Migraine Is Associated With Magnetic Resonance Imaging White Matter Abnormalities

A Meta-analysis

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Background: There is controversy as to whether migraine is associated with white matter abnormalities (WMAs) on magnetic resonance images. These abnormalities may be important as a risk factor for future stroke. Further, it is controversial whether any increased risk of WMAs is attributable to comorbidities such as vascular disease.

Methods: A meta-analysis of published case-control studies was undertaken to address the relationship between migraine and magnetic resonance imaging WMAs. Seven studies were identified. Data from studies reporting the incidence of magnetic resonance imaging WMAs in those with migraine and appropriate control populations were used to calculate odds ratios for WMAs in migraine for each study. A stratified meta-analysis was performed using studies that did and did not exclude subjects with disease comorbidities.

Results: The summary odds ratio shows that those with migraine are at increased risk for WMAs (odds ratio, 3.9 [95% confidence interval, 2.26-6.72]). The risk does not differ between studies that included subjects with comorbidities and those that did not.

Conclusion: This meta-analysis demonstrates that subjects with migraine are at higher risk of having WMAs on magnetic resonance images than those without migraine. This increased risk is present even in younger individuals who do not have co-occurring cerebrovascular disease risk factors. Prospective studies are needed to determine whether the increased risk of stroke in migraine is mediated or foreshadowed by the presence of WMAs.

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MIGRAINE HEADACHES are a common and significant cause of disability in our society.1 White matter abnormalities (WMAs) on magnetic resonance images (MRIs) can be seen with migraine, but they are also incidental findings in normal control populations. Magnetic resonance imaging WMAs are more common in individuals with cerebrovascular risk factors.2 There are conflicting studies showing either increased incidence3-6 or equal incidence7-9 of WMAs in subjects with migraine compared with those without migraine. Studies that report no increased incidence of WMAs imply that the reported increase can be accounted for by disease comorbidities, such as age, hypertension, diabetes, or demyelinating diseases. To resolve this issue, a meta-analysis was performed to identify published studies of MRI WMAs in subjects with migraine and healthy controls. Data from these studies were evaluated and, where appropriate, combined to ask 2 questions: (1) Are subjects with migraine at higher risk of having WMA on MRI than those without? (2) What is the risk of WMAs in subjects with migraine who do not have co-occurring cerebrovascular disease risk factors?

METHODS

A MEDLINE literature search was performed using Entrez PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi) using the keywords “MRI,” “migraine,” and “white matter” to identify studies that have investigated MRI signal abnormalities in subjects with migraine headaches. The search was limited to English-language publications and studies of humans only. Eligible studies focused on structural MRI signal abnormalities, while studies of diffusion tensor signal, magnetic resonance spectroscopy, or functional imaging techniques were excluded. Studies of specific diseases associated with headache (eg, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [CADASIL], arteriovenous malformations, or aneurysms) were excluded. Data from studies reporting the incidence of MRI WMAs in those with migraine and appropriate control populations were used to cal-

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Table. Incidence of White Matter Abnormalities (WMAs) in Migraine and Control Groups From the 7 Eligible Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients With Migraine and WMAs/Total Sample Size</th>
<th>No. of Controls With WMAs/Total Sample Size</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Benedittis et al, 1995</td>
<td>9/28</td>
<td>4/54</td>
<td>No control for comorbidities</td>
</tr>
<tr>
<td>Fazekas et al, 1992</td>
<td>8/24</td>
<td>2/14</td>
<td>Age, &lt;50 y; comorbidities excluded</td>
</tr>
<tr>
<td>Igarashi et al, 1991</td>
<td>15/51</td>
<td>11/98</td>
<td>Age, &lt;40 y; comorbidities excluded</td>
</tr>
<tr>
<td>Pavese et al, 1994</td>
<td>25/129</td>
<td>1/50</td>
<td>Age, &lt;45 y; comorbidities excluded</td>
</tr>
<tr>
<td>Robbins and Friedman, 1992</td>
<td>6/46</td>
<td>3/69</td>
<td>No control for comorbidities</td>
</tr>
<tr>
<td>Rovaris et al, 2001</td>
<td>5/16</td>
<td>0/17</td>
<td>Age, 18-55 y; comorbidities excluded</td>
</tr>
<tr>
<td>Ziegler et al, 1991</td>
<td>3/18</td>
<td>2/15</td>
<td>No control for comorbidities</td>
</tr>
<tr>
<td>Total</td>
<td>71/312</td>
<td>23/317</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Plot of odds ratios (ORs) and 95% confidence intervals (CIs) from the 7 eligible studies.

culate odds ratios (ORs) for WMAs in migraine for each study. A stratified meta-analysis was performed with a random-effects model using RevMan Analysis (version 4.2.3, http://www.cc-ims.net/RevMan, November 2003; Cochrane Collaboration, Oxford, England). Separate analyses were performed for: (1) studies that excluded subjects with disease comorbidities and (2) studies that did not exclude subjects based on comorbidities. The level of significance was set at α = .0125 to account for 3 comparisons.

