

# *Migraine Headache: Origins, Consequences, Diagnosis and Treatment*

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## **Origins**

It is believed that anyone can have a migraine, but only migraineurs are susceptible to recurrent attacks, and this susceptibility is due to a combination of environmental and genetic factors. The exact factors implicated in initiating and perpetuating an attack of migraine are still largely unknown, but several theories have evolved over time, based on an increased understanding of the potential underlying mechanisms involved. Several of the more popular theories and the implications of migraine triggers are discussed.

## **Migraine “Triggers”**

A variety of factors have been observed to be associated with the development of a migraine attack. Dietary changes, certain foods, alcohol, medications, artificial sweeteners, nitrates, nitrites, alteration in sleep pattern, stress, and hormonal changes can all trigger a migraine. Some triggers can have a direct effect on vasomotor tone, such as tyramine in certain foods. Other triggers can mediate neurochemical release, such as sleep altering serotonin release from dorsal raphe nucleus. Stress modifies catecholamine levels. Exactly how these triggers ultimately lead to the production of a migraine headache is still a subject of debate. The major theories of migraine pathogenesis are as follows.

## **The Vascular Theory**

The vascular theory, which has been popular since the 17<sup>th</sup> century, maintains that migraine is a vasospastic disorder, that begins with cerebral vasoconstriction. This vasoconstriction appears to be associated with migraine aura.<sup>1</sup> After the vasoconstriction phase, intra and extra cranial vessels dilate; activation of the trigeminal sensory nerves that surround meningeal blood vessels causes pain. Activation of trigeminal nerve fibers also causes the release of vasoactive neuropeptides, which further enhance vasodilatation and worsen pain. Thus vasodilatation is associated with the headache phase of migraine.

Support of the vascular theory comes from studies demonstrating oligemia during migraine aura, and increase in blood flow during the headache phase. Also, when a patient with migraine is given a vasodilator such as nitrate, the headache

worsens, but when given a vasoconstrictor such as a 5-HT agonist, the headache usually improves.<sup>2</sup>

## **The Cortical Spreading Depression Theory**

The theory of cortical spreading depression has been described in detail by A.A.P. Leao.<sup>3</sup> Cortical spreading depression is a wave of electrical depolarization that begins in the occipital cortex, and spreads relatively rapidly (3-5 mm/minute) to the front of the brain. After an initial brief wave of excitation (in migraine with aura), there follows a prolonged period of neuronal depression, which is associated with decreased neuronal metabolism and regional reduction in cerebral blood flow. The release of parasympathetic and trigeminal neurotransmitters contributes in part to initial hyperperfusion of the cortex in cortical spreading depression.<sup>4</sup>

A variety of genes coding for metalloproteinases and cyclooxygenase 2 (COX-2) are upregulated by cortical spreading depression. Metalloproteinase activation is associated with leakage of the blood brain barrier. This allows nitric oxide, potassium, and adenosine to reach and sensitize the dural perivascular trigeminal afferents, leading to headache.<sup>4</sup>

Cortical spreading depression has been demonstrated only in animals, but support of this theory comes from observations that in patients, a gradual spread of reduction of cerebral blood flow accompanies migraine with aura, which is similar to the rate of cortical spreading depression seen in animals.<sup>2</sup>

## **The Neurovascular (trigeminal) Theory**

Recently, the trigeminal system has been postulated to play a significant role in the pathophysiology of migraine.<sup>5</sup> It has been suggested that there is a “migraine generator” in the brainstem that leads to trigeminal activation.<sup>6</sup>

Although most of the brain is insensitive to pain, the trigeminal nerve innervates blood vessels in the meninges, circle of Willis, and extracranial arteries, and can carry pain impulses from these structures.

According to the neurovascular theory, cortical spreading depression or “triggers” of migraine may activate unmyelinated trigeminal nerve axons, which then release neuropeptides such as substance P, neurokinin A, and calcitonin gene-related peptide. These neuropeptides then promote vasodilatation and a sterile inflammatory response around nearby meningeal blood vessels.<sup>7</sup> In addition, these neuropeptides may sensitize nerve endings, which may result in prolongation of the headache.

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According to this theory, vasodilatation does not cause migraine headache, but accompanies the headache, which is actually caused by trigeminal nerve activation.

