

COMORBIDITIES OF MIGRAINE

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COMORBIDITIES OF MIGRAINE

OVERVIEW

ACTIVITY OVERVIEW

As many as 40% of people with migraine suffer from comorbid depression. There is strong evidence linking migraine with a variety of comorbid psychiatric and somatic disorders, from stroke to anxiety disorder. This compelling new CD-ROM program from the National Headache Foundation and Primary Care Network provides a comprehensive review of the literature on migraine comorbidities, a review of treatment approaches, and a practical, hands-on video case study of a man with migraine and comorbid depression. The monograph is in the form of PDFs, which may be printed from your computer to provide an enduring resource.

LEARNING OBJECTIVES

After viewing the video and reading the monograph, participating physicians should be better able to:

- Describe the various disorders that are comorbid with migraine
- Evaluate the evidence supporting the comorbid relationship between migraine and other disorders
- Describe guidelines for treating patients with migraine and comorbid conditions

ACCREDITATION STATEMENT

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FACULTY DISCLOSURE

Lisa K. Mannix, MD, is a board certified Neurologist, specializing in the treatment of headache. She is in clinical practice in Cincinnati, Ohio. Previously, she was on staff at the Headache Wellness Center in Greensboro, North Carolina. Dr. Mannix earned her medical degree at the University of Cincinnati College of Medicine. She then completed her internship and neurology residency at The Cleveland Clinic Foundation, where she also served as chief resident and completed a Seymour Diamond Clinical Fellowship in Headache Education. Dr. Mannix has received a Certificate of Added Qualification from the National Board for Certification in Headache Management.

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COMORBIDITIES OF MIGRAINE

The term ‘comorbidity’ refers to the greater-than-coincidental association of two or more conditions in the same person. Reports in the literature have associated migraine with a wide variety of psychiatric and somatic disorders. The quality of the evidence for migraine comorbidities is variable, which limits the validity of some reports. A meta-analysis of migraine comorbidities by *Low et al* has identified methodological problems common to many of these studies.¹ These include: idiosyncratic or less-than-rigorous definitions of migraine, the failure to incorporate confounding risk factors, and sampling bias.

Migraine is associated with higher than expected incidences of several neurological and psychiatric disorders, including epilepsy,² stroke,³ depression,⁴ bipolar disorder,⁵ and anxiety disorders.⁶ Migraine also appears to be associated with irritable bowel syndrome, mitral valve prolapse, asthma,⁷ chronic fatigue syndrome,⁸ low-tension glaucoma,⁹ and Raynaud phenomenon.¹⁰ Patients with migraine without aura have also been shown to score significantly higher than controls on indices of aggression-hostility.¹¹ Migraine may also be associated with impaired cognitive function.¹² Despite reports in the literature associating migraine with hypertension, heart disease, and gastrointestinal disorders, *Low et al* found the evidence supporting these associations to be weak or inconclusive.¹



Comorbidities impose
both limitations on,
and opportunities for,
therapy.



Lipton offered the following possible explanations for the association of migraine with higher than normal incidences of epilepsy, depression, anxiety, and stroke:¹³

1. One condition may cause the other. For example, a prolonged migraine aura may result in a cerebral infarction.
2. There may be a common mechanism underlying both conditions. For example, alterations in serotonin are thought to play an important role in both migraine and depression.
3. Genetic factors may cause a susceptibility to two or more neurologic disorders.
4. Environmental factors could alter brain function in a way that increases the likelihood of two neurological disorders occurring. Head injuries, for example, may lead to both chronic headaches and epilepsy.

Comorbidities have implications for both the diagnosis and treatment of migraine. Comorbidities impose limitations on, and opportunities for, therapy.¹⁴ When migraine and depression occur together, an antidepressant may treat both conditions; when migraine and epilepsy occur together, an anticonvulsant may treat both conditions. The coexistence of migraine and depression creates treatment problems and opportunities. For example, beta blockers are commonly used for migraine prophylaxis, but they would probably not be appropriate in a migraine patient prone to depression. On the other hand, amitriptyline might be successful in preventing migraine and depression in a patient who has both of these disorders. Table 1 lists general guidelines for treating patients with migraine and comorbid disorders.

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TABLE 1. Guidelines for treating patients with migraine and comorbid conditions (from Ruoff)¹⁰

- Use a drug that is effective for both migraine and the comorbid condition, if possible.
- Do not use a migraine agent that is contraindicated in the presence of the comorbid condition.
- Do not use a treatment for the comorbid condition that will aggravate migraine.
- If using multiple agents for migraine and comorbid conditions, avoid combinations that will result in drug interactions.
- Use caution in treating the woman who is pregnant or who plans to conceive, because some prophylactic agents have been associated with teratogenic effects.

