American Association for the Study of Headache

AASH

HEADACHE PROFILES

Volume I Number 1

# Welcome

Welcome to the inaugural issue of *AASH Headache Profiles*, a publication of the American Association for the Study of Headache, designed to help medical students and residents learn about one of the most common disorders they will see in practice, headache.

As benign conditions with few objective signs, migraine, tension-type headache and the other primary headache disorders receive relatively little attention in most medical curricula and training programs. Yet chronic headache is one of the ten most common reasons for a visit to the physician and the most common complaint seen by neurologists.

The field of headache medicine is in a state of rapid development and discovery. New insights into the pathophysiology of migraine and other headache disorders are advancing our ability to offer effective treatment to the millions of patients in the U.S. alone. Three new migraine medications have been approved and marketed over the past year, with a fourth currently awaiting approval and more in the pipeline. *AASH Headache Profiles* will help you keep up-to-date on the expanding options for the medical management of headache, including nonpharmacologic approaches of proven benefit.

Each issue of *AASH Headache Profiles* will present a detailed case vignette illustrating a typical headache presentation. These cases and accompanying articles will cover the fundamentals of taking a headache history, making a diagnosis, selecting treatment and doing appropriate follow-up. Internationally recognized headache specialists will offer focused discussions of the issues raised by the cases presented, as well as references for further reading.

We invite your feedback and suggestions for improving *AASH Headache Profiles*. You can reach us by email at aashhq@talley.com or at the address given on page 2.

AASH is a professional society of over 1,400 U.S. and international clinicians and researchers with a special interest in head and facial pain. Membership includes neurologists, internists, family medicine practitioners, psychologists, and other health care professionals. The journal *Headache* is published by the Association.

J. Keith Campbell, MD. Editor-in-Chief, *AASH Headache Profiles* and Past President, AASH

## U.S. Consultation and Diagnosis Rates

*From the 1998 American Migraine Study*
*Population: 1720 migraineurs identified using International Headache Society (IHS) criteria by a mailed questionnaire survey*

- 68% of the females and 57% of the males reported having consulted a doctor specifically for migraine
- 47% initially consulted a family practitioner
- 13% initially consulted a neurologist
- Of those who consulted, only 42% reported having received a medical diagnosis of migraine

*1989 National Heath Interview Survey Data*
*Population: Self-reported migraine in a sample of 116,929 individuals*

- 85% of the females and 77% of the males reported having consulted a doctor for migraine
- 8% reported hospitalization for migraine

*National Center for Health Statistics*

- 11 million ambulatory care visits specifically for headache in 1996

## CASE VIGNETTE

*"My kids need me.*
*I don't want to miss any more days."*

Sarah, a 28-year-old kindergarten teacher, presents with a complaint of infrequent but severe headaches. She is married with a 3-year-old son. Her vital signs taken by the nurse are normal. She reports that she is not taking any medication except occasional over-the-counter analgesics and that she has no other diagnosed conditions. This was her first consultation for headache.

***Describe a typical headache episode, Sarah. Where do you feel the pain? How long does the attack last? Do you have other symptoms in addition to head pain?***

Sarah says she gets a terrible throbbing pain in the head, either the right side or left. No, it doesn't switch sides during the headache but the pain can be on either side, and during the attack it may spread to the front and top of the head and even all over. She vomits repeatedly, even with an empty stomach. The headache lasts most of the day but is usually much better if she can sleep. She supposes they last from 6-12 hours, generally.

***How often do you get these headaches? Has their severity or frequency changed?***

Sarah says she gets them three or four times a year but she thinks they may be coming more often recently. No, there haven't been any recent changes in the pattern. She just started back as a teacher this year, and she doesn't want to miss any days if she can help it. She missed one last month because of a headache.

When asked, Sarah says the headaches started when she was 12. In the first year she had several attacks, four or five, and then went for nearly a year without headaches, and then they came back again, about three a year. She thinks the headaches were a bit different back then. The pain was all over the head and she does remember that it throbbed with her heartbeat. The headaches changed for the worse in her early twenties when she started an oral contraceptive, becoming more severe, clearly one-sided, with vomiting and prostration. She tried several different oral contraceptives but all seemed to aggra-

*Continued on page 2*

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*Continued from page 1*

vate the headaches, and finally switched to a different method of birth control.

When she was pregnant with her son at age 24 she was essentially headache-free for the latter half of her pregnancy, but had a series of quite severe headaches in the two weeks following the birth of her son.

***Does anyone else in your family have a headache problem?***
Sarah's mother told her that her grandmother used to have what she called "sick headaches," but they went away as she got older.

***Does anything seem to trigger your headaches? Can you connect them to anything?***
When she was a teenager, they seemed to be connected to her menstrual cycle, though her periods didn't become regular until she was 16. Her mother pointed out that they would sometimes come on with changes in the weather or with some big event. She remembers getting one right after her senior prom. Lately, the headaches seem to have more to do with skipping meals or being behind on sleep or under some kind of stress. She remembers having one come on suddenly when she was looking at sunlight reflecting off the surface of the lake, but that was unusual.

***Do you have any warning signs that tell you a headache is coming?***
Not really. The pain builds for about an hour, so she usually has a chance to get away before it's really bad and she starts vomiting.

