High risk of developing subsequent epilepsy in young adults with migraine: a nationwide population-based cohort study in Taiwan

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Summary

Background and purpose: This study evaluated the effect of migraine on the subsequent development of epilepsy.

Methods: A total of 10,016 patients diagnosed with migraine [ICD-9-CM (International Classification of Diseases, Ninth Revision, Clinical Modification) 346] during the period between 2000 and 2009 who were aged older than 20 years were identified as the migraine cohort. A comparison cohort including 40,064 people were enrolled in this study. We calculated the adjusted hazard ratio (aHR) for developing epilepsy (ICD-9-CM 345) in the two cohorts after adjusting for age, sex and comorbidities. Kaplan-Meier analysis was used to measure the cumulative epilepsy incidence, and the log-rank test was used to estimate the differences between two curves.

Results: The cumulative incidence of epilepsy was significantly high in the migraine cohort. The aHR for developing epilepsy in the migraine cohort was 1.85 (95% CI = 1.22–2.81). The aHR for developing epilepsy in the female migraineurs was significantly different compared with that of the non-migraine cohort (aHR = 2.04, 95% CI = 1.20–3.48) and male migraineurs (aHR = 1.53, 95% CI = 0.78–3.00). The incidence of developing epilepsy was increased in patients aged 20–44 years, yielding an aHR of 2.14 (95% CI = 1.24–3.68). The comorbidity-specific aHR for developing epilepsy associated with migraine was 2.33 (95% CI = 1.25–4.34) in patients without any comorbidities, and 1.73 (95% CI = 1.02–2.93) in those with comorbidities.

Conclusion: This population-based retrospective cohort study revealed a significant increase in subsequent epilepsy risk in young adults with migraine.

Introduction

Migraine is a common neurological disorder that affects the central nervous system, causing painful headaches and disability in the daily life of patients. In Asia, migraine is the most prevalent type of headache diagnosed at neurological clinics (66.6% of headache patients were diagnosed with...
migraine, ranging from 50.9 to 85.8% across various countries.\textsuperscript{1} The estimated annual prevalence of migraine is 18.2% in women and 6.5% in men in USA, and 16.8% and 7.5%, respectively, in European countries,\textsuperscript{2,3} and the prevalence is highest in both middle-aged men and women. Patients with migraine have been documented to exhibit a significantly high risk of developing vascular diseases because migraine is a neurovascular dysregulation disorder in nature.\textsuperscript{4,5} However, a hypothesis on migraine mechanisms posits that the existence of abnormal electrophysiological activities on the cortex plays a critical role in the brain of migraineurs.\textsuperscript{6,7} Based on the later theory, migraine attacks may be triggered by excessive neocortical cellular excitability, which behave similar to epileptic seizures.

Epilepsy is another common brain disease but more serious than migraine, with a prevalence of 0.5–1% in the worldwide general population.\textsuperscript{8,9} Regarding the pathogenesis of epilepsy, the disease is caused by an imbalance in the excitatory and inhibitory expression of ion channels in the brain and the electrophysiological instability on the cortex could be expressed as the spikes with hypersynchronization during an epileptic seizure. In people experiencing migraine, the hyperexcitability with cortical spreading depression is opposed to the hypersynchronization expressed during epileptic seizures. However, migraine and epilepsy have appeared to be comorbid disorders for decades by an epidemiologic co-occurrence.\textsuperscript{10,11} Migraine and epilepsy are linked by their symptom profiles, comorbidity and treatment. The presence of one disorder increases the likelihood that the other is also present. Usually, researchers focused on the studies that epilepsy patients might have higher incidences to develop other comorbid pain disorders, such as migraine and chronic pain,\textsuperscript{12} due to epilepsy would affect patients’ life span in addition to affect their life quality.

Migraine is generally not regarded as a life-threatening disease. On the other site, a recent study suggested a 2.5-time year-standardized mortality ratio in epilepsy patients compared with that in the general population of Taiwan.\textsuperscript{13} Therefore, we questioned whether migraine could be thought as a predisposing factor for epilepsy and migraineurs might have times of hazard ratio for developing subsequent epilepsy, and exhibit an increase in disease severity, daily disability and mortality. So we conducted this study by using the Taiwan nationwide population-based database to examine the risk of developing epilepsy in patients with migraine.