MIGRAINE AND STROKE

Both migraine and stroke are associated with altered cerebral blood flow, focal neurological deficits, and headache. In 1975, the *Collaborative Group for the Study of Stroke in Young Women* suggested that migraine may be a risk factor for stroke.¹⁵ In that case-control study, the risk for stroke was found to be doubled in women with migraine compared to community controls. In a subsequent case-control study, *Tzouzio et al* found a 400% increase in the risk of stroke in women with migraine under age 45.³ Smoking and hypertension may further increase the risk.¹⁶ The annual rate of cerebral migrainous infarction in migraineurs has been estimated at 3.36 cases per 100,000.

Stroke appears to be most strongly associated with migraine with aura.¹⁷ The causal relationship between migraine and stroke is complex and not fully understood. Migraine may coexist with stroke, stroke may occur with the clinical features of migraine, or stroke may be induced by migraine. In the last case, a prolonged migraine aura may cause a condition called ‘true migrainous infarction.’¹⁸ The deficits caused by migraine-related stroke may improve or resolve completely with treatment; in other cases the deficits are permanent.

Donaghy compared the incidence of ischemic stroke in 86 women with migraine to 214 matched controls.¹⁹ He found that migraine of more than 12 years’ duration had an odds ratio (OR) of 4.61 for ischemic stroke, initial migraine with aura had an OR of 8.37, and an initial frequency of attacks greater than 12 per year had an OR of 10.4. Patients with initial migraine with aura occurring more than 12 times per year had an especially high risk; increased frequency in the previous nine months also contributed to a higher risk. It should be noted, however, that even with an odds ratio of 10, the increased incidence of stroke is still very small. This work represents an additional analysis of a multi-center case-control study of the relation between stroke and migraine.²⁰

MIGRAINE AND EPILEPSY

An association between migraine and epilepsy has long been recognized. In a large study by *Lipton et al*, it was found that patients with epilepsy were 2.4 times more likely to experience migraines than their relatives without epilepsy.²¹ The prevalence of migraine was 24% among those with epilepsy and

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15% among their relatives without epilepsy (similar to the prevalence in the general population). Conversely, *Andermann* has shown that patients with migraine have a 5.9% prevalence of epilepsy; this compares with a 0.5% prevalence of epilepsy in the general population.²¹ However, *Low et al* note that variable definitions of epilepsy and its subtypes limit accurate risk assessment across studies; they call for additional studies to confirm the relationship between migraine and epilepsy.¹

Differential diagnosis between migraine and epilepsy may be difficult. Migraine with aura and complex partial seizures have several features in common, including an altered state of consciousness.²² The fact that both migraine and epilepsy can often be treated with anticonvulsants, such as valproate and topiramate, suggests a common mechanism for the disorders. *Lipton et al* propose that an increase in neuronal excitability, caused by genetic or environmental factors, underlies both conditions.² While anticonvulsant drugs may benefit both conditions, antimigraine drugs that lower the seizure threshold should generally be avoided. These include tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and neuroleptic agents.

MIGRAINE AND AFFECTIVE DISORDERS

Epidemiologic studies by *Merikangas et al*²³ and by *Breslau and Davis*²⁴ have shown that the occurrence over a lifetime of depression, anxiety disorders, and bipolar disorder are significantly higher in migraine sufferers than in the general population. *Merikangas et al* found odds ratios of 2.2 for depression, 2.9 for bipolar disorder, 2.7 for generalized anxiety disorder, 3.3 for panic disorder, 2.4 for simple phobia, and 3.4 for social phobia.²³ They also found that, in migraineurs with major depression and anxiety disorders, the onset of anxiety usually preceded the onset of migraine, while the onset of major depression usually followed the onset of migraine. *Breslau et al* conducted a prospective, longitudinal study of migraine and depression.⁴ They interviewed a random sample of young adults, aged 21-30, at intervals of 3.5 years. They were able to obtain second interviews in 97% of the original sample. Using these data, they estimated the relative risk for major depression associated with prior migraine and the relative risk for migraine associated with prior depression. In this

sample, the incidence of migraine per 1,000 person-years was 5.0 in males and 22.0 in females. The estimated relative risk for major depression associated with prior migraine was 3.2 (95% CI; 2.3-4.6). The relative risk for migraine associated with prior major depression was 3.1 (95% CI; 2.0-5.0). The investigators concluded that the association between migraine and depression results from bidirectional influences, with each disorder increasing the risk for first onset of the other.