## The Integrated Theory

This theory attempts to combine and consolidate these various theories of migraine pathogenesis. According to this theory, “triggers” of migraine, such as stress, noise, certain foods, dilatation of internal or external carotid arteries, or other factors initially activate certain brainstem centers, such as the locus ceruleus and the dorsal raphe nucleus. Activating the locus ceruleus causes elevation of epinephrine levels, and the dorsal raphe nucleus causes elevation of serotonin; this results in cerebral vasoconstriction, leading to localized decrease in cerebral blood flow. The decrease in cerebral blood flow is then thought to trigger cortical spreading depression, which in turn stimulates trigeminal nerve fibers, eliciting neurogenic perivascular inflammation, vasodilatation, and headache pain.

## Consequences

### Migraine Epidemiology

It is estimated that there are 25-30 million migraine sufferers in the United States.<sup>8</sup> The overall prevalence of migraine is approximately 12%.<sup>8,9</sup> Women are nearly three times as likely as men to develop migraine (~18% vs. 6%).<sup>8,9</sup> The peak of migraine prevalence occurs during the most productive years (age 25-45).<sup>8</sup>

### Impact of Migraine

Migraines have a tremendous economic impact, estimated to be 14 billion dollars annually in the United States.<sup>10</sup> Less than 10% of these costs are direct (medications, doctor/ER visits, etc) with the vast majority resulting from lost productivity of, or days missed from, work.<sup>10</sup> A single migraine headache may interfere with function for as long as a week. Although, by definition, the headache itself can last no longer than 3 days, some patients experience a prodrome for 1-2 days and a post-migraine exhaustion again for 1-2 days. During this time the patient may have impaired concentration or reduced ability to perform their job. Thus, it is essential that we diagnose and treat the patient with migraine to reduce the economic burden of this disease.

## Diagnosis

### Underdiagnosis

Nearly one half of patients with migraine are undiagnosed. Many have been diagnosed with other headache types, particularly sinus<sup>11,12</sup> or tension headache. Although some features of these other headaches overlap with migraine, if diagnostic criteria are applied, they are easily distinguished. Some headache patients experience multiple different types of headaches. We should try to classify the headache, not the patient.

## Criteria

The diagnosis of migraine headache is based entirely on the history. There are no radiologic studies or blood tests needed. Migraine should be suspected in those that have a family history and usually begins in teen years or early adulthood. The International Headache Society (IHS) has established criteria for migraine headache as noted in *Figure 1*.<sup>13</sup> In order to make a definitive diagnosis of migraine, there must be at least 5 headaches lasting from 4-72 hours, which meet the other criteria. Although the classic migraine is unilateral and throbbing, neither feature must be present to make the diagnosis. The key feature that distinguishes migraine from tension headache is that if the headache is aggravated by routine physical activity, it cannot be a tension headache. Thus, tension headaches are rarely disabling. In contrast, migraine headaches are disabling. Therefore, effective treatments are needed to abort migraine attacks or prevent them from occurring.

### Figure 1 International Headache Society Criteria Migraine

(At least 5 headache attacks lasting 4-72 hours fulfilling these criteria)

Two of the following descriptors of headache: **AND** One of the following associated symptoms:

- |   |   |
|---|---|
| <ul style="list-style-type: none"><li>• Unilateral location</li><li>• Pulsating quality</li><li>• Moderate or severe intensity (inhibits or prohibits daily activities)</li><li>• Aggravation by walking up stairs or similar routine physical activity</li></ul> | <ul style="list-style-type: none"><li>• Nausea</li><li>• Vomiting</li><li>• Photophobia and phonophobia</li></ul> |
|---|---|

Adapted from Olesen J. *Cephalalgia*. 1988;8 (Suppl 7): 1-96.

## Treatment

There are two primary methods of treating migraine: abortive and prophylactic. The choice of whether to use a prophylactic medication needs to be determined on a case-by-case basis. Some of the factors that determine whether or not prophylaxis should be used include the frequency of headache attacks, the response to abortive therapy, the occupation of the patient and comorbid medical conditions. Unless the prophylactic therapy is completely effective, all patients will require abortive therapy. The goal of abortive therapy in migraine is to eliminate the pain and associated symptoms as rapidly as possible to allow the patient to return to more normal functioning. The ideal abortive medication would completely eliminate pain without any side effects. It would work for every headache attack and the patient would only need to take one dose. Regardless of the agent chosen, episodic migraine may be converted to chronic daily headache if abortive medications are used too frequently.<sup>14</sup> Some available treatment options are discussed next.

