Migraine and Risk of Ischemic Stroke: An Evidence-Based Medicine Review

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Stroke is the third leading cause of death and a leading cause of serious long-term disability in the United States [1]. Stroke is also preventable through the management of modifiable stroke risk factors, such as hypertension, smoking, and carotid stenosis [2–5]. Migraine headaches represent a less well-documented potential stroke risk factor [6], and it is unclear how much this risk varies among different migraine sufferers. It is difficult for physicians practicing evidence-based medicine to counsel their patients with migraine because the risk associated with the condition is not well-established. The following review is a summary of the available evidence of stroke risk with migraine, the pitfalls of these studies, and recommendations for assessing and managing stroke risk in patients with migraine.

Studies of Migraine and Stroke Risk

Study Findings

Using the keywords “migraine” and “brain ischemia/cerebrovascular accident,” a search of the MEDLINE database produced a total of 12 controlled studies focusing on migraine and stroke risk (11 case-control/cross-sectional and 1 cohort). As shown in Table 1, 5 of 7 controlled studies of women under age 45 years [7–11] and 4 of 6 studies including men [12–15] showed increased odds of stroke with migraine. Of 5 studies that analyzed risk by migraine type, 3 [8,11,12] found an increased risk of stroke in those with migraine with aura, although in 1 cohort this was limited to women under age 45 [8]. Although the majority of the identified studies showed an increased risk of stroke in migraineurs, the specific study populations and methodologies differed across studies, limiting generalizability.

Migraine incidence and prevalence decrease with age [16], whereas ischemic stroke risk increases with age [1]. Therefore, the likelihood of an association between migraine and stroke differs according to the age-group being studied. Five of 10 studies reviewed included consecutive stroke patients of unselected age-groups (Table 1). The National Health and Nutrition Examination Survey (NHANES) cohort, an epidemiologic study that used cross-sectional and longitudinal analyses, demonstrated with age-stratified hazard ratios that subjects with migraine had an increased risk of stroke until age 70 [14]. The Physicians’ Health Study found a twofold increased risk of stroke in male physicians with a self-reported history of migraine [13]. In contrast, 2 studies of consecutive unselected stroke patients in France reported no significantly increased risk of stroke [7,12]. However, risk was increased in 1 cohort in subjects with migraine with aura (odds ratio, 2.6; 95% confidence interval, 1.1 to 6.6) [12]. In a case-control study targeting stroke patients of the age typical for this disorder (60 years or older), no association was found between a history of migraines and ischemic stroke [17]. The results of these studies suggest that in the age-group at the highest risk of stroke, migraine may be a minor contributor to overall risk.

Because of the concern for increased thrombotic tendency with oral contraceptive (OC) use, several studies have focused on the age-group of women that use these drugs (Table 1) [8,9,18]. This is also the age-group of women with the highest incidence of migraine headaches [16]. Several studies limited to this population have indeed shown an increased risk of stroke in migraineurs, independent of OC use [8–10]. The proposed mechanism of increased risk of stroke in women with migraines and using OCs may be cumulative based on the hypercoagulability induced by OCs and the increased platelet activation that has been documented during a migraine [19].

The combination of OC use and migraine with aura has been presumed to further increase ischemic stroke risk. Becker estimated the annual incidence of stroke in young women stratified by age (25 to 34 and 35 to 44 years), OC use, and the absence or presence of migraine with or without aura [20]. A woman aged 35 to 44 years who uses OCs and has migraine with aura had an estimated stroke rate of 78/100,000. The additional risk in women who use OCs and have migraine with aura is based on only limited case series found in the first several years of high-dose OC usage and were published more than 30 years ago [21,22]. Very few of the case-control or population-based studies associating stroke, migraine, and OC use have performed subgroup
analyses by migraine with or without aura. In the only case-control study to address this issue, 3 women (16%) with ischemic stroke transitioned from migraines without aura to migraines with aura [11].

To put migraine and stroke risk into perspective when counseling patients, population statistics are often useful. The most frequently reported annual incidence of stroke in women under age 45 is 10/100,000 woman-years. Tzourio et

