The association between migraine attacks and permanent neurological deficits has been recognized since the original description of persistent visual deficits by Féré in 1861 and Galezowski in 1881. Féré described 10 cases, of which four were left with permanent deficits that included hemianopia (3) and aphasia (1). The term ‘complicated migraine’ was coined by Charcot in 1890. Subsequently in 1915, Hunt expanded the range of neurological deficits associated with a migraine attack to include permanent paralysis.

More recently a wide range of descriptive terminology has emerged to define the complex relationship between migraine and stroke. This includes: ‘active migraine and stroke’, ‘migrainous infarction’, ‘migraine-induced stroke’ and ‘migraine-related stroke’. The definitions describe a causal spectrum that includes: migrainous infarction, in which the clinical deficit arises out of the migraine aura; migraine-induced stroke, in which the stroke occurs during a migraine attack, but not necessarily related to the aura; and migraine-related stroke, in which the causal linkage is less clear. In the case of ‘active

ABSTRACT: A significant association between migraine and ischemic stroke has been demonstrated in population and case-control studies. The risk of ischemic stroke appears to be higher in migraine with aura (MWA) than migraine without aura (MwoA). Migraine-stroke comprises a number of distinct entities, including migrainous infarction, in which ischemic stroke occurs during an attack of MWA and migraine-related stroke, in which the causal link is less clear. Migrainous infarction accounts for only one-third of migraine-stroke, strokes may occur during attacks of MwoA, and a number of cerebrovascular disorders may present as MWA or MwoA. Migraine may occur as a consequence of conditions that are known to cause stroke; therefore it remains to be determined whether migraine predisposes to stroke in the absence of any known disease associations, if it is an epiphenomenon of an underlying stroke diathesis, or if it requires the presence of another stroke risk factor to produce cerebral ischemia. Furthermore, it is unclear if ischemia results in migraine more often than migraine results in ischemia. Careful clinical studies that evaluate this bidirectional relationship are needed to determine why migraine patients are subject to a higher risk of ischemic stroke.

RÉSUMÉ: Migraine - accident vasculaire cérébral: une relation causale, mais dans quelle direction? Des études de population et des études cas-témoin ont montré une association significative entre la migraine et l’accident vasculaire cérébral ischémique (AVCI). Le risque de faire un AVCI semble plus élevé dans la migraine avec aura (MWA) que dans la migraine sans aura (MwoA). La migraine - AVC comprend plusieurs entités distinctes dont l’infarctus migraineux dans lequel l’AVCI survient pendant une crise de MWAet la migraine reliée à l’AVC dont le lien causal est moins clair. L’infarctus migraineux explique seulement le tiers des cas de migraine - AVC. Un AVC peut survenir pendant une crise de MWA et certains troubles vasculaires cérébraux peuvent avoir un mode de présentation semblable à celui de la MWA ou de la MwoA. La migraine peut survenir comme conséquence de pathologies reconnues comme causant l’AVC. Il reste donc à déterminer si la migraine prédépose à l’AVC en l’absence d’une association connue avec une autre maladie, si c’est un épiphénomène d’une diathèse sous-jacente d’AVC ou si la présence d’un autre facteur de risque d’AVC est nécessaire pour produire une ischémie cérébrale. Il faudrait effectuer des études cliniques minutieuses évaluant cette relation bidirectionnelle pour déterminer pourquoi les patients migraineux sont à plus haut risque d’AVCI.


PROGRESS IN CLINICAL NEUROSCIENCES:
Migraine-Stroke: A Causal Relationship, but Which Direction?

