Migraine Headaches, Part 1: Presentation and Diagnosis

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Continuing Medical Education

Goal

To describe the unique presentations of migraine headache in women and outline specific observations and tests that will expedite diagnosis.

Objectives

1. To discuss the latest findings on migraine pathophysiology that suggests a neurologic, as opposed to a vascular, origin.
2. To note the various clinical presentations, particularly with regard to misdiagnosed sinus headache and chronic daily headache due to inappropriate migraine management and analgesic rebound.
3. To explain the application of standardized criteria, the limited role of imaging studies, and the use of certain laboratory tests in diagnosis.

Accreditation

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Albert Einstein College of Medicine and Quadrant HealthCom Inc. Albert Einstein College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

This activity has been peer reviewed and approved by Brian Cohen, MD, professor of clinical OB/GYN, Albert Einstein College of Medicine. Review date: April 2003. It is designed for OB/GYNs.

The Albert Einstein College of Medicine designates this educational activity for a maximum of 1 category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she spent in the educational activity. Participants who answer 70% or more of the questions correctly will obtain credit.

To earn credit, see the instructions on page 57 and mail your answers according to the instructions on page 58.

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This article is the first of a three-part series on the causes, diagnosis, and treatment of migraine headache that focuses on the prevalence and special therapeutic considerations in women.

Even though 28 million Americans experience migraine headaches, most migraineurs have not received a physician diagnosis, choosing instead to self-medicate with over-the-counter (OTC) analgesics. In 1989, the American Migraine Study I[1] reported that of those individuals interviewed by telephone who reported headache symptoms fulfilling the diagnostic criteria for migraine, only 39% had received a physician diagnosis of migraine. The 1999 American Migraine Study II[1] demonstrated that 50% of the migraineurs interviewed still had no physician diagnosis. Today, 39% of migraineurs do not seek medical consultation for their disabling headaches, and 21% of diagnosed headache patients withdraw from medical care due to frustrations over inadequate treatment.[1]

Despite this widespread reluctance to seek physician care, more than 1 million headache consultations are performed annually—the majority (70%) by primary care physicians.[2] Approximately 20% of patients evaluated by primary care clinicians have headaches as a major complaint at their initial visit, but are often unwilling to discuss them.[2] Patients seem to feel that it is futile to raise the topic because little can be done.

Migraine is an inherited neurologic disorder. Nearly 90% of migraineurs have a primary relative with similar headaches.[3] Patients with migraine inherit a uniquely sensitive nervous system that can be disrupted by triggers such as sleep deprivation, strong odors, traveling, skipping meals, stress, and changes in hormone levels.

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Migraine affects women two to three times more often than men.[4] Although attacks can begin at any age, they typically start during childhood or adolescence. Before puberty, there is little gender bias in the prevalence of migraine. By early adolescence, however, the prevalence shifts toward women. In theory, the cyclic fluctuations in estrogen levels account for much of this disparity.[5] After age 60 years, migraine becomes less frequent, but may not resolve completely. In postmenopausal women, estrogen levels decrease significantly and stabilize, resulting in a decline in migraine frequency.

RISK FACTORS

A patient's first migraine attack can be precipitated by numerous factors, including menarche, stressful events, head trauma, and dental procedures. Some migraineurs develop headaches initially when using drugs such as nitrates, sildenafil, antihypertensive agents, oral contraceptives (OCs), and hormone replacement therapy. Migraine usually occurs when several provocative factors coincide, such as drinking red wine during menstruation while the patient is sleep-deprived. Thus, for many sufferers, these events are more easily understood as risk factors rather than triggers. Explaining this distinction prevents patients from needlessly avoiding a lesser trigger that may not cause migraine by itself.

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Approximately 59% of migraineurs experience one to four headache attacks per month, whereas 22% have 10 or more attacks per month. The headache phase of the attack typically lasts from 24 to 72 hours, with patients experiencing significant disability throughout. The impact of frequent, inadequately controlled migraine may disrupt family life, social interactions, and work. As a consequence, patients may have less access to health insurance and appropriate medical care. For these individuals, headaches can come to consume much of their daily routine. In a minority of migraine patients, poorly controlled migraine over time results in a downward socioeconomic spiral and increasing headache frequency.