Materials and Methods

Data source

In March 1995, the National Health Insurance (NHI) program was established to provide nationwide coverage and low copayments, and offers a comprehensive selection of hospitals and physicians in Taiwan. The NHI program covers nearly all citizens (over 99% of 23.74 million residents) in Taiwan. The National Health Insurance Research Database (NHIRD) was established by the National Health Research Institutes and the National Health Insurance Bureau of Taiwan. The study cohort was obtained from the Longitudinal Health Insurance Database (LHID), a subset of the NHIRD, for the period from 1996 to 2011. The LHID contains annual claims data, including the demographic status of patients and medical service records.

The identity of the insured population is encrypted to ensure privacy and data security. This study was approved from full ethical review by the Institutional Review Board (IRB) of China Medical University (IRB permit number: CMU-REC-101-012). The disease diagnosis was clarified using the International Classification of Diseases, Ninth Revision, Classical Modification (ICD-9-CM) in examining outpatient and inpatient data. Several studies have indicated the high accuracy and validity of diagnoses made using ICD-9 codes from the NHIRD of Taiwan, as well as similar study designs.\textsuperscript{14,15}

Study participants

We identified patients newly diagnosed with migraine (ICD-9-CM 346) during the period between 2000 and 2009 as the migraine cohort. We focused on the adult population and, therefore, selected only patients aged 20 years and older. The date of the first medical visit for migraine was defined as the index date.

The participants for which information on age or gender was missing and those diagnosed with epilepsy (ICD-9-CM 345) before the index date were excluded. In the two cohorts, all of the participants with brain tumors (ICD-9-CM 225, 191, 192, 194.3 and 194.4), head injury (ICD-9-CM 850–854 and 959.01) or stroke (ICD-9-CM code 430–438) before the end date were excluded, due to those were known as major epilepsy etiologies in adults. A total of 10 016 patients with migraine were enrolled in this study. For the comparison cohort, we randomly selected four non-migraine patients for each migraine patient by using the same exclusion criteria, and frequency-matched them with the
migraine cohort for age, gender and index year to form the non-migraine cohort containing a total of 40,064 people.

**Outcome measures**

The study patients were followed up until they were diagnosed with epilepsy (ICD-9-CM 345), which was identified based on the medical visit records. The follow-up period was from the index date to the date of epilepsy diagnosis, withdrawal from the NHI, death, or until 31 December 2011.

**Exposure variables**

A comparison of demographic characteristics, such as sex, age and comorbidities, was conducted between the migraine and non-migraine cohorts. The comorbidity histories identified before the end date included sleep disorders (ICD-9-CM codes 370.4 and 780.5), dementia (ICD-9-CM 290.0–290.4 and 331.0), anxiety (ICD-9-CM 300.0, 300.2, 300.3, 308.3 and 309.81) and depression (ICD-9-CM 296.2, 296.3, 300.4 and 311).

**Statistical analysis**

The distributions of categorical variables were compared between the migraine and non-migraine cohorts by using the Chi-squared test. The mean age of both cohorts was determined using the Student’s t-test. In addition, we calculated the incidence rate by using the demographic variables and comorbidity (yes/no) for each cohort. The incidence rate ratios (IRR) for epilepsy and 95% confidence interval (CI) were estimated in the two cohorts by using Poisson regression. We calculated the adjusted hazard ratio (aHR) for developing epilepsy in the two cohorts after adjusting for age, sex and comorbidities by using the multivariable Cox proportional hazard model.

All of the statistical analyses were performed using the SAS 9.3 statistical package (SAS Institute Inc., NC, USA), and a P value of <0.05 in the two-tailed tests was considered significant. We used R software (R Foundation for Statistical Computing, Vienna, Austria) to conduct a Kaplan-Meier analysis and thereby measure the cumulative epilepsy incidence for the migraine and non-migraine cohorts, and used the log-rank test to estimate the differences between the two cumulative incidence curves.

