ABSTRACT

Comorbidity is defined as the co-occurrence of 2 medical conditions more frequently than would be expected by chance alone. Migraine and epilepsy are highly comorbid and share clinical features that suggest overlapping pathophysiology. The Epilepsy Family Study of Columbia University demonstrates the comorbidity of migraine and epilepsy; this relationship cannot be explained by a unidirectional causality (ie, that one disorder causes the other), shared genetic risk factors, or shared environmental risk factors. Analysis of epidemiologic and biological data suggests that brain hyperexcitability due either to environmental or genetic risk factors may account for the co-occurrence of migraine and epilepsy. However, our current understanding of hyperexcitability is not yet clear. Comorbidity is critical because it affects diagnosis as well as treatment. When conditions are comorbid, it is a mistake to make a single diagnosis. When epilepsy is diagnosed, it is more likely, not less likely, that the patient also has migraine. The presence of comorbid disorders presents both therapeutic opportunities and limitations. In some cases, a single medication can be used to treat both disorders; in other cases, medication to treat one disorder may be contraindicated for the other disorder.

Comorbidity is important because it informs both diagnosis and treatment. Diagnostic skills, particularly in the field of neurology, are often guided by the principle of parsimony, for example, neurologists look for the unitary that explains all of a patient’s symptoms and signs. With migraine, applying Occam’s razor may reduce the chances of treatment success if the comorbid condition remains undetected and therefore untreated. Thus, the presence of one condition (ie, epilepsy) should heighten the index of suspicion of the other (ie, migraine), especially because the conditions share symptomology. Comorbidity also informs treatment options in at least 3 ways. It creates therapeutic opportunities in which a single medication can be used to treat both disorders (ie, a “two-fer”). However, comorbidity can also impose therapeutic limitations if the treatment of one disorder can exacerbate another disorder (eg, administering bupropion to a patient with epilepsy and comorbid depression). In the future, we hope to use the presence of a comorbid condition to identify overlapping pathogenic mechanisms and therefore common mechanisms of action for treatment strategies.

Migraine and epilepsy share numerous clinical features that suggest a theoretical common pathologic mechanism(s). Both migraine and epilepsy are chronic disorders with episodic manifestations. The episodic features are altered consciousness, focal neurologic deficits, and pain, and are described in this monograph by Dr Haut. Both have a genetic component to their etiology and both disrupt health-related quality of life in measurable ways.15-20

Epidemiologic Evidence of Comorbidity

A review by Andermann and Andermann of 13 studies reported that the prevalence of epilepsy in patients with migraine ranges from 1% to 17% with a median of 5.9%.21 Compared with rates of epilepsy in the general population (0.5%-1%, depending on age, sex, and study design), the prevalence of epilepsy in patients with migraine is clearly elevated.22 The prevalence of migraine in patients with epilepsy ranges from 8% to 23%.23 In general, the prevalence of migraine is twice as high in persons with epilepsy as in the general population (about 12%; 18% in women, 6% in men).21,23-25 Many studies of comorbidity are limited by selection bias, small sample sizes, and lack of contemporaneous control groups, so they are difficult to interpret. However, in aggregate, the results support the association between migraine and epilepsy.

The Epilepsy Family Study of Columbia University

The largest epidemiologic study of epilepsy and migraine included nearly 2000 adults with epilepsy and nearly 1500 of their relatives. The Epilepsy Family Study of Columbia University, lead by Ruth Ottman, included patients at least 18 years of age with epilepsy (proband). The probands all received the same structured telephone interview to ascertain epilepsy status, migraine status, and other covariates. The participation rate among identified probands was 84% and medical records were reviewed in 60% of the probands.23,26

In this study, epilepsy was defined as a lifetime history of at least 2 unprovoked seizures, and seizures were classified based on the International League Against Epilepsy criteria. Migraines were defined as severe headache with at least 2 of the following: unilateral, throbbing pain, visual aura, or nausea. This study was performed prior to the International

Figure 1. Cumulative Incidence of Migraine in Probands with Epilepsy and Their Relatives (with and without Epilepsy)

Among control subjects (ie, relatives without epilepsy), the cumulative incidence of migraine increases relatively linearly over time, from age 5 to 40 years. The cumulative incidence among probands and their relatives with epilepsy is much higher, reflecting the calculated 2.4 rate ratio. The curves for probands and their relatives with epilepsy are very similar.