MIGRAINE AND CHRONIC DAILY HEADACHE

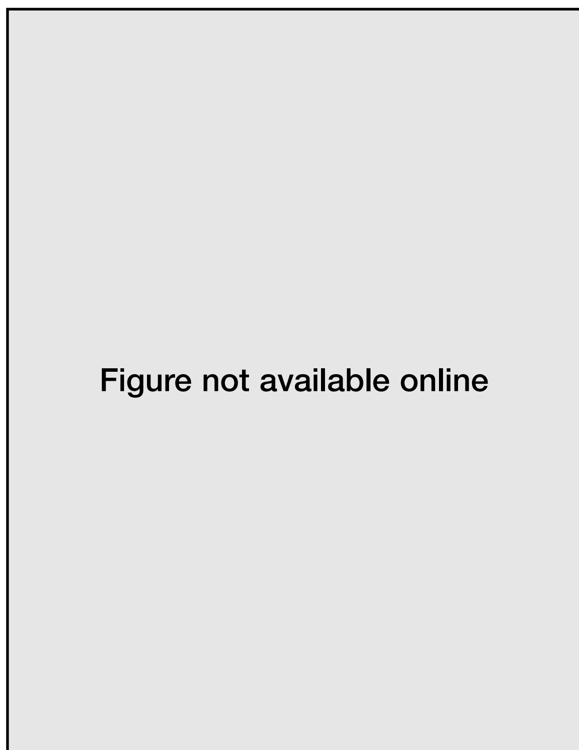
Migraine can also play a role in the development of chronic daily headache, which affects an estimated 4% of Americans.[6] For most of these individuals, the evolution of headache from episodic to chronic occurs gradually over many years. Susceptible individuals with intermittent migraine typically have a gradual increase in headache frequency, intensity, and duration.[7] Eventually, the headache pattern transforms from episodic and well controlled to daily and poorly controlled. This patient population is characterized by a persistent baseline headache with superimposed episodes of more disabling, migraine-like pain.

As headache frequency rises, patients may seek relief by increasing their use of prescribed and OTC analgesics. Overuse of these medications has been implicated in expediting the transformation process, leading to the potential "analgesic rebound" withdrawal headache.[8] Headache sufferers in the United States spend more than $2 billion annually on OTC headache medications, none of which carries a warning about the consequences of overuse. Thus, physicians must define clear limits for the use of symptomatic medications, and educate headache patients as to the mechanism and chronicity of analgesic rebound headaches. Patients should be warned against using symptomatic medications more than twice weekly for headaches to avoid transformation of episodic migraine into chronic daily headache.

PATHOPHYSIOLOGY

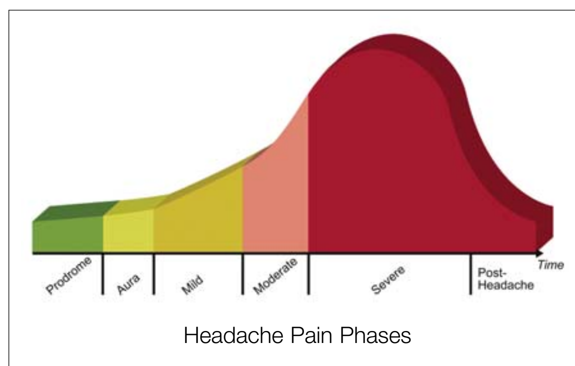
The migraine process begins in the nervous system. Rather than a vascular or muscular disorder, as was proposed in the past, migraine is a neurologic condition. Migraine begins when the sensitive nervous system of the migraineur is confronted with an environment that can reduce the migraine threshold and provoke headache. Numerous risk and trigger factors (eg, hormonal changes, skipping meals, sleep deprivation, alcohol consumption) may contribute to such an environment. In these circumstances, the neurochemical balance of the nervous system changes, and premonitory/prodromal symptoms may occur. This process can progress until the migraine threshold is crossed, and the "migraine generator" area of the brainstem is activated. A wave of spreading neuronal depression moves across the cerebral cortex, activating the trigeminal nerve branches and the vascular structures they innervate (Figure 1). As branches of the first