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design (control type)</th>
<th>Population</th>
<th>Migraine Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collaborative Group Study of Stroke in Young Women, JAMA 1975 [18]</td>
<td>Case-control (hospital and neighbor)</td>
<td>Women with stroke aged 15-44 from 91 hospitals</td>
<td>Trained interviewers (pre-IHS criteria)</td>
</tr>
<tr>
<td>Henrich and Horwitz, J Clin Epidemiol 1989 [12]</td>
<td>Case-control (hospital)</td>
<td>Consecutive patients aged 15-65 with IS at 2 hospitals in Paris</td>
<td>Questionnaire by telephone, HAs categorized by migraine and no migraine (pre-IHS)</td>
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<tr>
<td>Carolei et al, Lancet 1996 [10]</td>
<td>Case-control (hospital and community)</td>
<td>Patients aged 15-44 with TIA or stroke</td>
<td>Semi-structured questionnaire (no IHS criteria reported)</td>
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<tr>
<td>Henrich et al, J Neurol 1986 [40]</td>
<td>Cohort study</td>
<td>Consecutive stroke patients (Oxfordshire Community Stroke Project)</td>
<td>Personal interview by neurologist (pre-IHS criteria)</td>
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<tr>
<td>Mosek et al, Headache 2001 [17]</td>
<td>Case-control (hospital, myocardial infarction and no vascular disease)</td>
<td>Consecutive stroke patients aged &gt; 60</td>
<td>Personal interview by neurologist using IHS criteria</td>
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</tbody>
</table>

HA = headache; HR = hazard ratio; IHS = International Headache Society criteria for migraine with and without aura; IS = ischemic stroke; MA = migraine with aura; Mig stroke = migrainous stroke (see text); MO = migraine without aura; NHANES = National Health and Nutrition Examination Survey; OC = oral contraceptive; OR = odds ratio; RR = relative risk; TIA = transient ischemic attack.
al estimated a relative risk of 1.9 for migraine history, which increases the stroke rate to 19/100,000 [8]. Assuming a migraine prevalence of 20% in women under age 45 and a relative risk of 2, the risk of stroke attributable to migraine in this age-group is estimated to be 17%. Using statistics from the U.S. Census Bureau for 2000 and an incidence rate of 10/100,000, of the 53 million women between ages 20 and 44 years, about 5300 women will have ischemic strokes, and 900 (17%) of these could be attributable to migraines. Although the absolute incidence of stroke is low in this age-group, other risk factors in combination with migraine, such as smoking (relative risk, 7 to 10) [8,11] diabetes (relative risk, 6.8), and hypertension (relative risk, 3.7), have been shown to significantly increase risk [9].

Methodologic Differences Among Studies
In addition to the heterogeneity of the target populations, not all studies used standardized criteria to diagnose migraine. Some studies were performed before the development of the International Headache Society (IHS) criteria [23], and some did not incorporate these criteria into their methods for unclear reasons (Table 1). These differences in ascertainment of migraine (ie, the exposure in a case-control study) limit the validity and introduce bias [24]. Also, several studies did not differentiate between migraine with aura versus migraine without aura. This is important because of the proposed pathogenetic differences between migraine with aura and migraine without aura, and because of the possibility that stroke risk is increased in migraine with aura [25].

Summary
To summarize the available evidence, stroke risk appears to be highest in a woman aged 35 to 44 years who smokes, uses oral contraceptives, and has migraine with aura. Because of a lack of definitive studies, the risk is still uncertain in migraine without aura [20], in men, and in the elderly. Interpretation of the evidence is further complicated by a variety of disorders that include both migraine and stroke, disorders in which migraine and stroke may mimic each other, and the complexity of differentiating transient ischemic attacks (TIAs) from migraine aura.

Complicating Factors in Interpreting the Evidence
Disorders That Cause Both Migraine and Stroke
Over the last decade, several genetic and acquired disorders have been found to cause both ischemic stroke and migraines. Some examples include hypercoagulable disorders (antiphospholipid syndrome [APL]), vascular disorders (carotid or vertebral dissection), genetic disorders such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), and mitochondrial disorders such as mitochondrial encephalopathy with lactic acidosis and stroke-like symptoms (MELAS).

APL is an acquired hypercoagulable disorder that occurs in young patients, more commonly women, and includes recurrent arterial or venous thrombosis, pregnancy loss, or
thrombocytopenia in the setting of antiphospholipid antibodies (anticardiolipin [ACL] antibodies or lupus anticoagulant). Other associated neurologic symptoms may include migraine-like episodes, seizures, psychiatric disorders, and dementia [26]. Although multiple studies have shown an association between ACL antibodies and ischemic stroke, the importance of elevated titers without features of APL is uncertain [27]. In order to study the association of these antibodies with TIAs and migraine headaches, Tietjen et al compared ACL antibody titers in patients with transient focal neurologic events to those with migraines with and without aura, and controls. They found that the frequency of ACL positivity was 7% to 9%, and there was no significant difference in ACL titers between these groups, suggesting that ACL was not associated with migraines nor a significant risk factor for transient neurologic events and TIAs in this age-group [28]. Routine screening of ACL antibodies in patients with migraines but without a history of stroke or features of APL is not likely to be useful.

