

Migraines in the Presence of Glaucoma

Recent advances in diagnosis and management.

BY GEOFFREY T. EMERICK, MD

Because migraine is a common cause of headaches and visual disturbances, it is a common reason for patients' referral to an ophthalmologist. In addition, many patients with glaucoma also suffer from migraines, which means we are often called on to aid in the diagnosis and treatment of this problem. Current thinking on the pathophysiology of migraine differs markedly from when most of us were in medical school, and many new effective medications have entered the market over the past several years.

CLINICAL FEATURES

Migraine is the most common cause of recurrent moderate-to-severe headache. According to a survey, the lifetime prevalence of this syndrome is 43% for women and 18% for men.¹ Affected patients often begin to suffer from migraine headaches during adolescence or young adulthood and find that they change in character over time, usually decreasing after age 50. A positive family history of migraine can be very helpful in establishing the diagnosis. Possible triggers of migraines include bright lights, loud noise, hunger, stress, hormonal fluctuations, and too much or too little sleep. Ingested substances such as red wine can cause a migraine as well. Modifications in lifestyle to avoid such triggers can be very helpful for patients.

Migraine symptoms typically last 4 to 72 hours, and this form of headache can be quite debilitating. The pain is often unilateral, throbbing, and aggravated by movement. Nausea, vomiting, and photophobia are especially common features. An aura, consisting of visual disturbances or other neurologic symptoms, occurs in approximately one-quarter of patients.² They may perceive distortions of size or color or a "heat wave" effect, positive visual phenomena such as flashing lights or zigzags, and negative phenomena such as one or more scotomata. The scotoma often has a jagged border and expands gradually before dissipating.

PATHOPHYSIOLOGY

The pathophysiology of migraine is complex, but the full picture is becoming clearer. Physicians have largely dis-

carded the vascular hypothesis, which was based on findings of changes in blood flow during migraine attacks³ and the efficacy of some vasoactive substances in treating migraine symptoms. The pattern of migraine aura and headache cannot be fully explained, however, by changes in cerebral blood flow alone. The frequently described spreading depression in blood flow follows cytoarchitectural pathways, not major vascular territories. In addition, the areas of decreased blood flow do not directly correspond to the cortical areas responsible for the aura, and regional blood flow may remain depressed after the aura has resolved and the headache has begun. It therefore seems that changes in cerebral blood flow are likely secondary to a primary disturbance in brain function.⁴

During a migraine attack, the activation of cells in the trigeminal nucleus results in the release of vasoactive neuropeptides, especially calcitonin gene-related peptide (CGRP), at endings of the trigeminal nerve. Also involved is 5-hydroxytryptamine (5-HT or serotonin). The efficacy of the triptans relates to their ability to stimulate 5-HT_{1B/1D} receptors, which are located on both blood vessels and nerve terminals. The successful treatment of migraine with a triptan normalizes cranial CGRP levels. Thus, CGRP seems to play a central role.

TREATMENT

Acute

The pharmacologic management of migraine consists of acute or prophylactic treatment. Acute treatment is aimed at aborting the headache. Many patients have already tried nonsteroidal anti-inflammatory drugs (NSAIDs), and these can be very effective. I often suggest patients try two regular-strength aspirin (650 mg) or three ibuprofen (600 mg). Some patients find combining an NSAID with a cup of coffee adds to its efficacy. A combination of acetaminophen, aspirin, and caffeine (eg, Excedrin [Novartis Consumer Health, Inc., Parsippany, NJ]) can also work well.

Dihydroergotamine and ergotamine, often combined with caffeine, were once mainstays of migraine treat-

RESOURCES FOR PATIENTS

- **American Headache Society** <http://www.achenet.org>
- **National Institute of Neurological Disorders and Stroke** <http://www.ninds.nih.gov>

ment, but they are seldom used today. Side effects of ergot derivatives include nausea and vomiting.

Triptans, selective 5-HT_{1B/1D} receptor agonists, have been available since 1991. Six of these drugs are currently available in the US, including sumatriptan (Imitrex; GlaxoSmithKline, Research Triangle, NC), almotriptan (Axert; Ortho-McNeil Neurologics, Titusville, NJ), eletriptan (Relpax; Pfizer Inc., New York, NY), frovatriptan (Frova; Endo Pharmaceuticals [Chadds Ford, PA] and Vernalis [Winnersh, United Kingdom]), naratriptan (Amerge; GlaxoSmithKline), zolmitriptan (Zomig; AstraZeneca LP, Wilmington, DE), and rizatriptan (Maxalt; Merck & Co., Inc., Whitehouse Station, NJ). The fastest acting is subcutaneous sumatriptan or zolmitriptan in a nasal spray. Sumatriptan is also available in a nasal spray; zolmitriptan and rizatriptan come as orally disintegrating tablets. Frovatriptan and naratriptan both have a longer half-life and lower rate of recurrent headache.