FIGURE 1. Migraine Pathophysiology



1) Cortical Spreading Depression (CSD) and vasodilation of intracranial blood vessels. 2) Initial vasodilation stimulates nerve endings to release neuropeptides substance P, CGRP, and neurokinin A (blue spheres). 3) Neuropeptide release causes increased dilation and inflammation of vessels with platelet aggregation and serotonin release. (serotonin = yellow spheres). 4) Pain caused by the vasodilation and inflammation is carried through to the trigeminal nerve (first-order neuron). 5) Pain is carried from the trigeminal nerve to the nucleus caudalis (second-order neuron). 6) Nerve impulses are routed from the nucleus caudalis to third-order neurons in the thalamus and cerebral cortex.

FIGURE 2. The Migraine Process



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division of the trigeminal nerve (V1) are activated, neuropeptides (substance P, CGRP) are released from the trigeminal nerve at the neurovascular junction. These neuropeptides produce a sterile inflammation of the meningeal arteries associated with platelet aggregation and serotonin release, potentiating the migraine process.[9] Nerve impulses are transmitted back into the trigeminal nucleus caudalis in the brainstem via bidirectional conduction, where they are routed to various third-order neurons in the thalamus and cerebral cortex. Inputs from the upper cervical dermatomes (C-2, C-3) are also processed in the trigeminal nucleus caudalis, which may explain the high prevalence (75%) of neck pain associated with a migraine attack.[10]

As the process continues, brainstem reflexes are activated that produce migraine-related symptoms (eg, nausea, vomiting, photophobia/phonophobia). Autonomic activation may occur via the seventh cranial nerve, resulting in nasal congestion, rhinorrhea, and lacrimation in 46% of migraineurs.[11] Pain perceived in the face over the sinus cavities is common in migraine, and likely results from activation of the second branch of the trigeminal nerve (V2). Recent functional imaging studies suggest the presence of a migraine generator in the midbrain and pons, possibly in the periaqueductal gray (PAG). Chronic migraine has been associated with iron deposition in the PAG, which may be a biologic marker for transformation into chronic daily headache.[12]

CLINICAL PRESENTATION

Migraine is a complex neurologic process, and headache is only one of many symptoms that presents during an attack. Migraineurs may experience five different phases during a typical attack: premonitory or prodrome, aura, headache, resolution, and postdrome (Figure 2). Phase recognition is helpful in diagnosing migraine and formulating a proactive treatment strategy. However, a variety of different clinical presentations may accompany the attacks, depending on how far the migraine process progresses, and many patients do not experience all of the phases. For example, some migraineurs awaken from sleep with nausea, vomiting, and severe headache. Others may be able to predict from subtle signs that a headache will occur within 24 hours, and successfully utilize abortive measures.

Classic Migraine Phases

Most migraineurs experience a prodrome that lasts for 24 to 48 hours. In a significantly smaller percent, the prodrome is followed by a 5- to 60-minute aura that precedes the acute headache phase typically by less than 1 hour. The headache itself persists for 2 to 72 hours. Once the headache resolves, patients may experience a postheadache phase (postdrome) for 24 to 48 hours. Thus, a patient who experiences all five phases of the migraine process may be symptomatic for 5 to 7 days, interfering with her ability to function at home, school, and/or work.

Premonitory/prodrome.—Up to 80% of migraineurs note the presence of a prodrome beginning 24 hours before the headache.[13] Premonitory symptoms include fatigue, yawning, change in appetite, excitement, frequent urination, memory problems, weakness, cold hands, irritability, and loss of concentration. During the prodrome, neurologic functions are frequently altered. Exposure to environmental triggers such as light, sound, hormonal changes, certain foods, stress, and exercise may cross a critical threshold in the central nervous system (CNS), resulting in disinhibition of the migraine generator. This initiates the headache phase of migraine. Patients who experience and can recognize the prodrome, can use pre-emptive therapy and consistently abort or minimize the subsequent headache.[13]

