Strategies for migraine management

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■ According to widely accepted theory, migraine is a self-limited neurogenic sterile inflammation characterized by initial cerebral vasoconstriction, subsequent extracranial and intracranial vasodilation, sterile inflammation, and secondary muscle contraction. It is characterized by recurrent attacks of headache, usually unilateral and accompanied by nausea, vomiting, and, often, other symptoms. Frequency, duration, and intensity of attacks are widely variable. Migraine affects more women than men, and is often related to menses. Patients with classic migraine experience visual or neurologic prodromes, but vague "premonitions" occur in both classic and common migraine. Precipitating factors include foods, alcohol, medications, visual stimuli, changes in routine, and stress. The first-line agent for abortive therapy is ergotamine; corticosteroids are indicated for prolonged headache. Propranolol is recommended for daily prophylactic therapy, and alternatives include calcium channel blockers, nonsteroidal anti-inflammatory agents, and tricyclic antidepressants.

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AN ESTIMATED 16 to 18 million Americans suffer from migraine. Despite its straightforward diagnosis, treatment of migraine is complex. Depending on the frequency and duration of the patient's symptoms, a prophylactic strategy works best for some patients while an abortive approach is recommended for others. Many follow-up visits over several months may be needed to find the best regimen for a particular patient. Often, the regimen consists of more than one medication. Nonpharmacologic methods play a role, too.

CURRENT VIEWS ON PATHOPHYSIOLOGY

Studies by Wolff in the 1950s and early 1960s led to the vascular theory of migraine[1] that has been accepted almost without question ever since. According to the vascular theory, migraine is a self-limited neurogenic sterile inflammation. Wolff identified four dynamic events occurring during a migraine attack: initial cerebral vasoconstriction, correlated with the aura or warnings of migraine; extracranial and intracranial vasodilation, which causes pain; sterile perivascular inflammation that increases and prolongs the pain; and secondary muscle contraction. To support the vascular theory, several vasoactive substances associated with inflammation have been identified, including catecholamines, histamine and serotonin, peptide kinins, prostaglandins, and the slow-reacting substance of anaphylaxis (SRSA), an acidic lipid.

In the early 1980s, work by Olesen and colleagues[2,3] cast some doubt on the vascular theory and indicated that migraine might be a purely neurologic disease. They used a radioactive isotope injected into the carotid artery to study regional cerebral blood flow during induced migraine attacks. In patients with classic migraine, they observed oligemia that started in the occipital region and spread anteriorly at a speed of 2 mm/min through the hemisphere but did not cross the central or lateral cerebral sulci. Because the oligemia did not reach a primary sensorimotor area until after the nonpain symptoms had ceased, however, the

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authors suggested that these "painless headache phenomena" were caused by a spreading depression of cerebral cortex activity, similar to that described by Leao[4] in rabbits in 1944. The striking oligemia observed in patients with classic migraine was not seen in those with common migraine, a finding that suggests these are two separate disorders.

Olesen's work had several drawbacks, the foremost of which is that most researchers who have tried to repeat these experiments have failed. In addition, the migraine attacks were induced, and most of the participants in the study were men, despite the preponderance of women among migraine patients. Nevertheless, this work is valuable because, although it does not replace the vascular theory, it suggests that mechanisms in addition to those described in the vascular theory are involved in migraine.

Much research today is directed to the role of serotonin in migraine pathophysiology and the development of serotonin antagonists for use in migraine therapy. In most migraine patients, the plasma serotonin level increases before migraine attacks and falls during the headache phase.[5] These changes in plasma serotonin level may be an index of changes in serotonergic transmission within the central nervous system.

Serotonin participates in two neurologic pathways that may apply to migraine: a direct projection from the raphe nuclei of the brain stem to the cerebral cortex, and the inhibitory system that descends from the nucleus raphe mangus and operates the enkephalinergic pain control system.[6] Although serotonin receptors have not yet been classified definitively, there appear to be two specific binding sites in the brain, the 5HT1 and 5HT2 receptors. Serotonin receptors also exist in the peripheral nervous system, where they mediate smooth muscle contraction.[7] Serotonin agonists such as sumatriptan have received much publicity recently, but their clinical use is still several years away.