Mitsikostas and Thomas studied the clinical profiles of patients with primary headache syndromes who also suffered from mood disorders.²⁵ Headache outpatients (n=470) and sex-matched healthy subjects (n=150) were screened using a specific questionnaire that included Hamilton rating scales for anxiety and depression. The average anxiety and depression scores were significantly higher in headache sufferers (17.4 and 14.2, respectively) than in healthy people (6.8 and 5.7, respectively). Headache frequency, headache history, and sex (women more than men) were correlated with the Hamilton rating scale for both anxiety and depression. Sixteen headache patients (3.4%) met DSM-IV criteria for major depression or dysthymia compared with one among headache-free subjects (0.6%; odds ratio 5.2). Patients who overused prescription or nonprescription drugs or had migraine with aura had odds ratios for major depression or dysthymia of 35 and 17 compared with controls. The investigators concluded that headache patients with a long history and high frequency of headaches, or patients suffering from migraine with aura or drug overuse might benefit from psychiatric evaluation.

PSYCHIATRIC COMORBIDITIES AND MIGRAINE DISABILITY

Migraine comorbidities may add to the affected person's burden of disability, chronically disrupting work, personal, and family activities. The most important comorbidity of migraine is depression, which affects as many as 40% of patients with migraine.⁴ Little is known about the mechanisms linking migraine and depression, but there may be an underlying disorder of serotonin regulation common to both.^{4,26,27} *Low et al* found the evidence from

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large-scale, prospective, community samples strongly supportive of a relationship between migraine and major depression and between migraine and bipolar disorder.¹

The presence of a comorbid psychiatric disorder may increase the likelihood that a person will seek medical care for headache.¹⁴ In a population-based study, *Stewart et al* reported that 14.2% of women and 5.8% of men who had a headache in the previous year sought medical care for their headaches.²⁸ A surprisingly high percentage of those who sought care had a history of panic disorder: 15% of women and 12.8% of men between the ages of 24 and 29. Women with panic disorder who recently saw physicians for headaches had more frequent, severe, and debilitating headaches and often had prolonged disability, compared with those without panic disorder. These results suggest that a clinic-based study would overestimate the association between the two disorders. A more recent survey by *Breslau et al* showed that the lifetime prevalence of panic disorder was significantly higher in people with migraine and in people with other severe headaches, compared with controls.²⁹ Migraine and other severe headaches were also associated with an increased risk for first onset of panic disorder (hazard ratios: 3.55 and 5.75, respectively). Panic disorder was associated with an increased risk for first onset of migraine or other severe headaches, although the influences in this direction were lower (hazard ratios: 2.10 and 1.85, respectively). The authors concluded that comorbidity of panic disorder is not specific to migraine and also applies to other severe headaches.

Chronic disability in people with migraine may be strongly influenced by the presence of comorbid psychiatric and neurologic disorders.³⁰ Studies of

disability among injured workers³¹ and patients with back pain³² have shown that psychological variables, such as depression, fear, anxiety, and stress are better predictors of chronic disability than are physical variables. The perception of pain severity is complicated by a number of cognitive variables, such as coping ability, level of expectation, previous experience, and affective state. For this reason, clinical improvement may be more objectively assessed by the patient's capability to resume normal daily activities than by the patient's own assessment of head pain.

MIGRAINE AND COGNITION

Waldie et al conducted a longitudinal birth cohort study to investigate the association between migraine and cognitive ability.¹² They found that enrolled subjects with migraine showed subtle but significant impairment on tests of verbal ability (especially language reception), compared with subjects who were headache-free or had tension-type headaches.

MIGRAINE AND NARCOLEPSY

A group of German investigators studying 100 patients with narcolepsy found that 37 (37%) also suffered from migraine.³³ The prevalence of migraine was 28.3% for men in the study and 44.4% for women. These numbers represent a two- to four-fold increase in the risk for migraine in patients with narcolepsy. Patients with migraine in the study tended to have developed narcolepsy first; the onset of migraine occurred an average of 12.3 years after the first symptoms of narcolepsy. Thus, their migraines began relatively late in life, when the risk of developing migraine is generally low.