Aura.—Approximately 15% to 20% of migraineurs experience an aura prior to the headache.[14] Auras typically last 5 to 60 minutes, and usually stop as the headache begins. Auras represent focal neurologic symptoms resulting from a spreading wave of cortical depression moving from the occipital cortex of the brain forward at the rate of 2 to 3 mm/sec.[15]

Occasionally, patients may experience an aura without headache. The most common auras are visual—eg, scotomata, teichopsia (zigzag lines). Sensory auras also occur, and can be worrisome to the patient. Digital lingual paresthesia (DLP) results in a progressive numbness on one side of the face and one arm. Unlike a transient ischemic attack, the symptoms of DLP become more widespread over time, and then quickly disappear in the order of occurrence. Dysarthria (difficulty with speech) may also occur as an aura. Individuals may experience syncope, dizziness, confusion, dysarthria, diplopia, and vomiting prior to the onset of basilar migraine.[16] Retinal migraine occurs primarily in women older than 45 years, and is associated with a large scotomata and loss of vision.[17] This aura may not be followed by a headache, but can interfere with safety and activities such as driving. An aura that lasts for more than 60 minutes, results in paralysis or syncope, or occurs for the first time in a patient over age 50 years or after initiating OCs warrants a diagnostic work-up.

Headache.—The headache phase of migraine typically lasts for 4 to 72 hours in adults. The pain of migraine may be unilateral (60%) or bilateral throbbing, moderate to severe in intensity, and exacerbated by activity. Migraine-associated symptoms can include nausea, vomiting, light and/or sound sensitivity, dizziness, and loss of concentration. Migraine that occurs in the early morning hours can awaken the patient from sleep, but paradoxically can be relieved by sleep induction. Exertion typically worsens headache, so most migraineurs prefer to remain in a quiet, dark environment as their headache slowly resolves.

During the early headache phase, pain may be mild, diffuse, and nondescript. The headache phase of migraine typically progresses to moderate and finally to severe pain intensity. The patient may notice discomfort in the neck or face (ie, following the disinhibition of the trigeminal system). Associated symptoms (nausea, vomiting, light and sound sensitivity) may not be fully developed during the mild headache phase. Many patients interpret this pain as a "stress headache," or may realize that the migraine process is underway. Ideally, acute therapy should be initiated when the headache is mild, rather than waiting until neurovascular inflammation peaks and pain is moderate to severe.[18] Delaying treatment with a migraine-specific medication for more than 90 minutes may limit the efficacy of the therapy.

As the headache phase progresses and pain becomes severe, patients may develop cutaneous allodynia (ie, a painful response to a nonpainful stimulus). Thus, rubbing the head or combing the hair can become painful. The chest, extremities, and back muscles may become tender. Allodynia may develop within 1 hour after the migraine process begins. The presence of cutaneous allodynia suggests central sensitization, wherein central neurons in the activated trigeminal system are recruited to produce and transmit more pain sensations.[19] Patients may experience more sustained pain, vertigo, and increased sensitivity to common migraine triggers. The goal of acute therapy should be to prevent this stage of migraine, as acute drugs are considerably less effective when administered after the CNS is sensitized. Acute management of migraine at this phase may require the use of rescue medications and result in headache recurrence.

Postdrome.—After the headache pain resolves, many patients experience a postdrome. Although pain-free,

patients may experience a "migraine hangover" that is characterized by fatigue, cognitive difficulty, dizziness, and a fear that the headache may return at any time—a feeling of "walking on eggshells."[20]

"Sinus" Presentation

An estimated 4 million Americans are treated annually for recurrent sinus infections, and countless others use OTC analgesics for self-described "sinus headaches" and "sinusitis." More than 100 million physician visits in the United States are coded every year for sinusitis. Now, evidence suggests that these headaches often meet migraine diagnostic criteria.[21]

In 2001, Cady and Schreiber[22] evaluated 30 patients with the self-diagnosis of sinus headache, and determined that 96% met International Headache Society (IHS) diagnostic criteria for migraine (Table 1). Patients were asked to treat two "sinus headaches" with the migraine drug sumatriptan, 50 mg, and record their outcomes in a headache diary. Two hours after using the sumatriptan, 74% of patients noted improvement in their headache intensity, and 36% were pain free. When asked to express their satisfaction with sumatriptan versus their usual sinus medication, 62% favored the triptan compared with 33% who preferred the OTC drugs.