Triptans should be avoided in pregnancy and should not be used in patients with coronary artery disease, cerebrovascular disease, or uncontrolled hypertension. The medications work well in most but not all patients, and these drugs carry a risk of cardiac or cerebral ischemia.

In the search for more effective, safer medications, recent studies have demonstrated the utility of calcitonin gene-related peptide (CGRP) antagonists. Interestingly, CGRP is the most potent vasodilator yet discovered, but CGRP antagonists are not vasoconstrictive. CGRP antagonists undergoing clinical trials include BIBN4096BS and MK-0974.^{5,6} In a large randomized study, pain relief at 2 hours was achieved in 68% of subjects with MK-0974 300 mg and in 70% of patients with rizatriptan 10 mg. Sustained pain relief at 24 hours occurred in 52% of subjects receiving MK-0974 and in 35% of patients taking rizatriptan.⁶ Both medications were well tolerated. Importantly, CGRP antagonists do not appear to have any cardiovascular side effects. It is not clear whether they work in the brain or periphery, and they may have trigeminovascular, brainstem, and thalamic targets.

Preventive

A large number of preventive treatments for migraine exist, but many have significant side effects. Currently approved therapies include beta-blockers (propranolol

and timolol) and seizure medications (topiramate and valproate). Tricyclic antidepressants have been used as well. The dose of timolol used to prevent migraine is 10 to 15 mg twice a day, an oral dose about 20 times that in two drops of timolol 0.5% solution. Topiramate (Topamax; Ortho-McNeil Neurologics) is especially effective in migraine prophylaxis, with significant but fewer side effects than other agents used for prophylaxis. In two recent large trials, more patients experienced at least a 50% reduction in the monthly occurrence of migraine with topiramate 50 to 200 mg per day (range, 36% to 52%) than with placebo (23%).^{7,8} Adverse effects of the drug can include paresthesias, fatigue, cognitive dysfunction, weight loss, and the well-known but uncommon angle-closure glaucoma.

Calcium-channel blockers, which have been used in patients with normal-tension glaucoma, do not appear to be effective in the prevention of migraine.

MIGRAINE AND GLAUCOMA

Initial interest in a migraine/glaucoma connection stemmed from the earlier theory of migraine as a primarily vascular disease.⁹ Thus, migraine was examined as a potential risk factor in the Collaborative Normal-Tension Glaucoma Study. As expected, most migraine headaches occurred in women, but the syndrome emerged as an independent risk factor for visual field progression. Migraine was reported in 15.6% of the study group. The risk ratio for migraine in the Collaborative Normal-Tension Glaucoma Study was 2.58 and, for female gender, was 1.85.¹⁰ The ophthalmic investigators identified migraine based on patients' histories. The investigators felt that migraine might be a "surrogate for vasospasm or vascular dysregulation."¹⁰ Lowering the IOP did slow the rate of visual field progression in patients with migraine, although they still seemed to experience faster progression than other treated patients.¹¹

The story from other published studies is inconclusive. The Beaver Dam Eye Study found no relationship between open-angle glaucoma and migraines.¹² The Blue Mountains Eye Study also found no overall association but did report a significant odds ratio of 2.5 for glaucoma in people aged 70 to 79 years who had a history of migraines.¹³ The European Manifest Glaucoma Trial examined the risk associated with a self-reported history of migraine. The investigators found an insignificant univariate hazard ratio of 1.37 and no association in multivariate analyses.¹⁴ Finally, the Canadian Glaucoma Study is a multicenter, prospective longitudinal study examining a variety of systemic risk factors, including migraine, for the progression of glaucoma.¹⁵ At baseline, 9.2% of the men and 19% of the women in the study have a history of migraine. With a median fol-

low-up of 5.3 years, migraine did not emerge as a risk factor for glaucomatous progression.¹⁶

CONCLUSION

Although migraine is a common, sometimes debilitating condition, its particular role in glaucoma is unclear. As glaucoma specialists, we often look for modifiable factors other than IOP. In some patients, the only identifiable risk factor for normal-tension glaucoma is severe migraines. My impression is that glaucomatous progression slows in such patients when their migraines are less frequent or severe, whether by natural history, through changes in lifestyle, or through medications. If migraine is in fact a risk factor for the development or progression of glaucoma, controlling the condition might improve visual outcomes. Many patients with migraine remain undiagnosed or undertreated. As more effective, better-tolerated medications become available, the motivation for referring affected patients to a primary care physician or neurologist for treatment becomes even greater. □

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