CADASIL is a hereditary syndrome characterized by recurrent subcortical ischemic strokes occurring in mid-adulthood, migraine with aura, and bipolar-like mood disorder symptoms [29]. MELAS may also include recurrent headaches that resemble migraines; however, this syndrome typically has other features that distinguish it from a young person with migraines alone; these include short stature, symptom onset before age 15, cognitive regression in childhood, seizures, cortical blindness, hemiparesis, or an abnormal muscle biopsy with ragged red fibers [30].

Although these disorders are rare, case-control studies that inadvertently included subjects with these other disorders could have falsely elevated the number of stroke patients with migraine. The headaches reported in these disorders, although similar to migraine, would not meet the standard IHS criteria because of the presence of a secondary cause [23]. Including subjects with secondary causes of migraine means that migraine is an “innocent bystander” because it is associated with the pathogenesis and the underlying cause of ischemic stroke [31].

Vascular Disorders That Mimic Migraine

Vascular disorders may present with a prodrome of migraine with or without auras, and auras without headache (Table 2). The most commonly reported vascular cause of migraine-like symptoms is carotid or vertebral artery dissection, which may occur spontaneously or in the setting of trauma. In the setting of arterial dissection, migraine symptoms may occur in those with no prior history of migraines, or as a flurry of migraines identical to previous episodic headaches [25]. The association between migraines and carotid dissection may be related to serum elastase activity levels, an enzyme involved in the degradation of the extracellular matrix [32].

Other underlying ischemic causes of migraine-like headaches that may be new onset or occur in patients with a migraine history include severe carotid stenosis from causes other than dissection, middle cerebral artery embolism [25], arteriovenous malformations [33], postpartum cerebral angiopathy [34], and moyamoya disease [35]. Ischemia-induced migraines may occur from reduced blood flow as a result of vessel narrowing, resulting in a lower threshold for migraine aura with or without headache in susceptible patients [25]. However, if migraine headaches are closely associated with these vascular conditions that cause stroke, as with carotid artery dissection and serum elastase, the presence of migraines may be more than just a symptom. Further studies are needed to better understand these relationships and to differentiate migraine sufferers who may be at increased risk for these vascular disorders.

Additional vascular disorders that may present with headache are listed in Table 3.

Migraine as a Mimic (and Cause) of Ischemic Stroke

Migraines have been reported to cause ischemic stroke in the setting of a typical migraine attack. Migrainous strokes are
thought to occur because of an abnormal neurovascular response to some challenge, ultimately leading to cerebral ischemia in rare cases [19]. These types of episodes have been termed migrainous stroke, cerebral infarction associated with migraine, and migrainous cerebral infarction. Migrainous cerebral infarction was defined according to the IHS criteria in 1988 [23], and has since been expanded and clarified by Welch and Levine [19] (Table 4). This newer general classification of migraine-related strokes includes clinical features, the onset of migraine (new versus established), and the presence or absence of risk factors. This classification, although helpful, was developed after a few case series of migrainous infarction patients were published [36,37] and was not used by others [38,39]. Unfortunately, this lack of standardized criteria complicates comparisons among studies to identify migraine patients at risk for migrainous strokes. Thus far, the clinical features associated with migrainous infarction differ depending on the study design and comparison group. In 1 small series, more of the patients with migrainous infarction had strokes in the posterior cerebral artery distribution compared to the control group (infarction of unknown origin) [39]. Another case series found that the patients with migrainous stroke were more likely to have migraine with aura than migraine controls [38], but this finding would depend entirely on their definition of migrainous strokes. The incidence of migrainous stroke was measured in a cohort study of all stroke patients enrolled in the Oxfordshire Community Stroke Project (OCSP). They found an incidence of 3.36/100,000 and concluded that migrainous strokes were rare in their stroke population [40]. The incidence of migrainous stroke in other series of young patients with migraines has ranged from 0% to 20% [41].

The 1-year prevalence of migraines was estimated to be 10% to 12% in Europe and North America, and approximately one third had migraine with aura [42]. Given the high prevalence of migraine with aura, why don’t more migraine sufferers have strokes? One possibility is that several risk factors are required in order to cross the threshold for ischemia [19], or there may be rare genetic susceptibilities that have yet to be uncovered. Another possible explanation is that migrainous stroke is a rare presentation of a common disease (ischemic stroke). The prevalence of migrainous infarction is unknown because of the lack of defined criteria, and the time at which the diagnostic evaluations were performed in patients in these series pre-dated many of the disorders that are now relatively easy to evaluate. More studies are needed to establish the criteria for this rare disorder based on the pathogenesis. Then physicians will be better able to identify migraine patients at high risk of stroke.