Headache Society (IHS) classifications of headache, but the definition corresponds closely with IHS criteria for migraine.23,26

The goal of the study was to estimate the prevalence of migraine in persons with epilepsy using, as a comparison group, their relatives without epilepsy. In relatives without epilepsy, the prevalence of migraine was 15%; among probands, the prevalence of migraine was 24%. Using reconstructed cohort methods to take age of onset for migraine and epilepsy into account, probands with epilepsy were 2.4 times more likely to develop migraine than their relatives who do not have epilepsy (rate ratio = 2.4). This ratio was the same in relatives with epilepsy, suggesting that the probands who volunteered for the study did not have a more severe form of epilepsy. Figure 1 shows the cumulative incidence of migraine to age 40 among the 3 study groups, illustrating the higher rate of migraine among probands with epilepsy and relatives with epilepsy compared with their relatives without epilepsy.23,26

These data demonstrate that migraine and epilepsy are comorbid disorders. However, they do not address the mechanism of comorbidity. We considered 4 models to explain these data, as outlined in Figure 2. They include unidirectional causality, shared environmental risk factors, shared genetic risk factors, or a common causal pathway. Unidirectional causality implies that either migraine is a risk factor for epilepsy, or epilepsy is a risk factor for migraine. This is a biologically plausible hypothesis. For example, in a subset of migraine patients, ischemia during migraine aura could result in strokes that become epileptic foci. Conversely, during a seizure, if meningeal trigeminal afferents are activated, repeated activation may lower the threshold for initiating migraine. If the unidirectional cause theory were true, then the risk of epilepsy would be elevated after the onset of migraine but not before it, or the risk of migraine would be elevated after the onset of epilepsy, but not before it. As shown in Figure 3, the risk of migraine is elevated both before and after epilepsy onset, suggesting that the risk is bidirectional. Of note, these data could be consistent with bidirectional causality (ie, that migraine causes epilepsy and epilepsy causes migraine).23,26

To test for a common environmental factor, we analyzed the risk of migraine in those with generalized versus partial seizures, on the assumption that generalized seizures are much less likely to have an identifiable environmental risk factor. As shown in Table 1, the

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**Figure 2. Exploration of Causal Models for Comorbid Migraine and Epilepsy**

- **Unidirectional causation**
  - Migraine → Epilepsy
  - Epilepsy → Migraine

- **Shared environmental or genetic risk factors**
  - Risk Factor
    - Migraine
    - Epilepsy

- **Common causal pathway**
  - Environmental Risk Factors
  - Genetic Risk Factors
  - Brain Hyperexcitability
    - Migraine
    - Epilepsy

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**Figure 3. Cumulative Incidence of Migraine Headache by Age in Probands After and Before Epilepsy Onset**

- Probands after epilepsy onset
- Probands >5 years before onset
- Probands 1-5 years before onset
- Relatives without epilepsy

The risk of migraine is elevated both before and after epilepsy onset, suggesting a unidirectional cause is not possible. Reproduced with permission from Ottman et al Comorbidity of migraine and epilepsy. Neurology. 1994;44(11):2105-2110.23
risk of migraine is elevated in both types of epilepsy. Comparing idiopathic/cryptogenic seizures with symptomatic seizures, the rate ratios are very similar (2.3 and 2.6, respectively) to the entire group (2.4). Though the rate ratio with head injury is slightly higher, environmental risk factors do not appear to explain comorbidity.23,26