**Results**

Table 1 shows the comparison of the demographic variables and distributions of comorbidities. Both cohorts exhibited a similar gender and age distribution. The study participants were mostly female patients (75.1%) and aged <65 years (94.5%). The migraine cohort was more likely to have a high prevalence of comorbidities compared with that of the non-migraine cohort (P < 0.05). As shown in Figure 1, the cumulative incidence of epilepsy was significantly higher in the migraine cohort than in the non-migraine cohort (log-rank test: P < 0.0001).

Table 2 shows the incidence and aHR of epilepsy in the migraine cohort stratified by gender, age and comorbidity (yes/no) compared with that of the non-migraine cohort. The overall incidence of developing epilepsy was higher in the migraine cohort than in the non-migraine cohort (5.90 vs. 2.53 per 10,000 person-years), with an aHR of 1.85 (95% CI = 1.22–2.81). When the migraine cohort was stratified according to gender, the aHR of epilepsy for the women yielded a statistically significant difference compared with that of the women in the non-migraine cohort (aHR = 2.04, 95% CI = 1.20–3.48), and that of the men was not significantly different compared with the aHR of epilepsy for the men in the non-migraine cohort (aHR = 1.53, 95% CI = 0.78–3.00). The age-specific incidence of developing epilepsy increased as age increased in both cohorts; the highest incidence was observed in the migraine cohort for those aged over 65 years (20.8 per 10,000 person-years). However, the aHR for developing epilepsy yielded a statistically significant difference in only those patients aged 20–44 years (aHR = 2.14, 95% CI = 1.24–3.68). The comorbidity-specific analyses indicated that the patients with

![Figure 1](image-url). Comparison of cumulative incidence of developing epilepsy between migraine cohort (dashed line) and non-migraine cohort (solid line).
comorbidities (any one or more of the following: sleep disorders, dementia, anxiety and depression) in the migraine cohort exhibited the highest incidence rate of developing epilepsy (6.63 per 10 000 person-years). However, when adjusted with the comparison cohort, the comorbidity-specific aHR for developing epilepsy associated with migraine was 2.33 (95% CI = 1.25–4.34) in patients without any comorbidities and 1.73 (95% CI = 1.02–2.93) in patients with one or more comorbidities.

Table 3 shows the effects of interactions between comorbidities and migraine on the risk of developing epilepsy. When the comorbidities and migraine interacted, the aHR for developing epilepsy increased (aHR = 2.98, 95% CI = 1.81–4.90 for sleep disorders; aHR = 6.64, 95% CI = 0.90–49.0 for dementia; aHR = 3.14, 95% CI = 1.80–5.48 for anxiety and aHR = 5.17, 95% CI = 2.77–9.64 for depression); however, significant interaction was not achieved. The aHR of epilepsy in participants with migraine and dementia did not have statistically significant difference to reference group because the subgroup number was too small.

Discussion

People with epilepsy exhibit a high risk of premature death and most die from vascular diseases, such as heart disease or stroke.16,17 A 2.5-time year-standardized mortality ratio in epilepsy patients was reported recently based on a data analysis of the Taiwanese population, similar to that conducted in this study.13 As we known, migraine is a neurovascular disorder, and is associated with higher risks of ischemic stroke and other vascular events.3,18–20 In this study, we demonstrated that migraine could be considered as a predisposing factor for developing subsequent epilepsy, especially in females and in the patients younger than 45 years old. A new perspective on the pathogenesis linkage between these two types of brain disease, particularly in migraineurs aged 20–44 years, was provided. Putting the findings and previous literatures together, we proposed that migraine, vascular diseases and epilepsy might have some connections based on the endothelial, structural and genetic factors of vessels.19,20 However, migraine with aura (MA) was reported to have more tendencies to link with vascular diseases and unprovoked seizures than migraine without aura (MO) being.4,21 Unfortunately, we could not distinguish the patients with MA from the MO ones due to we were unable to contact the encrypted patients themselves to get their symptom details in this study. These two subcategories of migraine might be differentially associated with the risk of developing epilepsy also.21