Migraine Aura without Headache as a Mimic of TIA
Migraine aura symptoms, such as aphasia, visual scotoma, and paresthesias may closely mimic TIAs. Migraine headaches decrease in severity with age, and auras without headache become more common [43]; therefore, differentiating TIA from aura becomes more challenging in patients over age 50. One case-control study in Italy found that TIA was significantly associated with migraine whereas ischemic stroke was not, and careful attempts were made to distinguish TIA from migrainous aura (Table 1) [10]. Case-control studies that include Tias with strokes are difficult to interpret because of the occurrence of auras without headache.

How Should We Apply the Evidence?
Is the association between migraine and stroke risk a result of biased case-control studies, a chance finding of high prevalence of migraine in a population with a low stroke risk, or is migraine a true risk factor for stroke? The evidence gives a limited picture of this association because of the lack of standardized migraine criteria and the targeting of heterogeneous populations of stroke patients. Given these limitations, how should a physician counsel a patient with migraine and risk factors for stroke?

The evaluation of migraine patients includes the same preventive approach used for any patient at risk for cerebrovascular or cardiovascular disease. This should include smoking cessation, blood pressure control, diabetes management, and treatment of total cholesterol greater than 200 mg/dL or LDL cholesterol greater than 130 mg/dL [44]. Antiplatelet therapy is also recommended for secondary stroke prevention [45].

### Table 4. Classification of Migraine-Related Stroke

<table>
<thead>
<tr>
<th>Category</th>
<th>Feature</th>
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<tbody>
<tr>
<td>I</td>
<td>Coexisting stroke and migraine</td>
</tr>
<tr>
<td>II</td>
<td>Stroke with clinical features of migraine</td>
</tr>
<tr>
<td>A</td>
<td>Established (symptomatic migraine)</td>
</tr>
<tr>
<td>B</td>
<td>New onset (migraine mimic)</td>
</tr>
<tr>
<td>III</td>
<td>Migraine-induced stroke</td>
</tr>
<tr>
<td>A</td>
<td>Without risk factors</td>
</tr>
<tr>
<td>B</td>
<td>With risk factors</td>
</tr>
<tr>
<td>IV</td>
<td>Uncertain</td>
</tr>
</tbody>
</table>
MIGRAINE AND STROKE RISK

Although the evidence has not been established in recent randomized trials, women who have a history of migraine with aura and have development of more prolonged or additional aura symptoms after starting OCs should be advised to discontinue this medication and consider other forms of contraception. Likewise, women with migraine without aura who develop auras after initiating OCs should consider discontinuing these drugs. Women over age 34 with migraines who also smoke, have uncontrolled hypertension, or have diabetes should not take OCs. Of course, therapy still must be individualized for each patient based on her preferences and weighing of the risks and benefits [20].

Evidenced-based recommendations for the preventive treatment of migraine headaches have been published [46]. Despite the level and quality of the evidence for the use of β blockers for migraine prophylaxis, there have been reports of patients with migraine who developed ischemic stroke attributed to β-blocker use [47–50]. Although metoprolol appeared to produce minor changes in aura symptoms in a randomized controlled double-blinded study of metoprolol for migraine prophylaxis, there were no reports of adverse events resembling ischemic stroke [51]. Despite the uncertain risk, experts recommend cautious use of β blockers in migraine patients with aura and a clear risk of ischemic stroke [52].

Abortive migraine therapies such as ergotamines and triptans could cause ischemia or other cardiovascular complications in the setting of a complicated migraine (ie, hemiplegia or aphasia) or of migraine with prolonged aura, or in persons with cerebrovascular risk factors such as uncontrolled hypertension, prior stroke, congestive heart failure, or coronary artery disease. Therefore, these drugs are contraindicated in patients with this level of risk for ischemic stroke, and analgesics such as non-steroidal anti-inflammatory medications are recommended instead instead [52].

Future Directions

Further studies are needed to elucidate the pathogenesis of migraine with and without aura and migrainous infarction. Better understanding of these mechanisms will allow for improved therapies and better methods to identify migraine patients with an increased risk of stroke. Other unanswered questions include the role of migraine preventive therapies and whether decreasing the number of migraine attacks reduces stroke risk.

Based on the current evidence, migraine may increase the risk of stroke, but this risk is minor and decreases with age. The evaluation of established cerebrovascular risk factors is still the main consideration in patients with migraine, regardless of age-group.

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Financial disclosures: None.

References

16. Stewart WF, Linet MS, Celentano DD, et al. Age- and