Ralph Z. Kern

The CANADIAN JOURNAL OF NEUROLOGICAL SCIENCES


From the Division of Neurology, Mount Sinai Hospital, Toronto, Ontario, Canada


Reprint requests to: Ralph Z. Kern, Division of Neurology, Mount Sinai Hospital, 431-600 University Ave, Toronto, Ontario M5G 1X5 Canada
migraine and stroke’, the authors have specified that the subject experience ‘at least two migraine attacks in the previous two months before the acute stroke onset’.5

Not all strokes that occur within the context of a migraine attack are causally linked to migraine with aura (MWA). For example, Hoekstra-van Dalen et al9 studied 14 patients with cerebral infarction accompanying migraine and found that the neurological deficit was similar to previous auras in only three patients. In a case series reported by Milhaud et al,5 15 of 24 subjects who experienced strokes during migraine attacks, did so during attacks of migraine without aura (MwoA). In response to these clinical observations, Welch and Levine10 suggested that the term ‘migrainous infarction’ should be redefined in the IHS classification as a complication of MWA and MwoA.

The relationship between migraine and stroke is further complicated by reports of stroke-induced migraine1 1,12 and the frequent occurrence of headache at stroke onset.1 9 In fact, some authors have questioned whether migraine and stroke are two common but independent disorders or whether they share a commonality of cause.1 4 In the present review, the epidemiology and pathophysiology of migraine-stroke will be analyzed. It will be argued that the relationship between migraine and stroke is complex, bidirectional, and may be mediated by a common underlying cause.

**Epidemiology**

Migraine appears to be an important cause of occipital5,9,15,16 and cerebellar17 infarction, however involvement of the middle5 and anterior18 cerebral artery territories has also been reported. A significant nonrandom relationship between migraine and stroke has been demonstrated in several large population and case-control studies. In five large population databases,19-23 the adjusted relative risk of clinical stroke in migraine subjects ranged from 1.7-2.1 and the adjusted hazard ratio ranged from 1.5-1.8 (Table 1). This compares in magnitude to an adjusted relative risk of stroke associated with hypertension of 2.1 (95% CI 1.7-2.7).19 Five hospital-based case control studies examined the relationship of migraine and stroke24-28 (Table 2). Schwaag et al26 calculated a summary odds ratio of 2.1 (95% CI 1.7-2.6). This is similar in magnitude to the relative risk observed in population studies and is independent of other stroke risk factors such as age, hypertension, smoking, oral contraceptive use, and gender.

One study that looked at headache, rather than migraine, observed a lower adjusted stroke risk.22 According to Merikangas et al,19 the higher stroke risk associated with migraine extends past the age of 60, although a smaller case-control study suggested that migraine was not a significant stroke risk factor in patients over the age of 60.29 The higher stroke risk is unrelated to the use of triptans.30 Therefore, a significant non-random association between migraine and stroke has been clearly established in individuals less than 60 years of age. The relative contribution of migrainous infarction and MWA must be understood in order to further define this risk at the individual patient level.

**Migrainous infarction**

Migrainous infarction (IHS classification 1.6.2),31 specifies that the subject have a history of previous episodes of migraine with aura and that the neurological deficit occurs in the same vascular distribution as the aura. Since the migraine aura may be prolonged and continue for up to seven days,32 the IHS definition requires that the deficit persist beyond seven days. Welch’s definition of migraine-induced stroke33 requires that the neurological deficit must exactly mimic the migrainous

### Table 1. Population studies of migraine stroke risk.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Diagnosis</th>
<th>N</th>
<th>Risk for ischemic stroke</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merikangas et al19 (National Health and Nutrition Examination Survey)</td>
<td>Prospective baseline and first follow-up data</td>
<td>Migraine</td>
<td>14,407</td>
<td>2.1 (RR)</td>
<td>1.5-2.9</td>
</tr>
<tr>
<td>Velentgas et al20 (United Healthcare/Ingenix Research Database (UHC), US)</td>
<td>Retrospective cohort</td>
<td>Migraine</td>
<td>130,411</td>
<td>1.7 (RR)</td>
<td>1.3-2.1</td>
</tr>
<tr>
<td>Hall et al21 (General Practice Research Database (GPRD, UK)</td>
<td>Retrospective cohort</td>
<td>Migraine</td>
<td>63,575</td>
<td>1.5 (AHR, non-triptan users)</td>
<td>1.3-1.8</td>
</tr>
<tr>
<td>Jousilahti et al22 (Finnish population)</td>
<td>Prospective observational cohort</td>
<td>Headache</td>
<td>35,056</td>
<td>Males 1.8 (AHR) Females 1.12 (AHR)</td>
<td>1.3-2.7 0.7-1.8</td>
</tr>
<tr>
<td>Buring et al23 (Physician’s Health Study, US)</td>
<td>Prospective observational cohort</td>
<td>Migraine</td>
<td>22,071 (1479 migraine)</td>
<td>2.0 (RR)</td>
<td>1.1-3.6</td>
</tr>
</tbody>
</table>