Table 1. IHS Diagnostic Criteria for Migraine Headache*

Migraine Without Aura

1. At least 5 attacks fulfilling criteria Nos. 2 through 4
2. Headache attacks lasting 4-72 hours
3. Headache has at least two of the following four characteristics
   - Unilateral distribution
   - Pulsating quality
   - Moderate to severe pain intensity affecting daily activities
   - Exacerbated by routine physical activity
4. At least one of the two following symptoms occur during the headache
   - Nausea and/or vomiting
   - Photophobia and phonophobia
5. At least one of the following three characteristics is present
   - History and physical/neurologic findings do not suggest head trauma; vascular disorders; nonvascular intracranial disorders; use/withdrawal of certain drugs or other substances; noncephalic infection; metabolic disorders; or disorders of the cranium, eye, ear, neck, sinus, nose, mouth, teeth, or other cranial/facial structures
   - History and/or physical/neurologic findings do suggest one of these disorders, but it has been ruled out by appropriate investigations
   - One of these disorders is present, but migraine attacks do not coincide with the disorder.

Migraine With Aura

1. At least two attacks fulfilling criterion No. 2
2. Headache has at least three of the following four characteristics
   - One or more fully reversible aura symptoms indicating focal cerebral cortical and/or brain stem dysfunction
   - At least one aura symptom develops gradually over more than 4 minutes, or two or more symptoms occur in succession
   - No aura symptom lasts more than 60 minutes (if there is more than one aura symptom, the accepted duration is proportionally increased)
   - Headache follows the aura with a symptom-free interval of less than 60 minutes (it may also begin before or with the aura)
3. At least one of the following three characteristics is present
   - History and physical/neurologic findings do not suggest head trauma; vascular disorders; nonvascular intracranial disorders; use/withdrawal of certain drugs or other substances; noncephalic infection; metabolic disorders; or disorders of the cranium, eye, ear, neck, sinus, nose, mouth, teeth, or other cranial/facial structures
   - History and physical/neurologic findings do suggest one of these disorders, but it has been ruled out by appropriate investigations
   - One of these disorders is present, but migraine attacks do not coincide with the disorder.

*Adapted from the International Headache Society/World Headache Alliance (http://www.i-h-s.org/).head trauma; vascular disorders; nonvascular intracranial disorders; use/withdrawal of certain drugs or other substances; noncephalic infection; metabolic disorders; cranium, eye, ear, neck, sinus, nose, mouth, teeth, or other cranial/facial structures

TABLE 2. Four Questions to Help Differentiate Migraine from Other Headache Disorders

1. Do you have headaches that interfere with work, social, or family functions?
2. Has your headache pattern remained stable over the past 6 months?
3. How frequently do you experience headaches?
4. How effective is your current headache treatment?

TABLE 3. Migraine Diagnostic "Comfort Signs"

- Positive family history of migraine
- Headaches related to menstrual cycle
- Headaches preceded by typical aura
- Headaches remaining periodic and stable over time
- Normal physical and neurologic findings.

Patients who believe they have sinus headaches commonly experience a watery nasal discharge and facial pressure with the headaches. In addition, they notice that weather changes trigger the attacks. These observations were recently confirmed in a large, multicenter clinical study including subjects with self- and/or physician-diagnosed sinus headaches. As in the pilot study, 88% of the subjects' "sinus" headaches met diagnostic criteria for IHS migraine and responded to interventions with sumatriptan.[23] Thus, it seems highly probable that many presumed sinus headaches are actually migraine. Patients who are treated with migraine-specific drugs for such headaches often become pain free within 2 to 4 hours. Decongestants and antibiotics are often prescribed inappropriately for the presumptive diagnosis of sinus headache/sinusitis, and do not terminate the migraine process.