## Analgesics

Non-steroidal anti-inflammatory agents are frequently effective in treating migraine. This efficacy may be related to the inflammation in pain sensitive structures in the meninges that occurs in migraines.<sup>15</sup> Non-steroidal anti-inflammatory agents (often in combination with anti-emetic agents) are useful in the emergency room where patients often present after long-standing migraine and often after failure of maximum doses of triptans.<sup>16</sup> Corticosteroids are helpful in status migranosis. In mild and infrequent migraine attacks, non-steroidal agents alone may be effective early in the course of migraine and use of the more expensive triptans can be avoided.<sup>16</sup> Narcotics must sometimes be used when no other medication is effective or when comorbid medical conditions prevent use of other agents.

## Ergot

Ergotamine with caffeine is still occasionally used in patients with infrequent headaches who have a history of tolerating the drug well. Ergotamine-caffeine is best used for infrequent migraine since as it predisposes to chronic daily headache if taken frequently.<sup>14</sup> Dihydroergotamine (DHE) is sometimes useful when triptans fail, perhaps because it affects dopamine and other neurotransmitters in addition to serotonin receptors.<sup>15</sup> DHE nasal spray is used for acute migraine attacks. Parenteral DHE is occasionally used for acute migraine but is more often used in a protocol designed to treat chronic daily headache associated with abuse of analgesics. In the protocol, analgesics are discontinued and DHE it is given in doses of 0.3 to 1.0 mg every 8 hours for up to 72 hours. Generally antiemetic agents must be given to control nausea.<sup>17</sup>

## Triptans

The triptans are selective 5-hydroxytryptamine agonists. It is generally agreed that triptans are the treatment of choice for migraine headache. These medications are generally more effective and less likely to produce nausea than are the ergots. The medications include: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan. The triptans vary in their headache response rates, recurrence rates, side effects, cost and dosage forms. A complete discussion regarding a comparison of the triptan agents is beyond the scope of this article. It is not always possible to predict which patient will respond best to a given triptan, especially if one also takes into consideration variations in side effect profile.<sup>18</sup> Because of this, failure to respond to one, or even two, of the triptan medications should not preclude trying another member of the class. The route of administration may be a more important factor in treatment of some headaches than is the specific triptan chosen. For example, headaches of rapid onset and headaches with very early development of vomiting should be treated with parenteral triptans because of their quick onset of action and resistance to vomiting. The primary disadvantage of the triptans is their cost.

However, given the disabling nature of migraine, triptans are felt to be cost effective since they are more likely to relieve headache and allow the patient to return to normal functioning.

## Prophylactic Treatment


There are several medications that have been proven in large trials to be effective for migraine prophylaxis. These include amitriptyline, propranolol, and valproate.<sup>19</sup> Numerous other medications have been used for prophylaxis, but the evidence of their effectiveness is either inconsistent, limited or lacking. Migraine prophylaxis is indicated in patients that have frequent attacks, who respond poorly to abortive therapy and, therefore, must visit the emergency room, and in those that have occupations in which even a single migraine could have severe consequences. The goals of prophylactic treatment are to reduce the frequency and/or severity of migraine attacks with the least side effects. The primary limitations of prophylactic therapy are the side effects of the medications used and the reluctance or noncompliance of patients to take a daily medication.

The choice of a prophylactic medication may be based on comorbid medical conditions. Propranolol might be a good choice for a patient with hypertension or essential tremor. Valproate or topiramate may be appropriate for a patient with epilepsy or bipolar disorder. Amitriptyline may be useful in those that also have insomnia or chronic pain. As mentioned above, the primary limiting factor is often the side effects. Amitriptyline has a myriad of adverse reactions including sedation, weight gain and orthostatic hypotension. Propranolol may cause fatigue and sexual dysfunction among other side effects. Tremor, weight gain, pancreatitis and liver function abnormalities are all potential side effects of valproate. Topiramate, which has recently been approved by the FDA for migraine prophylaxis, can cause cognitive slowing or paresthesias. Naproxen, another medication that has proven to be effective, particularly in menstrual migraine, may result in GI bleeding.