Abbreviations: AHR-adjusted hazard ratio; RR-relative risk.; CI-confidence interval
symptoms preceding the attack and that all other causes of stroke be excluded, although risk factors such as hypertension, diabetes, mitral valve prolapse or use of oral contraceptives would not be a cause for exclusion.

A number of investigators have estimated the incidence of migrainous infarction in stroke databases (Table 3). The pooled results indicate that migrainous infarction accounts for approximately 0.5-1.4% of all new strokes. In the Oxfordshire Community Stroke Project, only a minority (3/7) of subjects with ‘migrainous infarction’ were free of other known stroke risk factors. Migrainous infarction is estimated to account for 10-14% of ‘young strokes’ (less than 45 years) and approximately 1/3 of migraine-related stroke. Based on these observations, it may be concluded that migrainous infarction does not account for all strokes occurring during migraine attacks, and accounts for only a minority of migraine-related strokes.

**MWA and migraine-stroke**

There is a wide range of MWA prevalence estimates due to variable use of IHS criteria and other methodological factors such as the length of the observation period. In a recent large population study in the Netherlands, up to 1/3 of migraine subjects experienced attacks that included aura within the preceding year. The prevalence of MWA appears to be higher in migraine-stroke subjects than in matched control migraineurs. Four case-control studies (Table 2) have demonstrated a higher stroke risk associated with MWA compared to MwoA. Donaghy et al analyzed specific MWA characteristics that increase the risk of stroke and concluded that migraine duration of more than 12 years (odds ratio=4.6), onset as MW A (odds ratio=8.4), and attack frequency of greater than 12/year (odds ratio=10.4) were significant risk factors for stroke. Therefore, it can be concluded that MWA carries a higher stroke risk than MwoA and that specific MWA characteristics appear to be important determinants of that risk.

The association of MWA and migraine infarction is confounded by the occurrence of prolonged auras (longer than one hour and less than seven days) in 20% of attacks. Further complicating this association is the observation that MWA occurs within a diverse biological continuum that includes: familial hemiplegic migraine; basilar artery migraine; MELAS; HaNDL syndrome; and CADASIL. Furthermore, the relative importance of MWA in migrainous infarction is a matter of controversy. Whereas Linetsky et al observed that all six subjects with migrainous stroke had MWA, most case series have come to a different conclusion. Rothrock et al described the occurrence of ischemic stroke in five patients with ‘common’ migraine. Narbone et al reported two patients with a history of MwoA who experienced cerebral infarction during attacks of MwoA. Saquegna et al reported a case series in which ‘migrainous stroke’ was defined as a ‘sudden-onset focal neurological deficit not fully reversible within seven days and/or associated with neuroimaging confirmation of cerebral infarction – occurring during a common migraine attack or following the