Generally, the prevalence of migraine increases, starting from adolescence, and is the highest in both men and women aged between 35 and 45 years,2,22 and more prevalent in the female gender. Our study demonstrated that female migraineurs also had a higher risk than male ones to develop subsequent epilepsy (aHR: 2.04 vs. 1.53). This interesting finding should be due to that 63.3% of the subjects in our cohorts were younger than 45 years old and
with menstrual cycles in female ones. The change of estradiol/progesterone ratio during the cycle is well known to be a trigger of seizure attack. The hypotheses about the common pathogenetic mechanisms of epilepsy and migraine have been reported in several ways. First, related to the dysfunction of ion channels, it has been assumed that channelopathies may be the link between epilepsy and migraine, particularly when these two are in comorbid existence. Second, a hypothesis has been suggested a causal unidirectional relationship. Migraine can cause cerebral ischemia or cerebral

### Table 2: Incidence and aHR of epilepsy stratified by gender, age and comorbidity (yes/no) between migraine and non-migraine cohorts

<table>
<thead>
<tr>
<th>Variables</th>
<th>Migraine</th>
<th></th>
<th>Compared with non-migraine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>Event</td>
</tr>
<tr>
<td>Overall</td>
<td>69</td>
<td>273 233</td>
<td>2.53</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>41</td>
<td>206 608</td>
<td>1.98</td>
</tr>
<tr>
<td>Men</td>
<td>28</td>
<td>66 625</td>
<td>4.20</td>
</tr>
<tr>
<td>Age, year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-44</td>
<td>37</td>
<td>175 895</td>
<td>2.10</td>
</tr>
<tr>
<td>45-64</td>
<td>21</td>
<td>84 063</td>
<td>2.50</td>
</tr>
<tr>
<td>≥65</td>
<td>11</td>
<td>13 275</td>
<td>8.29</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>41</td>
<td>198 732</td>
<td>2.06</td>
</tr>
<tr>
<td>Yes</td>
<td>28</td>
<td>74 501</td>
<td>3.76</td>
</tr>
</tbody>
</table>

PY, person-year; Rate, incidence rate (per 10,000 person-years). *Multiple analysis including age, gender and comorbidities.

### Table 3: The aHRs of epilepsy associated migraine interaction with comorbidity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Migraine</th>
<th>Sleep disorders</th>
<th>N</th>
<th>Event</th>
<th>Adjusted HR (95% CI)</th>
<th>P value*</th>
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<tr>
<td></td>
<td>No No</td>
<td>31 673</td>
<td>49</td>
<td>1.00</td>
<td>0.7785</td>
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<tr>
<td></td>
<td>No Yes</td>
<td>8391</td>
<td>20</td>
<td>1.50 (0.89-2.54)</td>
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<tr>
<td></td>
<td>Yes No</td>
<td>5188</td>
<td>18</td>
<td>2.23 (1.30-3.83)**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes Yes</td>
<td>4828</td>
<td>23</td>
<td>2.98 (1.81-4.90)**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No No</td>
<td>39 937</td>
<td>67</td>
<td>1.00</td>
<td>0.6225</td>
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</tr>
<tr>
<td></td>
<td>No Yes</td>
<td>127</td>
<td>2</td>
<td>5.17 (1.21-22.0)*</td>
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<tr>
<td></td>
<td>Yes No</td>
<td>9959</td>
<td>40</td>
<td>2.37 (1.60-3.50)**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes Yes</td>
<td>57</td>
<td>1</td>
<td>6.64 (0.90-49.0)</td>
<td></td>
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<tr>
<td></td>
<td>No No</td>
<td>35 995</td>
<td>56</td>
<td>1.00</td>
<td>0.4334</td>
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<tr>
<td></td>
<td>No Yes</td>
<td>4069</td>
<td>13</td>
<td>1.92 (1.04-3.53)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes No</td>
<td>7007</td>
<td>25</td>
<td>2.32 (1.45-3.72)**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes Yes</td>
<td>3009</td>
<td>16</td>
<td>3.14 (1.80-5.48)**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No No</td>
<td>38 172</td>
<td>56</td>
<td>1.00</td>
<td>0.1059</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No Yes</td>
<td>1892</td>
<td>13</td>
<td>4.71 (2.57-8.64)**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes No</td>
<td>8472</td>
<td>29</td>
<td>2.31 (1.48-3.62)**</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Yes Yes</td>
<td>1544</td>
<td>12</td>
<td>5.17 (2.77-9.64)**</td>
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</tr>
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</table>