CLINICAL PRESENTATION

The outstanding feature of migraine is recurrent attacks of headache—migraine is not a daily headache. The pain is commonly unilateral, but may become generalized. Some patients have more than one kind of headache; to avoid misdiagnosis and treatment failure, a fundamental question in the history is "How many kinds of headache do you have?"

During a migraine attack, headache is usually accompanied by loss of appetite, nausea, and vomiting. Photophobia, phonophobia, and mood changes often occur, and some patients report scalp tenderness. In addition, migraine attacks may be accompanied by a variety of autonomic symptoms including constipation, diarrhea, cold extremities, dry mouth, excessive sweating, chills, localized edema, vertigo, blurred vision, double vision, tremors, ataxia, and dysarthria.

Patients with classic migraine experience a prodrome of visual or neurologic symptoms. Patients with either classic or common migraine may describe vague warning symptoms. Three less common types of migraine, called complicated migraine by some, are ophthalmoplegic, with paralysis of the third nerve; hemiplegic, with strokelike symptoms including paresis of one side of the body; and basilar artery, in which the posterior circulation is affected. Basilar artery migraine usually affects women younger than age 21. Because symptoms include disorientation, confusion, and syncope, these patients are often suspected of drug abuse.

The frequency, duration, and intensity of attacks is widely variable among migraine patients. Most patients experience one to four attacks a month, but some have one attack every year or two while those with cyclic migraine may have as many as 16 a month. An attack generally lasts 4 to 24 hours, but some patients have prolonged attacks lasting several days. The pain of migraine is typically described as throbbing, which reflects its vascular nature, and is usually incapacitating.

While migraine rarely wakes the patient from a sound sleep, it is often present upon awakening. There is some evidence that this disorder is worse in the spring and fall than in summer or winter. Migraine is hereditary, with 70% of migraine sufferers reporting a positive family history. Some patients with migraine have a childhood history of colic, motion sickness, or cyclic vomiting.

Age of onset is usually in the second through fourth decade of life, although migraine can occur in early childhood and occasionally begins after age 40. Patients older than age 40 who begin to experience headaches, even if they are characteristic of migraine, should undergo computed tomography and magnetic resonance imaging.

Some 60% to 70% of migraine patients are women, and in 70% of women with migraine, the attacks are related to menstruation. Often migraine onset occurs with menarche. Except for the small number of women who experience a first migraine attack during pregnancy, pregnancy usually produces a remission. In 75% of women with migraine, attacks cease with menopause.

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The possible existence of a "migraine personality" has generated much disagreement. In 1937, Wolff[8] described migraine patients as ambitious, perfectionist, persistent, and unforgiving. In 1964, Bille[9] described children with migraine as fearful, tense, sensitive, and easily frustrated. In 1945, Ross and McNaughton[10] used the Rorschach method to perform personality studies in migraine patients and found characteristics such as rigidity, persistence toward success, difficulty in sexual adjustment, perfectionism, conventionality, intolerance, and obsessive-compulsive features. Clinical experience suggests that most patients with migraine possess these personality features.

Prodrome v premonition

The visual or neurologic auras or prodromes of classic migraine include, in order of frequency: scotomata or blind spots; teichopsia, or fortification spectra[11]; photopsia, or flashing lights and colors; paresthesias; and visual and auditory hallucinations. The distortions caused by fortification spectra are understandably frightening and disorienting to those affected.

Paresthesias preceding or accompanying migraine must be differentiated from a transient ischemic attack (TIA). In TIA, paresthesias are usually stationary and of short duration, whereas in migraine, the abnormal sensation usually moves along the affected extremity and lasts from five minutes to several hours.

Vague warning symptoms, or premonitions are four times more common than the focal prodromes of classic migraine. Premonitions occur in both classic and common migraine and may begin anywhere from two to 72 hours before an attack. They include feelings of well being, bursts of energy, talkativeness, hunger, anorexia, drowsiness, depression, irritability, tension, and restlessness. The famous neurologist Charles Aring reported such a surge of energy during the two days preceding a migraine that he was able to write two or three scientific papers.