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**Table 2. Case-control studies of migraine as a risk factor for ischemic stroke.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Migraine</th>
<th>Controls</th>
<th>Odds ratio of migraine in ischemic stroke (95% CI)</th>
<th>MwoA</th>
<th>MWA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tzourio et al27</td>
<td>212</td>
<td>212</td>
<td>1.3 (0.8-2.3) all subjects 4.3 (1.1-21.4) F&lt;45 years</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Tzourio et al28</td>
<td>72 F</td>
<td>173 F</td>
<td>3.5 (1.8-6.4) F 15-44 years</td>
<td>3.0 (1.5-5.8)</td>
<td>6.2 (2.1-18.0)</td>
</tr>
<tr>
<td>Caroli et al31</td>
<td>308</td>
<td>591</td>
<td>1.9 (1.1-3.1) all 2.5 (1.2-4.9) &lt;35 years 1.3 (0.7-2.4) &gt;35 years</td>
<td>1.5 (0.9-2.5)</td>
<td>5.2 (1.4-20.0)</td>
</tr>
<tr>
<td>Chang et al35</td>
<td>291 F</td>
<td>736 F</td>
<td>3.5 (1.3-9.6) all subjects</td>
<td>3.0 (0.7-13.5)</td>
<td>3.8 (1.3-11.5)</td>
</tr>
<tr>
<td>Schwaag et al26</td>
<td>160</td>
<td>160</td>
<td>2.1 (1.2-3.8) all subjects 2.7 (1.2-5.7) F&lt;45 3.5 (1.3-8.0) F&lt;35 years 1.4 (0.6-3.2) F&gt;35 years</td>
<td>2.5 (1.3-6.3)</td>
<td>1.0 (0.3-3.6)</td>
</tr>
<tr>
<td>All Studies</td>
<td>1043</td>
<td>1872</td>
<td>2.1 (1.7-2.6)26</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: RR- Relative Risk; 95% CI- 95% Confidence Interval; MWA- Migraine with Aura; MwoA- Migraine without Aura; NA-not analyzed; F-females.

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**Table 3. Incidence of migrainous infarction (% of new strokes).**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Incidence of migrainous infarction (% of new strokes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kittner SJ et al34</td>
<td>428</td>
<td>1.4%</td>
</tr>
<tr>
<td>Sochurkova D et al36</td>
<td>2389</td>
<td>0.5%</td>
</tr>
<tr>
<td>Arboix A et al38</td>
<td>2000</td>
<td>0.77%</td>
</tr>
<tr>
<td>Linetsky et al35</td>
<td>750</td>
<td>0.8%</td>
</tr>
</tbody>
</table>


**Review: Migraine MRI Abnormalities**

**Comparison:** 01 migraine versus controls

**Outcome:** 01 MRI White Matter Abnormalities (MWA): II studies

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>OR (random)</th>
<th>95% CI</th>
<th>Weight %</th>
<th>OR (random)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Benedittis et al</td>
<td></td>
<td></td>
<td></td>
<td>17.84</td>
<td>5.92 [1.63, 21.53]</td>
</tr>
<tr>
<td>Fazekas et al</td>
<td></td>
<td></td>
<td></td>
<td>10.04</td>
<td>3.00 [0.54, 16.77]</td>
</tr>
<tr>
<td>Igarashi et al</td>
<td></td>
<td></td>
<td></td>
<td>39.31</td>
<td>3.30 [1.38, 7.86]</td>
</tr>
<tr>
<td>Pavese et al</td>
<td></td>
<td></td>
<td></td>
<td>7.23</td>
<td>11.78 [1.55, 89.45]</td>
</tr>
<tr>
<td>Robbins et al</td>
<td></td>
<td></td>
<td></td>
<td>14.33</td>
<td>3.30 [0.78, 13.93]</td>
</tr>
<tr>
<td>Rovaris et al</td>
<td></td>
<td></td>
<td></td>
<td>3.33</td>
<td>16.74 [0.84, 332.58]</td>
</tr>
<tr>
<td>Ziegler et al</td>
<td></td>
<td></td>
<td></td>
<td>7.92</td>
<td>1.30 [0.19, 9.02]</td>
</tr>
</tbody>
</table>

**Total (95% CI):**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th><strong>Total events:</strong> 71 (Migraine), 23 (Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test for heterogeneity: Chi² = 4.13, df = 6 (P = 0.66). χ² = 0%</td>
<td>Test for overall effect: Z = 4.89 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Total (95% CI): 100.00 3.90 [2.26, 6.72]</strong></td>
</tr>
</tbody>
</table>

**Figure:** Plot of odds ratios and 95% confidence intervals.


---

neurological symptoms of classic migraine. In this case series, 5/6 strokes occurred during an attack of 'common migraine'. Milhaud et al also noted that only nine of 24 strokes arising from a migraine attack occurred in the context of MWA.