Model adjusted for age and gender. *P value for interaction. *P < 0.05, **P < 0.01, ***P < 0.001.
damage in a patient, and results consequently epileptic seizures. On the other way, an epileptic seizure can trigger the trigeminal-vascular system through mechanisms encephalic trunk and causes migraine. Third, the common environmental risk factors, such as head injury, can increase the risks of developing both migraine and epilepsy in a person. Fourth, the genetic hypothesis has ever been proposed due to that the relatives of patients with both migraine and epilepsy would have an increased incidence of developing epilepsy when compared with the relatives of patients with epilepsy only.\textsuperscript{24} Scher et al.\textsuperscript{25} reported that according to genetic perspectives, middle-aged and young adults exhibit an increased prevalence of the methylenetetrahydrofolate reductase (MTHFR) C677T variant and a high risk of MA. Furthermore, the association between the MTHFR C677T variant and MA was low in the aged population.\textsuperscript{25} The hypotheses in channelopathies and genes might convince us that these two brain disorders are more easily to develop together in young and middle ages than that in old age. By combining the findings of these studies with this study, migraine can be regarded as an unstable brain condition that typically occurs in the young and middle ages of a person’s life and most likely involves the risk of developing another brain instability disorder, such as epilepsy. As age increases, the pathogenesis for migraine in channelopathies and genes would become obscure in the older population and may cause another comorbid disease, such as stroke.

Figure 1 indicates that the risk of developing epilepsy increased in the migraine cohort as the follow-up time increased. As shown in Tables 2 and 3, we analyzed the interactions between comorbidities included sleep disorders, dementia, anxiety, depression and epilepsy in our cohorts by considering the major confounding factors for developing epilepsy. We observed that migraineurs without any comorbidities exhibited a higher risk of developing epilepsy compared with that of migraineurs with one or more comorbidities (aHR: 2.33 vs. 1.73). The different aHRs in the cohorts with and without comorbidities is interesting and appears to demonstrate that those four comorbidities are not the responsible confounder or mediator driving the relationship between migraine and later epilepsy. All these results in the study implied that migraine might be a predisposing factor for developing epilepsy. In addition, the common pathogenesis of migraine and epilepsy might play a role in young migraineurs to develop subsequent epilepsy.

The strengths of this study are the nationwide population-based design and representativeness of the cohort. However, this study has several limitations. First, information on migraine frequency (with or without aura), smoking habits, alcohol consumption, body mass index, socioeconomic status and family history were not available in the NHIRD, all of which might be confounding factors for developing epilepsy in the study groups. Second, the evidence derived from a cohort study, and a cohort study design is subject to several biases related to adjusting for confounders. Despite our meticulous study design, a key limitation was that bias could remain if unmeasured or unknown confounders were present. Finally, the diagnoses in the NHI claims data are primarily used for administrative billing and do not undergo verification for scientific purposes. We could not approach the patients directly to obtain their detailed medical history nor information on the medication used by the migraineurs because of the anonymity of their identification numbers. However, several studies have reported the high accuracy and validity of diagnoses made using ICD-9 codes in the NHIRD and similar study designs,\textsuperscript{14,15} which indicated that the results of this study are valuable for understanding the linkage between migraine and epilepsy.

**Conclusion**

The results of this population-based cohort study indicated a significant association between young adults with migraine and an increased risk of developing epilepsy. Additional large, unbiased, population-based studies are necessary before any confirmatory conclusion can be drawn.

**Acknowledgements**

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