A shared genetic risk factor would result in higher rates of migraine in pedigrees where the cause of epilepsy is genetic. We identified probands with epilepsy who had a family member with epilepsy as an approach to finding individuals likely to have a genetic form of epilepsy. Migraine is no more likely in pedigrees with a history of epilepsy than in pedigrees without a family history (Table 2). Thus, genetic risk factors appear unlikely to explain comorbidity between the 2 disorders.23,26,27

We proposed that environmental and genetic risk factors may converge to produce a brain state of hyperexcitability that predisposes both to migraine and epilepsy, building on the hypothesis of Welch that migraine is a condition of brain hyperexcitability.28 Hyperexcitability can be thought of as a lower threshold to attacks of migraine, epilepsy, or both. The precise mechanism of hyperexcitability is unknown.

Numerous lines of evidence support the concept of hyperexcitability in migraineurs. Earlier studies have suggested that the visual abnormalities experienced with migraine, particularly migraine with aura, are interpreted as originating from a hyperexcitable brain state.29-31 Perhaps the most compelling evidence for brain hyperexcitability in migraine are the human studies that suggest migraine aura originates from cortical spreading depression. Despite its name, cortical spreading depression begins as a wave of neuronal excitation followed by a wave of inhibition that marches over the cortical mantle at a rate of about 3 mm per minute; it is believed to be the substrate for migraine aura.32 Functional magnetic resonance imaging and single-photon emission computed tomography studies show waves of decreased blood flow and metabolic changes that march across the cortex at about the same rate.33-35 Magnetoencephalography studies show magnetic evidence for cortical spreading depression.36 More recent work using transcranial magnetic stimulation has also shown reduced thresholds for generating phosphene relative to controls, suggesting a state of increased excitability.37-44

An additional piece of evidence for brain hyperexcitability comes from measuring evoked potentials in response to stimuli. If a warning stimulus is presented to a subject followed by a target stimulus, which records a response, electrical activity over the motor cortex can be recorded. Between the warning and target stimuli, there is a negative shift in electrical activity interpreted as a correlate of motor preparation (a contingent negative variation). In persons with migraine, the negative shift is greater than in nonmigraine controls and increases with headache frequency.

An effective migraine preventive drug, propranolol, decreases attack frequency and decreases contingent negative variation.45-47 There is also evidence, in both adults and children, for a loss of habituation during

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**Table 1. Rate Ratio for Migraine in Probands with Epilepsy by Type of Epilepsy and Other Features**

<table>
<thead>
<tr>
<th>Category</th>
<th>N</th>
<th>Rate Ratio (95% confidence intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial-onset seizures</td>
<td>1627</td>
<td>2.5 (2.1-3.1)</td>
</tr>
<tr>
<td>Generalized seizures</td>
<td>225</td>
<td>1.9 (1.3-2.7)</td>
</tr>
<tr>
<td>Idiopathic/cryptogenic seizures</td>
<td>1523</td>
<td>2.3 (1.9-3.5)</td>
</tr>
<tr>
<td>Head trauma</td>
<td>153</td>
<td>4.1 (1.8-2.9)</td>
</tr>
<tr>
<td>Other symptomatic</td>
<td>233</td>
<td>2.6 (2.0-3.1)</td>
</tr>
</tbody>
</table>

Data from Ottman et al.23

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**Table 2. Rate Ratios for Migraine in Relatives of Probands with Epilepsy**

<table>
<thead>
<tr>
<th>Category</th>
<th>Total with Migraine</th>
<th>Rate Ratio (95% confidence intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history for epilepsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>160 (18.5%)</td>
<td>1.1 (0.75-1.66)</td>
</tr>
<tr>
<td>Negative</td>
<td>1245 (15.3%)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>Etiology of proband epilepsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>1136 (16.0%)</td>
<td>1.0 (0.7-1.4)</td>
</tr>
<tr>
<td>Postnatal</td>
<td>250 (15.6%)</td>
<td>1.0 (ref)</td>
</tr>
</tbody>
</table>

Data from Ottman et al.23,27
cognitive processing in persons with migraine as measured by auditory, event-related potentials (P300).\textsuperscript{48-50} All of these results support the idea that the migraine brain is hyperexcitable.