DIAGNOSIS

Migraine is defined as a stable pattern of recurrent, disabling headaches with no evidence of an underlying cause. According to the IHS criteria (Table 1), the headache of migraine should be moderate to severe, last for 4 to 72 hours, throbbing, associated with nausea or vomiting and light and/or sound sensitivity, and aggravated by activity.[24]

Four questions can assist in differentiating migraine from other primary and secondary headache disorders (Table 2). Chronic, periodic, disabling primary headaches should be considered migraine until proved otherwise. A new-onset headache type or change in headache pattern should be considered for investigation of a possible secondary headache disorder such as infection, aneurysm, or brain tumor. Progressively worsening headaches may require further evaluation, especially in children. Often an increase in frequency, intensity, and duration of headaches indicates migraine transformation into chronic daily headache. Patients who at one time experienced an intermittent disabling headache and now suffer from headaches almost every day may be overusing symptomatic medications. The primary medical focus for these patients should be headache prevention and avoidance of analgesic drug overuse. Those who treat their headaches with symptomatic medications more than twice weekly may be at risk for rebound headache. Headache education, lifestyle interventions, and preventive medications are necessary to alleviate these headaches and restore normal function.

Most headache patients do not require an extensive or expensive work-up to establish a diagnosis. Migraineurs often have "comfort signs" that help to reassure the clinician as to the benign nature of the headache type (Table 3). By contrast, there are also certain danger signs or symptoms that should alert the physician to the possibility of a secondary or life-threatening headache disorder (Table 4).

Imaging

In 2000, the US Headache Consortium[25] conducted an evidence-based review of published medical literature and issued guidelines for performing magnetic resonance imaging (MRI) and computed tomography (CT) scans in patients with nonacute headache. Patients who should undergo such imaging studies include those with a nonacute headache in association with abnormal neurologic findings or those with atypical headaches that may not be a primary (benign) headache disorder. For patients who require imaging, MRI is preferred to evaluate a possible structural lesion in the brain, whereas CT should be used to investigate a suspected subarachnoid hemorrhage.

Only one in 250,000 headaches is due to a life-threatening disorder, whereas one in eight people in the United States have migraine.[26] The chance of a migraineur having typical migraine symptoms, normal neurologic findings, and abnormal MRI results is less than 0.2%.[27] Therefore, neuroimaging is not usually warranted for patients with migraine and normal neurologic findings. However, any woman with a change in her headache pattern should undergo an imaging study.

Table 4. Headache Danger Signs

- Headache characterized as "the worst headache of my life"
- Sudden onset of a severe ("thunderclap") headache
- New onset of headache in a patient older than 50 years
- Presence of fever, confusion, neck stiffness, loss of consciousness, or any focal neurologic finding
- Any change in headache pattern (eg, progressive headaches without symptom-free intervals).

Laboratory Tests

Migraine patients should undergo laboratory testing for thyroid disorders and anemia, as correcting these common medical problems can significantly reduce headache frequency. Patients who have migraine with complex or atypical aura should be tested for serum levels of anticardiolipin antibodies; positive results could indicate an increased risk for future stroke.[28] Patients with aura who smoke, use OCs, and test positive for anticardiolipin antibodies should begin prophylactic aspirin therapy and stop smoking immediately due to the heightened risk of stroke. Oral contraceptives should be used only with informed consent in such an individual.

CO-EXISTING DISORDERS

Several medical disorders are observed more frequently in migraine patients than in nonmigraineurs.[29] Depression is 3 times more common in migraineurs, while anxiety and panic disorder are 6 to 8 times more prevalent. Irritable bowel syndrome is 8 times more frequent, and stroke is 4 times more common. Migraine patients often suffer from dysmenorrhea, fibromyalgia, epilepsy, seasonal allergies, and toxemia of pregnancy as well. These co-existing disorders are all thought to be caused by CNS abnormalities of serotonin (5HT). Therefore, patients with depression should be evaluated for migraine headaches and vice-versa. Likewise, migraineurs should be monitored for symptoms of depression and panic disorder.

Part 2 of this series, which will appear in an upcoming issue of The Female Patient, *will discuss acute and prophylactic migraine therapies and how to tailor them to the individual patient.*

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