MANAGING PRECIPITATING FACTORS

A first step in migraine management is to help the patient identify factors that precipitate an attack. With some triggers, avoidance is the only way to escape the effect, but with others, the impact can be lessened pharmacologically or otherwise.

For many patients with migraine, attacks are precipitated by foods or beverages that contain vasoactive substances such as tyramine. These foods, including aged cheeses, chocolate, and meats preserved with sodium nitrite, should be avoided. Because alcoholic beverages are vasodilators, they can precipitate an attack and should be avoided. Smoking and medications with vasodilating activity such as reserpine, hydralazine, minoxidil, and nitrates also affect migraine sufferers.

If a patient finds that looking at bright lights or watching a movie or television precipitates attacks, tinted glasses may help. For patients in whom traveling in an airplane or to a higher altitude causes a headache, acetazolamide taken the day before and the day of travel may forestall the attack.

Oversleeping on weekends, holidays, or vacations may provoke a "weekend" headache. For many patients, arising at the usual time, using the toilet, eating something, and then returning to bed help avoid this problem. Other headache triggers include missing a meal, keeping late hours, anxiety, depression, anger, repressed hostility, and fear. Some patients report that changes in weather precipitate an attack.

DRUG THERAPY

Finding the best treatment regimen is time-consuming. Success requires several office visits and open lines of communication between physician and patient to assess the effectiveness of therapy. To avoid discouragement, the patient must understand the complexity of the situation. More than one medication is usually necessary, so the risk of drug interactions must be considered.

Abortive therapy

When a patient experiences more than two headaches a month, or if the headache is prolonged and interferes with daily activity, prophylactic therapy should be considered. An ergotamine preparation is the drug of choice for abortive therapy. To be effective, ergotamine must be taken as early as possible in the attack, preferably within the first four hours. To avoid rebound headaches, drug tolerance, or ergotism, patients must be cautioned not to use it daily. Ergotamine can be used on the first day of the attack, but must not be used again for least four days. Once a patient falls into the trap of daily ergotamine use, hospitalization is usually needed for detoxification.

Ergotamine may be administered by various routes including oral, sublingual, rectal, and inhalation, and the choice is based mainly on common sense. For example, a suppository preparation would be inappropriate for a patient whose headaches tend to start during the bus ride to work. Oral and suppository forms

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are combined with caffeine, but sublingual and inhaled forms contain only ergotamine tartrate. The ergot derivative dihydroergotamine may be administered intramuscularly or intravenously.

Ergotamine is contraindicated for elderly patients or for those with cardiovascular, cerebrovascular, or peripheral vascular disease. Also, the presence of infection may precipitate symptoms of ergotism, including symptoms of ischemia such as burning, tingling, numbness, and claudication, followed by gangrene of the hands, feet, and legs.

An alternative for patients who cannot tolerate ergotamine is the combination of isometheptene mucate, acetaminophen, and dichloralphenazone, which has mild vasoconstrictive and sedating properties. The nonsteroidal anti-inflammatory drugs (NSAIDs), in particular naproxen sodium, appear to abort migraine attacks in some patients if administered early enough.[12]

Once the headache is manifest, the patient may need pain relief with a narcotic analgesic, such as meperidine or codeine. However, these agents should be strictly limited. For a prolonged attack lasting more than 24 hours, corticosteroids rather than analgesics are indicated. Parenteral administration of long-acting dexamethasone acetate (16 mg) or methylprednisolone acetate (80 mg) may be effective. If the patient is reluctant to leave home for an injection, dexamethasone (0.75 mg) tablets or methylprednisolone tablets may be prescribed. If corticosteroids are ineffective, dihydroergotamine mesylate (0.5 mg) combined with metoclopramide (10 mg) and administered intravenously every six hours for nine doses may resolve the attack. This regimen requires hospitalization, but when a migraine attack persists for a week or longer, the patient may need hospitalization because of dehydration. Sleep therapy has also been used in resistant cases of status migraine.

During pregnancy, only analgesics approved by the obstetrician should be used.

Prophylactic therapy

The goals of prophylactic therapy are to prevent the onset and reduce the frequency and severity of attacks. It is indicated for patients who experience two or more migraine attacks a month and for those whose attacks continue for two days or more. Prophylactic therapy should also be considered for patients whose headaches disrupt work or daily life, even if they last less than two days and occur less often than twice a month.