Possible mechanisms of hyperexcitability include alterations in energy metabolism, presence of channelopathies, and differences in levels of magnesium, neurotransmitters, or amino acids. Migraine-like symptoms may be caused by a mitochondrial disorder such as mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS).\textsuperscript{51} Two “migraine genes” have been identified, but only in familial hemiplegic migraine. One of those genes codes for a neuronal PQ-type calcium channel (CACNA1A, located on chromosome 19).\textsuperscript{52} Animal knock-in models (ie, animals in which the target gene has been inserted at a specific chromosomal locus) have shown alterations in calcium currents that could provide a substrate for excitability.\textsuperscript{53} However, the CACNA1A gene accounts for only about half of all familial hemiplegic migraine, and familial hemiplegic migraine constitutes less than 1% of all migraine.

Some recent evidence shows reduced levels of brain magnesium in persons with migraine. Low magnesium can result in calcium channel opening, increased intracellular calcium, glutamate release, and increased extracellular potassium, which may in turn trigger cortical spreading depression.\textsuperscript{54-58} Magnesium has been used for treating migraine headaches.\textsuperscript{59} As reviewed elsewhere in this monograph (by Drs Silberstein and Krumholz), some of the most commonly used and effective preventive medications for migraine have a number of potential roles in regulating neuronal hyperexcitability, with action on sodium channels, calcium channels, or excitatory amino acid receptors. However, hyperexcitability is such a broad construct that central nervous system-acting drugs will almost inevitably have some mechanism that could be described as influencing hyperexcitability. If pathophysiology of hyperexcitability in migraine and epilepsy could be precisely defined, that might improve treatment.

**CONCLUSION**

Migraine and epilepsy are comorbid—they occur together 2.4 times more often than would be expected by chance. This association applies to all types of epilepsy. Recognizing comorbidity is important because it suggests the need for a concomitant diagnosis, which renders the principle of parsimony in the diagnostic process inappropriate in this setting. Comorbidity can affect treatment decisions both by creating therapeutic opportunities (to treat both disorders with one drug) or by limiting options (because of contraindications). The association between migraine and epilepsy cannot be accounted for by simple unidirectional causal models, shared environmental risk factors, or shared genetic risk factors alone. Instead, we suggest that shared genetic and environmental risk factors converge to create a state of hyperexcitability, which predisposes to both disorders. Numerous areas of research have shown physical and behavioral evidence to support this concept, but the exact definition of hyperexcitability remains to be discovered.

**DISCUSSION**

**Dr Lewis:** If migraine represents the spreading wave of alldynia with spreading cortical depression, and partial epilepsies often represent a spreading wave of hyperpolarization, why isn’t this an inverse phenomenon? Why are migraine and epilepsy not a continua of each other?

**Dr Lipton:** The first thing to say, of course, is that the term “spreading depression” is in many ways a misnomer, because what first marches across the cortical mantle is a wave of excitation. The excitation is relatively brief and presumably accounts for the positive features of the aura. It is followed by a wave of inhibition, which is more enduring. In a sense, your question is related to 2 of the questions that I was going to ask. If hyperexcitability is the common substrate, why aren’t migraine and epilepsy more strongly associated? Why don’t these disorders occur together all the time? And when I asked myself that question, my first answer was that the site of predilection for the hyperexcitability is different. I know this is painting in incredibly broad strokes, but I would argue that the primary location of hyperexcitability in migraine with aura is the occipital cortex. Almost all auras are visual; although I know that there are sensory and motor auras, and, perhaps, premonitory features that reflect aura and association cortex. If there was one site of predilection for hyperexcitability in epilepsy, presumably it would be the temporal cortex, in the hippocampus. Why is that? I know that there are focal epilepsies that arise in many brain regions, and that the appearance of spikes in the temporal lobe in part
reflects the transmission of impulses from foci that are extratemporal. It would be useful to understand why the sites of predilection are different.

