43/12/3421

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