It is unclear if the simultaneous occurrence of MWA or MwoA and stroke represents a migrainous infarction since migraine headaches may occur during acute stroke and MWA may be the presenting manifestation of a diverse group of disorders including: occipital and brainstem arteriovenous malformations; occipital lobe tumors; subarachnoid hemorrhage; occipital lobe epilepsy; radiation-induced and post-partum cerebral vasculopathy; moyamoya disease; and basilar artery dissection.59

Shuaib60 cautioned against the uncritical use of the term migraine-stroke in a case series in which five subjects identified as suffering from migraine-stroke were found to have other significant stroke etiologies, including arterial dissection, endocarditis, and atherosclerosis. A recent case-control study by Tzourio et al61 observed that MwoA is more common in subjects with cervical artery dissection compared to hospitalized controls, further supporting the hypothesis that an underlying arterial wall disease may be a predisposing condition for migraine. The diagnosis of dissection must be made with caution as migrainous arterial spasm may be confused with dissection on angiography.62

In a recent case-series, Olesen et al63 have suggested that ‘ischemia-induced migraine attacks may be more frequent than migraine-induced ischemic insults’. Therefore, migraine may occur as a consequence of stroke, stroke may occur as a consequence of migraine, and both may occur as a result of other pathologies. Conclusions from epidemiological studies are limited by these complex relationships and the multiplicity of definitions in common usage. Greater understanding of the pathophysiology of migraine-stroke is needed before direction-specific causation may be implied.

**Pathophysiology**

A practical conceptual framework of migraine-stroke pathophysiology must take into account the common occurrence of white matter signal abnormalities in migraine patients, the possibility that stroke may arise from the putative mechanisms of MWA, as well as the complex relationships between coagulation abnormalities, oral contraceptives, cardiac disorders and migraine.

**Magnetic resonance image white matter abnormalities in migraine: a marker for stroke?**

White matter abnormalities on magnetic resonance imaging (MRI) can be seen in migraine subjects; however they are also incidental findings in normal control populations. Magnetic resonance imaging white matter signal abnormalities are more common in individuals with cerebrovascular risk factors. There are conflicting studies showing either increased, 55-68 or equal incidence of MRI white matter abnormalities in subjects with migraine compared to those without migraine. Studies that report no increased incidence of MRI white matter abnormalities imply...
that the reported increase can be accounted for by disease co-
morbidities, such as age, hypertension, diabetes or demyelinating
diseases. A recent meta-analysis by Swartz and Kern of seven
published case-control studies, demonstrated that subjects with
migraine are at higher risk of having MRI white matter
abnormalities (odds ratio 3.9, 95% CI 2.3 – 6.7) than those
without migraine (Figure). In addition, this increased risk is
present even in younger individuals who do not have other risk
factors for ischemic stroke (odds ratio 3.6, 95% CI 1.5 – 8.4).
While a clear association between migraine and MRI white
matter abnormalities has been demonstrated, the significance of
these findings is still unclear. The MRI abnormalities may be
interpreted as: an incidental finding; accumulated microvascular
cerebral damage after repeated migraine attacks; or pre-
symptomatic and/or asymptomatic strokes. Therefore if they are
confirmed to be a marker for increased stroke risk, the MRI
white matter abnormalities may be used to identify a migraine
subpopulation that is at higher risk for ischemic stroke.