**Dr Silberstein:** Is the association between migraine and epilepsy different for migraine with or without aura?

**Dr Lipton:** I think it probably is. In the study I did with Ruth Ottman, however, our aura cases had other features of migraine. We only had a couple of questions on aura, and our aura questions generated false positives. Aura as a sole feature was not specific enough. In our study, we were not in a position to look separately at the association between aura and no aura. Clinically, my impression is that the association is stronger for migraine with aura.

**Dr Krumholz:** We know that migraine is much more common, I believe, in women than in men. Epilepsy may be a bit more common in men than in women. How does this relate to the comorbidities?

**Dr Lipton:** The issue really is that gender is a potential confounder of the relationship between migraine and epilepsy. We dealt with it in Ruth Ottman’s study in 2 ways. First, the rate ratios were gender-adjusted to remove the influence of gender. Second, we did stratified analyses where we separately analyzed the data in men and women. The objective is not to control for gender, but to see if the association follows different patterns in men and women, and we did not see any differences. There are powerful estrogen effects on both migraine and epilepsy. There are catamenial seizures as well as menstrual migraine. There may be a sex difference not at the comorbidity level of disease, but at the level of attack pattern and temporal profile.

**Dr Silberstein:** Is it the presence of epilepsy or the epilepsy frequency that predisposes to migraine?

**Dr Lipton:** In the data that I have, it would be a difficult question to answer for a number of reasons. We have the seizure frequency question, but we have a sample that is very skewed towards people with difficult-to-control epilepsy.

**Dr Silberstein:** What about the patients with epilepsy with or without migraine? Is there any way you can tell the difference between why they go from one group to the other?

**Dr Lipton:** One study shows that in persons with epilepsy and migraine, their epilepsy is more difficult to control, and they have more frequent seizure attacks.

**Dr Haut:** What about dual intractability?

**Dr Lipton:** Many studies look for migraine in an epilepsy population. Although the risk is bidirectional, 2.4 times 11% is a lot of migraine in epilepsy populations, and 2.4 times 0.5% in a migraine population is not a lot of epilepsy. A number of clinic-based studies indicate after a review of 500 patients in a subspecialty practice that 25% or 30% of them have migraine, and the attacks are mostly temporally dissociated. I am not sure if those studies reported on dual intractability. It is a great question.

**Dr Haut:** In epilepsy, we have a very clear idea of what is well controlled versus intractable. Do you have something similar in migraine?

**Dr Lipton:** Yes, but it is quite different in epilepsy because the goal is to have no seizures at all, so patients can drive. In migraine, freedom from attacks is not achievable.

**Dr Haut:** I would say patients with epilepsy settle out into 2 groups: a larger group that seems to be well controlled with appropriate medications, and a group in which no matter what medication they take, they do not achieve control. But there is some overlap in between. Is that same pattern seen in migraine?

**Dr Lipton:** The way I think about well-controlled migraine is in terms of disability and quality of life. The reality is that the best preventive therapy decreases attack frequency by 50% to 70% in half of patients. So, everyone who has frequent migraine who goes on preventive treatment also continues with acute treatment for managing their attacks. My notion of success is that the attack frequency is low enough and acute treatment is effective enough so that patients feel in control. I want function restored within 2 hours and no more than a couple of attacks a month, and in subspecialty care, that is doing very well.

**Dr Silberstein:** I agree with you. Is the prevalence of chronic daily headache higher in this population, based on your study with Ann Scher?

**Dr Lipton:** The issue of comorbidity as a source of intractability is a great question. In our study, we did not look. The problem is the phone interview for...
ascertaining and subtyping epilepsy. Ruth Ottman’s validated phone interview in someone with seizures is a 25- to 30-minute interview. It takes a long time.