Many patients need more than one prophylactic agent to achieve the goals of therapy. Although few patients benefit from biofeedback therapy alone, it is a useful adjunct to drug therapy. The medications used for migraine prophylaxis may have annoying side effects, and patients who are warned about them at the onset of therapy are more likely to continue the medication.

The first-line prophylactic agent is propranolol, which is effective in about 70% of patients.[13,14] The long-acting form is more convenient and seems to enhance compliance. The effective daily dosage ranges from 60 to 160 mg. With the long-acting preparation, side effects are usually minimal but may include diarrhea and fatigue.

Propranolol is the only beta-adrenergic receptor blocking agent approved by the Food and Drug Administration for migraine prophylaxis. However, others, including atenolol, metoprolol tartrate, nadolol, and timolol also work. Because metoprolol is cardioselective, it is preferred for patients with asthma.

If a beta blocker is ineffective or is contraindicated, an alternative should be tried, such as a calcium channel blocker, NSAID, or tricyclic antidepressant.

Of the calcium channel blockers, verapamil is preferred for prophylaxis.[15] A dosage of at least 350 mg/d is probably necessary, and benefit is unlikely to be observed until after a month of therapy. Including high-fiber foods in the diet will help to counteract the constipating effect of verapamil. Nimodipine, approved for postaneurysm rupture, is effective for migraine prevention, but its price is prohibitive.

Of the NSAIDs, fenoprofen calcium, naproxen, and ketoprofen have all demonstrated effectiveness in migraine prevention.[16] The dosage of fenoprofen is 600 mg bid; that of naproxen is 250 mg tid, and that of ketoprofen is 75 mg tid.

Tricyclic antidepressants are also effective for prophylaxis in some patients and have a variety of effects that can be tailored to the patient's needs *(Table)*.

Clonidine, an alpha receptor agonist, has been used extensively in Europe for migraine prophylaxis. In this country, it is reserved for patients who do not respond to other medications; the dosage is 0.1 mg bid. Another option for resistant cases, assuming compliance in avoiding sympathomimetic drugs and tyramine-containing foods, is a monoamine oxidase inhibitor (MAOI) such as phenelzine or isocarboxazid.[17] For cyclic migraine, characterized by more than 12 attacks a month, lithium, 300 mg tid, is usually effective.

An NSAID, particularly naproxen, ketoprofen, or mefenamic acid, is the drug of choice for menstrual

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TABLE
EFFECTS OF SELECTED TRICYCLIC ANTIDEPRESSANTS

Drug	Serotonin inhibition	Norepinephrine inhibition	Dopamine inhibition	Sedative effects	Anticholinergic effects
Amitriptyline	Moderate	Weak	Inactive	Strong	Strong
Desipramine	Weak	Potent	Inactive	Mild	Moderate
Doxepin	Moderate	Moderate	Inactive	Strong	Strong
Imipramine	Fairly potent	Moderate	Inactive	Moderate	Strong
Nortriptyline	Weak	Fairly potent	Inactive	Mild	Moderate
Protriptyline	Weak	Fairly potent	Inactive	None	Strong

migraine. The patient begins therapy 3 days before and continues it through the menstrual period. If NSAID therapy is ineffective, an alternative is a combination agent of ergotamine tartrate, 0.6 mg, with phenobarbital and belladonna alkaloids, one tablet bid beginning 3 days before and continued through the menstrual period. For menstrual migraine which is resistant to both an NSAID and ergotamine tartrate, methysergide, 2 mg bid before and during the period, may be effective. Although methysergide has received FDA approval for prophylactic migraine therapy, it should not be used daily because of the risk of retroperitoneal and cardiopulmonary fibrosis.

For migraine during pregnancy, prophylactic therapy with a tricyclic antidepressant or propranolol may be started after the first trimester, in consultation with the obstetrician.

It takes time and persistence to find the combination of pharmacologic and nonpharmacologic measures that is best for a particular patient. Consequently, the most important aspect of migraine therapy is continuity of care.

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