Cortical spreading depression and stroke

A number of imaging techniques (including positron emission
tomography and functional MRI) have demonstrated changes in
cerebral blood flow during attacks of MWA that are
similar to cortical spreading depression, a phenomenon
characterized by marked transient electrochemical and
cerebrovascular perturbations within the brain. One study using
perfusion-weighted MRI was unable to confirm these findings.
Despite these important observations, it remains unclear if the
vascular changes seen during the migraine aura are of sufficient
magnitude to produce ischemia without the coexistence of
additional stroke risk factors or whether they require the
invocation of other phenomena, such as: inverse coupling
between neuronal activation and ischemia; mitochondrial
abnormalities; and/or platelet accumulation in hypoperfused
cerebral areas. The alternative hypothesis is that cortical
spreading depression may be a manifestation of cerebral
ischemia. Evidence supporting this hypothesis includes the
observation that endothelin, produced by ischemia, is a potent
inducer of cortical spreading depression and the demonstration
that peri-infarct depolarization, a phenomenon similar to
cortical spreading depression, is seen in animal models of stroke.
Therefore, it is possible that cerebral ischemia induces cortical
spreading depression more often than cortical spreading
depression induces cerebral ischemia, providing theoretical
support to the empirical observation that stroke may induce
MWA more often than MWA induces stroke.

Coagulation and platelet abnormalities

Coagulation and platelet abnormalities may be important
contributors to the migraine process, mediate the causal link
between migraine and stroke, or serve as pathological disorders
that give rise to both conditions. The relationship between
migraine and disorders of hemostasis has been reviewed by
Crassard et al. There is inconsistent evidence of increased
platelet activation in migraine. Sarchielli et al suggest that
studies using impediometry on whole blood have demonstrated
an increase in the index of platelet function only at the end of
migraine attacks. This observation does not preclude the
possibility that platelet activation at the end of a migraine attack
may contribute to migraine-stroke. Essential thrombocythemia is
a specific clinical scenario in which abnormal platelet number
and function gives rise to both migraine and stroke, and this
process may be modified by the use of antiplatelet agents.

Evidence linking factor VLeiden mutations with symptoms of
migraine was observed in a case-control study that measured
activated protein C resistance and factor V mutations. However,
this finding has not been confirmed in a large case-control study
in Italian children and adolescents experiencing MWA. Tietjen
et al have found higher levels of von Willebrand factor (a
possible marker of endothelial damage) in migraineurs with
prior stroke. Hering-Hanit et al observed evidence for activation
of the coagulation system in MWA by measuring prothrombin
factor 1.2. At this time, there is insufficient evidence to establish
a definite role of coagulation abnormalities in migraine-stroke,
however in individual patients, the coexistence of a coagulation
risk factor and migraine may be important.

A significant relationship between antiphospholipid
antibodies and migraine was suggested in a seminal report by
Levine et al. A number of case reports have demonstrated a
higher occurrence of antiphospholipid antibodies in migraine
subjects who experienced episodes of cerebral ischemia or
transient focal neurological events. However, a recent
prospective study that looked at IgG and IgM antcardiolipin
antibodies in MWA (n=518), MwoA (n=497) and controls
(n=366) did not observe a statistically significant higher
occurrence of antcardiolipin antibodies in migraine. A large
European case-control study of patients with antiphospholipid
antibodies (n=1000) demonstrated a higher occurrence of
migraine compared to controls only in females. Tietjen et
al have reported a higher incidence of livedo reticularis in
migraine, a condition known to be associated with
antiphospholipid antibodies and stroke.

Therefore, while the relationship of coagulation and platelet
abnormalities and migraine remains unclear, in some individuals
with migraine-stroke these abnormalities may be an important
contributing factor, or in some situations, as in the case of
essential thrombocythemia, give rise to both conditions.