The Medline search identified 46 articles. Of these, 7 retrospective case-control studies were found that examined structural MRI signal abnormalities in individuals with migraine compared with control samples without migraine (Table). There were no prospective studies. One study compared signal abnormalities in both the spinal cord and brain. It is not clear from the data presented in the present analysis the numbers of subjects with WMAs from the migraine and control groups are shown in the Table. Three of the 7 studies did not exclude patients based on the presence of comorbidities that might result in WMAs on MRI. In the 4 studies that selected patients to be free of comorbidities, reasons for exclusion included age, cerebrovascular disease risk factors (hypertension, hypercholesterolemia, diabetes mellitus), CADASIL, demyelinating diseases, inflammatory conditions, and valvular heart disease.

Odds ratios from the 7 studies and the meta-analysis summary are shown in Figure 1. Tests for heterogeneity13 show that the results of the 7 studies are not heterogeneous (χ²=4.13; P=.66; heterogeneity=0.34). The summary OR suggests that individuals with migraine are close to 4 times more likely to have WMAs than controls (OR, 3.90 [95% confidence interval (CI), 2.26-6.72]).

Data from the 4 studies that excluded individuals with disease comorbidities are shown in Figure 2. These data show that, after controlling for comorbidities, those with migraine are still more likely to have WMAs than controls (OR, 4.14 [95% CI, 2.05-8.37]; test of heterogeneity: χ²=2.49; P=.48; heterogeneity=0.526).

Data from the 3 studies that did not select patients based on comorbidities are shown in Figure 3. The OR from these studies was not greater than the OR from the studies that excluded comorbidities (OR, 3.56 [95% CI, 1.51-8.42]; test of heterogeneity: χ²=1.65; P=.44; heterogeneity=0.64).
The results from this meta-analysis demonstrate that subjects with migraine are at higher risk of having WMA on MRI than those without migraine. In addition, this increased risk is present even in younger individuals who do not have co-occurring cerebrovascular disease risk factors. While it is recognized that migraine confers an increased risk of stroke,16 the relationship between migraine and silent white matter changes has been more controversial. Several authors have suggested that there is no relationship between migraine and WMA after excluding cerebrovascular disease risk factors or other disease comorbidities related to MRI signal changes.7,9 The data presented here show that there is a strong relationship between migraine and MRI WMA, regardless of comorbidities. Individuals with migraine are close to 4 times more likely to show these changes than age- and sex-matched controls. This applies even to studies of young (<55 years) people with no other identified risk factors beyond migraine.

This may be significant since white matter hyperintensities are related to an increased risk of stroke.15 Indeed, having migraine increases the risk of stroke in young people.16 The same pathophysiologic characteristics that predispose individuals to migraine may underlie the increased risk of stroke. This raises the intriguing possibility that pharmacological therapy for migraine prophylaxis could reduce the long-term risk of both silent and symptomatic strokes. It has been suggested that the concept of disease modification in migraine may have come of age.17 Our observations lend support to this claim. Prospective trials evaluating this hypothesis need to be undertaken.

The presence of MRI WMA may reflect pathologic conditions other than ischemia, such as demyelinating disease, CADASIL, or other connective tissue disease. The studies reviewed in the present analysis did not report the volume or number of white matter changes, but in most migraine-related WMA the changes are multiple, small, deep white matter or small and periventricular in location. Extensive periventricular abnormalities or large lacunar infarcts in the deep white matter or deep gray matter nuclei should increase suspicion for other processes (eg, CADASIL or small-vessel disease, respectively). Therefore, careful clinical correlation would be required before ascribing the observed WMA to migraine. Other investigations such as cerebrospinal fluid analysis or appropriate serologic tests may be indicated and should be ascertained on a case-by-case basis.

There are several important limitations to this study. First, by definition, a meta-analysis of published literature has a selection bias; negative results are more difficult to publish. Second, none of the studies were population-based analyses of all individuals in a cohort with and without migraine. The selection of individuals for study could thus have been biased as well. Third, some of the identified WMA may represent enlarged Virchow-Robin spaces and not vascular injury. However, this is considerably less likely in the adult population than in children with migraine.18 Finally, this analysis did not explore differences with migraine subtypes (such as differences between those with and without aura).

Despite these limitations, the data reviewed here suggest that individuals with migraine are 4 times more likely than subjects without migraine to have white matter changes when MRI is performed and that this cannot be explained by the presence of disease comorbidities. These white matter changes may be a marker for subsequent risk of stroke. It remains to be prospectively evaluated whether those people who have migraine and WMA are at greater risk of stroke than those with migraine but without WMA.

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