**Dr Kossoff:** In epilepsy, sometimes even within the first month or 2, we are able to predict the intractable patients based on factors such as the frequency of seizures and the presence of remote symptomatic epilepsy. Is there any way in your migraine population that you can tell in 1 or 2 months that a patient is going to be more intractable?

**Dr Lipton:** There are predictors of intractability, but they operate over a longer time frame. In our studies, intractability was defined as chronic daily headache (ie, headache 15 or more days per month). Ann Scher and I looked at predictors of developing chronic daily headache in individuals who had episodic headache, and the predictors are female gender, having migraine, being obese, snoring, medication overuse, and caffeine consumption, among others.60-63

**Dr Haut:** When you say obese and snoring, which is a more recognized cause of epilepsy, you essentially are saying sleep apnea.

**Dr Lipton:** In our study all we had was self-reported snoring and body mass index. We did not have sleep studies, but the effect of snoring and the effect of obesity were independent effects.

**Dr Gidal:** In our VA [Veterans Affairs] population, there are a significant number of patients—they tend to be younger guys in their 40s and 50s—who appear to have chronic daily headaches, and typically have relatively poorly controlled seizures. We hardly ever see it in those who are very well controlled.

**Dr Gidal:** I noticed that the graph from your study ended at 40 years. What was the oldest group of patients that you had? In other words, did you have any or enough people that had new-onset epilepsy past their sixth decade of life?

**Dr Lipton:** Yes, but not in this study. I think the oldest person in the sample was 55. We truncated at age 40 because the data became very thin after age 40. We decided not to try to make inferences past the age where we had adequate information. Migraine is largely an early-onset disorder. Half of all cases begin before the age of 20, and there are gender differences as well with boys having an earlier age of onset than girls. Epilepsy has a bimodal distribution of incidence.

There is not a late peak for migraine incidence, although there are individuals who at 50 years of age and older develop what are called “late-life accompaniments.” These are migraine auras in the absence of headache, but the differential diagnosis includes transient ischemic attacks and seizures. We are looking in children, but not in the elderly. The idea of looking at migraine-epilepsy comorbidity in an elderly population is a good one.

**Dr Gidal:** We treat a lot of new-onset epilepsy in the elderly, but I seldom see new-onset headaches develop in those patients. If they develop seizures later, maybe they have had a history of migraine, but I have not ever thought about that before.

**Dr Kossoff:** Stroke is almost like a third comorbidity. We are trying to build a Sturge-Weber Center at Johns Hopkins. It is amazing how many of those children have both epilepsy and migraine. If anything, the migraine is worse than their epilepsy. Do you see in the adult population an increase in comorbidities with vascular malformations, AVMs [arteriovenous malformations], or strokes?

**Dr Lipton:** You raise several issues. Persons with migraine, particularly women under the age of 45 who have migraine with aura, are at increased risk for ischemic stroke. The evidence for men and for persons over 45 is equivocal, based on some cohort studies and case-controlled studies. There is no evidence that migraine is a risk factor for either intracerebral hemorrhage or hemorrhagic infarction.

In terms of the neurocutaneous syndromes, there is a distinction made between primary and secondary headache. Migraines are primary headaches, meaning that the headache disorder is the problem and not attributable to some underlying illness. In the setting of an underlying illness (even if the headache has the phenotypic features of migraine), if the clinician believes that the headache is attributable to the underlying cause, then the headache is a secondary headache and it is not called migraine. It might be called migraine-like to describe the phenotype, but it would be called a secondary headache.

There is no question that migraine-like headaches are associated with a broad range of cranial vascular malformations, and deciding whether the cranial vascular malformation is the cause of the headache in individuals can be tricky. It helps if the headache is ipsilateral to the vascular malformation. You can look
at issues of temporality and treatment effect to try to sort it out, but I think of the migraine-like headaches associated with vascular anomalies as being secondary headaches and not migraine.

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