Oral contraceptives

In a recent review, Bousser and Kittner suggest that the
wide reported range of stroke risk associated with the use of oral
contraceptives (OCs) may be related to variable control of risk
factors and/or stroke definition. In a Dutch population-based,
case-control study of women aged 18-49 who used OCs,
Kenmeren et al observed an increased risk ischemic stroke
(odds ratio 2.3, 95% CI 1.6-3.3). Gillum et al calculated a
summary relative risk of 1.93 (95% CI, 1.3-2.7) in a recent meta-
analysis of population-based studies that controlled for smoking
and hypertension. However several other risk-adjusted case-
control studies did not observe a higher stroke risk among
women who use low-dose OCs. In these studies there may be
a dose-effect above the 20-30 µg estrogen dose, particularly
when combined with second-generation progestins. Therefore,
in addition to methodological factors, specific treatment issues
such as dose, type of estrogen preparation, or combination of
estrogen and progestin may contribute to the variable observed
stroke risk associated with use of OCs.

The relationship between use of OCs, migraine and stroke has
been recently reviewed by Becker. He recommended cautious
use of OCs in women who experience MWA, older women or those who have other stroke risk factors such as hypertension or smoking. Tzourio\textsuperscript{29} emphasized the compounding of stroke risk in female migraineurs who use OCs and smoke. Using multivariate analysis, Milhaud et al\textsuperscript{3} demonstrated an increased risk of stroke associated with the use of OCs in \textquoteleft active migraine\textquoteright; patients less than 45 years of age (odds ratio 2.7, 95\% CI 1.2-6.0). Gillum et al\textsuperscript{104} reported an increased adjusted relative risk of ischemic stroke associated with the use of OCs in migraine (adjusted relative risk 3.2, 95\% CI 1.4-7.2), based on a meta-analysis of four case-control studies in four countries. Pooled analysis from two US population-based case-control studies demonstrated a somewhat lower ischemic stroke risk (odds ratio 2.1, 95\% CI 1.2-3.7),\textsuperscript{105} suggesting that the magnitude of ischemic stroke risk may vary by country.

The relative risk of ischemic stroke associated OCs in MWA compared to MwoA has not been well studied. Bickerstaff\textsuperscript{101} suggested that the conversion of MwoA to MWA following the introduction of oral contraceptive might be associated with a higher stroke risk, although this was not confirmed by Chang et al\textsuperscript{25} in a case-control study. There is a suggestion that the interaction of migraine and use of OCs may be important in young women who experience lacunar infarction.\textsuperscript{111} Therefore, the stroke risk associated with use of OCs in migraine may be viewed as: an independent stroke risk factor; mediated by the induction of MWA by OCs; a consequence of the interaction with other risk factors such as smoking; or may be related to specific mechanisms of stroke such as lacunar infarction. In this regard, the stroke risk associated with use of OCs in migraine subjects with MRI signal abnormalities may be an important area for clinical study.

Cardiac abnormalities

The relationship of migraine to cardiac abnormalities such as mitral valve prolapse, atrial septal defect and patent foramen ovale has been evaluated in a number of case-control studies. Spence et al\textsuperscript{112} observed a higher prevalence of mitral valve prolapse in migraine subjects (odds ratio 2.7, 95\% CI 1.2-6.3). However, this relationship is of uncertain significance in the migraine-stroke debate since an increased risk of stroke associated with mitral valve prolapse in young adults was not demonstrated by Gilon et al\textsuperscript{113} (odds ratio 0.59, 95\% CI 0.12-2.50). This may be explained in part by the observation that the risk of stroke in mitral valve prolapse may be related to associated cardiac abnormalities such as atrial fibrillation and congestive heart failure.\textsuperscript{114}

A recent meta-analysis by Overell et al\textsuperscript{115} has demonstrated an increased stroke risk associated with isolated atrial septal aneurysm (odds ratio 2.3, 95\% CI 1.5-3.8), isolated patent foramen ovale (odds ratio 1.83, 95\% CI 1.2-2.7), and combined atrial septal aneurysm and patent foramen ovale (odds ratio 5.0, 95\% CI 2.4-10.4) in subjects of all ages. In the same study, an even higher risk of ischemic stroke was observed in subjects less than 55 years of age with isolated patent foramen ovale (odds ratio 3.1, 95\% CI 2.3-4.2), and isolated atrial septal aneurysm (odds ratio 6.1, 95\% CI 2.5-15.2). Isolated atrial septal aneurysm is observed more frequently in MWA compared to MwoA or controls,\textsuperscript{116} raising the possibility that MWA may be a consequence of this cardiac abnormality.