## Migraine in Pregnancy

In pregnancy no drug is ideal. Fortunately, the majority of migraineurs improve while pregnant.<sup>20</sup> Analgesics are widely used, as are anti-emetics such as prochlorperazine and metoclopramide. Although the use of sumatriptan during pregnancy has been reviewed and found to be safe with respect to birth defects,<sup>21</sup> it has not won FDA approval for that use, nor have the other triptans. The anticonvulsant migraine prophylactic agents are a last resort because of their potential teratogenic effects.<sup>20</sup>

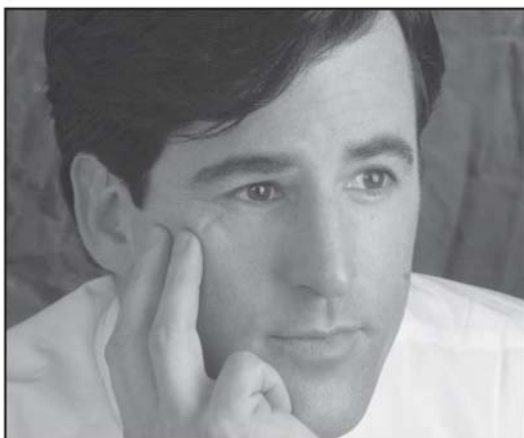
## Summary

Migraine headaches are common, costly and easily diagnosed if the proper criteria are applied. Although the exact cause of migraine is still elusive, theories regarding their pathophysiology are useful in understanding some of the symptoms and response to treatment. Individualized selection of a treatment plan should result in successful management of migraine for most patients. 

## References

1. Johnson ES. A basis for migraine therapy—the autonomic theory reappraised. *Postgrad Med J* 1978;54:231-242.
2. MerckMedicus Modules: Migraine—Pathophysiology. Website: <http://www.merckmedicus.com> accessed 02/21/2005.
3. Leao AAP. Pial circulation and spreading depression of activity in the cerebral cortex. *J Neurophysiol* 1944;7:391-396.
4. Sanchez-Del-Rio M, Reuter U. Migraine aura: new information on underlying mechanisms. *Curr Opin Neurol* 2004;17(3):289-293.
5. Buzzi MG, Moskowitz MA. The trigemino-vascular system and migraine. *Pathol Biol* 1992;40(4):313-317.
6. Weiller C, et al. Brain Stem activation in spontaneous human migraine attacks. *Nature Med* 1995;1:658-660.
7. Moskowitz MA. The neurobiology of vascular head pain. *Ann Neurol* 1984;16(2):157-168.
8. Lipton RB et al. Prevalence and burden of migraine in the United States: Data from the American Migraine Study II. *Headache*. 2001;41:646-657
9. Smith R Diagnosing headache. *Hosp Med*. 1997;58:26-42.
10. Hu XH, Markson LE, Lipton RB et al. Burden of migraine in the United States: disability and economic costs. *Arch Int Med*. 1999;159:813-818.
11. Lipton RB, Scher AI, Kolodner K et al. Migraine in the United States. Epidemiology and patterns of health care use. *Neurology*. 2002;58:885-894.
12. Cady RK, Schreiber CP. Sinus headache or migraine?: Considerations in making a differential diagnosis. *Neurology*. 2002;58(Suppl 6):S10-S14.
13. Olesen J. et al Classification and diagnostic criteria for headache disorders, cranial neuralgia and facial pain 1988;8(Suppl 7):1-96.
14. Colas R et al. Chronic daily headache with analgesic overuse. *Neurology* (2004) Apr 27; 62(8):1338-42.
15. Rapoport AM and Bigal ME. Preventive migraine therapy: what is new. *Neurol Sci* (2004) Oct;S117-185.
16. Narbone MC, Abbate M, Gangemi S. Acute drug treatment of migraine attack. *Neurol Sci* (2004) Oct; 25 Suppl 3;S113-8.
17. Silberstein SD, Silberstein JR. Chronic daily headache: long-term prognosis following inpatient treatment with repetitive IV DHE. *Headache* (1992) Oct;32(9):439-45.
18. Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans in acute migraine treatment: a meta-analysis of 53 trials. *Lancet* (2001) 358: 1668-77.
19. Silberstein SD, Goadsby PJ. Migraine: preventive treatment. *Cephalalgia*. 2002;22:491-512
20. Silberstein SD. Headaches in pregnancy. *Neurol Clin*. (2004) Nov;22(4):727-56.
21. Hilaire ML, Cross LB, Eichner SF. Treatment of migraine headaches with sumatriptan in pregnancy. *Ann Pharmacother*. (2004) Oct;38(10):1726-30

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