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MIGRAINE AND ASTHMA

Davey *et al* conducted a very large, matched, case-control study to examine whether there is an association between migraine and asthma in the United Kingdom.⁷ Medical practices in the UK provided data on 5,110,619 patients to the General Practice Research Database (GPRD). Subjects in the study were patients with one or more diagnoses of migraine plus treatment for migraine. Each case was matched by general practice, sex, and age with one control who had never been given a diagnosis of migraine. Case and control groups were compared for prevalence of asthma, chronic obstructive pulmonary disease (COPD), respiratory symptoms treated with inhalers or hay fever. Investigations were conducted to determine whether the association between migraine and asthma was stronger among patients with hay fever or those without hay fever. Among 64,678 case-control pairs, the risk of asthma among patients with migraine was 1.59 (95% CI; 1.54-1.65). Among definite migraine cases, relative risks of COPD, respiratory symptoms, eczema, and hay fever were all raised (1.22, 1.85, 1.55, and 1.67, respectively). The association between migraine and asthma was stronger in patients without a diagnosis of hay fever than in those with hay fever (1.32 and 1.19, respectively). The investigators concluded that this large-scale case-control study provides evidence for an association between migraine and asthma. However, they cautioned that the patients' frequent visits to a general-practice office may confound this association. In their meta-analysis, *Low et al* found a strong and consistent association between migraine and asthma (as well as other allergic conditions) in clinical studies of both children and adults.¹

MIGRAINE AND CHRONIC FATIGUE

Peres et al studied 63 migraine patients, using the Fatigue Severity Scale (FSS), the Chalder fatigue scale, and the CDC diagnostic criteria for chronic fatigue syndrome (CFS).⁸ Fifty-three patients (84.1%) had FSS scores greater than 27, 42 patients (66.7%) met the CDC criteria for CFS, and 32 patients (50.8%) met the modified CDC criteria (without headache). In addition, Beck depression scores correlated with FSS, mental, and physical fatigue scores. Trait anxiety scores also correlated with fatigue scales. Women had significantly higher FSS scores than men ($p < 0.05$).

The association of physical fatigue with fibromyalgia was statistically significant ($p < 0.05$). The investigators concluded that the identification of fatigue and its subtypes in headache disorders and the recognition of headaches in CFS patients have important implications for the pathophysiology, diagnosis, and treatment of these disorders.

MIGRAINE AND RAYNAUD PHENOMENON

In a study of 93 patients with Raynaud phenomenon and 93 age- and sex-matched controls, migraine was diagnosed in 57 (61%) of patients with primary Raynaud phenomenon and in 21 (23%) of the control group (OR: 5.4; 95% CI, 2.8 to 10.3). The incidence of musculoskeletal chest pain was also significantly greater among patients with Raynaud phenomenon ($p = 0.003$). The link between migraine and Raynaud phenomenon has not been elucidated, although vascular pathology is common to both disorders.¹⁰

CONCLUSIONS

Physicians in training are often taught to be suspicious of patients who present with 'too many' disorders. However, a diagnosis of migraine should increase the level of vigilance for a variety of comorbid disorders.¹⁴ It is a cliché in neurology that, if you find one thing wrong in the brain, you'll find more than one. This is often true of patients with migraine, in part because migraineurs with comorbid disorders are more likely to seek medical attention. Certainly, the initial work-up of a patient with migraine should investigate thoroughly the potential presence of comorbid disorders. There is considerable symptomatic overlap of migraine with several of these disorders, so careful differential diagnosis is often necessary. Physicians should be particularly alert to the possible presence of major depression, because of its high prevalence among migraineurs and its potential contribution to the patient's disability.

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POST~TEST

Seven correct answers are required for credit.

- Which of the following are comorbidities of migraine?
 - A. Epilepsy
 - B. Stroke
 - C. Depression
 - D. Bipolar disorder
 - E. A, B, and C above
 - F. All of the above
- Patients with migraine may show subtle impairments on tests of verbal ability.
 - A. True
 - B. False
- In the *Peres et al* study of fatigue in migraineurs, women had significantly higher scores on the Fatigue Severity Scale (FSS) than men.
 - A. True
 - B. False
- Migraine and stroke may share which of the following features?
 - A. Altered cerebral blood flow
 - B. Focal neurological deficits
 - C. Headache
 - D. A and B above
 - E. All of the above
- Stroke is more strongly associated with migraine with aura than with migraine without aura.
 - A. True
 - B. False
- In the Donaghy study, which patients were at highest risk for ischemic stroke?
 - A. Patients with initial migraine with aura
 - B. Patients with migraine with aura of more than 12 years' duration
 - C. Patients with initial migraine with aura occurring more than 12 times per year
- In the general population, the prevalence of epilepsy is 0.5%. What was the prevalence of epilepsy among migraineurs in the Andermann study?
 - A. 3.4%
 - B. 5.9%
 - C. 7.6%
- Tricyclic antidepressants, selective serotonin inhibitors, and neuroleptic agents should generally be avoided in migraine patients with epilepsy.
 - A. True
 - B. False
- In the longitudinal study of migraine and depression by *Breslau et al*, what was the relative risk for major depression associated with prior migraine?
 - A. 1.5
 - B. 2.3
 - C. 3.2
- Approximately what percentage of migraine patients also have depression?
 - A. 20%
 - B. 30%
 - C. 40%

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