In a prospective study of 581 patients with cryptogenic stroke, Lamy et al\textsuperscript{117} demonstrated patent foramen ovale in 46\% and these patients were more likely to experience migraine than the other cryptogenic stroke subjects. In this study migraine did not correlate with the degree of right-to-left shunt. Using transcranial Doppler and intravenous saline injection in an unselected cohort of migraine patients, Anzola et al\textsuperscript{118} demonstrated a significant relationship between patent foramen ovale and MWA but not MwoA. It is unclear if this relationship is the consequence of a common pathogenesis or a shared genetic predisposition.\textsuperscript{110,119} The pathogenesis of migraine in patients with right-to-left shunts has been attributed to microemboli causing endothelial injury and possibly endothelin production\textsuperscript{82} or due to vasoactive chemicals bypassing the pulmonary filter into the systemic circulation.\textsuperscript{121} Several authors have reported complete or partial resolution of migraine following surgical or transcatheter closure of patent foramen,\textsuperscript{121,122} particularly MWA.\textsuperscript{123} A recent meta-analysis by Khairy et al,\textsuperscript{124} suggests that transcatheter closure of patent foramen ovale may be more efficacious than medical management in preventing ischemic stroke. In individual patients the presence of migraine, patent foramen ovale and factor V Leiden mutation may coexist and lead to stroke.\textsuperscript{94}

Therefore, cardiac abnormalities may mediate the relationship between migraine and stroke through a common underlying pathological process or through the induction of MWA as an independent stroke risk factor. The possibility that both may be inherited through a common genetic mechanism requires further study.

Conclusion

A significant nonrandom relationship between migraine and ischemic stroke has been demonstrated in population and case-control studies. Magnetic resonance imaging white matter abnormalities are seen more frequently in migraine patients, and may foreshadow the development of ischemic stroke. The association between migraine and stroke has been described by a wide range of definitions that include: migrainous infarction, migraine-induced stroke, and migraine-related stroke. However, the terms are largely descriptive in the absence of sufficient understanding of the underlying pathophysiological mechanisms, and consequently a greater understanding of the specific direction of the causal link in migraine-stroke would likely lead to more valid terminology.

Migraine may occur as a consequence of conditions that are known to predispose to stroke; therefore it remains to be determined whether migraine predisposes to stroke in the absence of any known disease associations, if it is an epiphenomenon of an underlying stroke diathesis, or if it requires the presence of another stroke risk factor to produce cerebral ischemia. Furthermore, it is unclear if ischemia results in migraine more often than migraine results in ischemia. A recent case-control study by Kern et al\textsuperscript{125} suggests that stroke risk factors differ in MWA and MwoA. Migraine with aura patients who developed stroke were more commonly found to have a patent foramen ovale or other cardiac abnormality and OC use compared to MwoA. Conversely, MwoA patients who experienced stroke more commonly were found to have
hypertension, diabetes, hypercholesterolemia, and coagulopathy compared to MWA. Further clinical studies that evaluate this bidirectional relationship are needed to determine why migraine patients are subject to a higher risk of ischemic stroke. These studies may improve our understanding of basic stroke mechanisms and may suggest an important role for disease management in migraine care.120

ACKNOWLEDGEMENTS

Thanks to Rick Swartz BSc PhD and Ashfaq Shuaib MBBS FRCP(C) for reviewing a draft of this manuscript and for providing helpful suggestions. RZK is a Closure I co-investigator and has provided paid consultative services to, and received speaking honoraria from, AstraZeneca, MerckFrosst, and Jansen-Ortho Biotech.

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Volume 31, No. 4 – November 2004