***What do you usually do when a headache comes on? What seems to make them better, or what will make them worse?***
Sarah says she tries to lie quietly in bed with the shades pulled down if she can, but with a small boy to take care of she can't always manage to get away by herself. Aspirin and acetaminophen don't really help. She'll take a double dose to help her sleep but that's about it. Sleep is the best thing, but she keeps having to run to the bathroom to vomit and that makes the pain worse. Moving around always makes the pain worse.

***Do the headaches have any impact on your social and family activities?***
The headaches aren't so frequent that it's been a big problem, but Sarah says she worries that people won't understand and will think she's just making excuses. Her husband and her mother have both been very understanding about helping her out when she's sick with a headache.

***On a scale of one to ten, with one being no pain at all and ten the worst pain imaginable, how would you rate the severity of your head pain during an attack?***
Sarah says it would be about a 6, but worse when she has to move around. Really, the vomiting is worse than the headache.

***So it sounds like it would really be important to you to be able to avoid missing schooldays because of headache. You need something to control the vomiting as well as something for the headache itself. Is that right?***
Yes, that's right. Sarah explains that she'd rather not take a lot of drugs if she can help it, but she'd like to minimize the risk of missing schooldays.

***We may have to try several medications before we find the treatment that is best for you, but I'm confident we can improve your headaches. We may also be able to help you prevent headaches by avoiding some of those triggers you mentioned, like missing sleep or feeling stressed. Let's talk first about what kind of headache you have.***

## PRETEST

1. What is the diagnosis?
2. Which of the following features were most important in making the diagnosis?
   a. onset in early adolescence
   b. unilateral location
   c. initial bilateral location
   d. throbbing character
   e. duration of headaches
   f. resistance to common analgesics
   g. vomiting associated with headaches
   h. aggravation by oral contraceptives
   i. aggravation by movement
   j. sensitivity to light
   k. sensitivity to changing estrogen levels
   l. relieved by sleep
   m. positive family history
3. Name three medications that could be tried.
4. What side effects should be avoided for this patient?

# COMMENTARY

Sarah has migraine without aura (common migraine). An association with her menstrual cycle (menstrually associated migraine) is likely, but it would be necessary to have her to keep a calendar recording the timing of her headaches and menses through several episodes to verify the diagnosis. Given the fact that her attacks are relatively infrequent, several abortive medications would be suitable to try.

Headache diagnosis depends very much on skillful interviewing. With a little guidance, Sarah gave all the information needed to make the diagnosis and the initial treatment selection.

***Describe a typical headache episode, Sarah. Where do you feel the pain? How long does the attack last? Do you have other symptoms in addition to head pain?***
Sarah readily provides enough information to make the diagnosis: her headaches are unilateral (but may

# ACUTE TREATMENT OPTIONS

*Elizabeth Loder, MD. Director, Headache Management Program. Spaulding Rehabilitation Hospital. Boston, MA*

Although preventive lifestyle changes and trigger avoidance can be important parts of treatment for headache patients, as Sarah's case makes clear, even the best-managed patients will need periodic acute treatment of headache at some point. Pain relief is most important to patients, but other factors should be taken into account as well in selecting the most appropriate acute treatment for an individual patient.

Acute pharmacologic treatment of migraine can be divided into two categories: ***nonspecific*** medications, which may relieve the symptoms of migraine, such as pain and/or nausea; and ***specific*** medications, which work directly on the underlying mechanisms involved in the migraine attack. While nonspecific medications may relieve symptoms, their activity is not targeted against migraine. They are effective for pain and nausea caused by other conditions as well. In contrast, specific treatments eliminate pain, nausea and other symptoms by their direct action on the underlying causes of migraine.

Nonspecific medications also often cause unintended and unwanted side effects because of their broad spectrum of activity at multiple receptor sites. With some nonspecific agents, these unintended effects include sedation or anti-anxiety effects, and the drugs may be prone to misuse or abuse for reasons other than headache. With others, these unwanted side effects include aggravation of nausea or vomiting, already a problem for many migraine patients. Rebound headache can occur with frequent use, and in some instances the pronounced vasoconstrictive actions of nonspecific or semi-specific agents can cause vascular complications. As a busy mother and kindergarten teacher, Sarah probably cannot afford the drowsiness or reduced performance associated with many nonspecific headache medications. Despite the fact that these medications may be cheaper than newer, more targeted drugs, the "costs" in lost work time, reduced job performance and attentiveness associated with sedative medications are important to consider. Migraine is a lifelong illness which is most active during the busy middle years of a woman's life. It is therefore hard to defend setting the example for a patient that the way to handle it is to "check out" by taking a medication that causes drowsiness or impairs function.

**Ergotamine compounds**, in clinical use for migraine since the early part of this century, are perhaps best thought of as semi-specific treatments for migraine. Despite their activity at the serotonin 1B and 1D receptor sites thought to be important in migraine, their actions at a host of other receptors produce numerous unintended side effects. Activity at dopamine receptors, for example, is likely responsible for the nausea and vomiting which often complicated therapy with ergotamine. This commonly forces the use of anti-nausea medications, which are associated with their own set of side effects, such as sedation or dystonic reactions. The pronounced vasoconstrictive actions of ergotamine are responsible for the vascular side effects seen in susceptible individuals. Nausea and vomiting are prominent features of Sarah's migraine attacks, and it is possible these symptoms would be aggravated by the use of ergotamine. **Dihydroergotamine (DHE)**, a related compound, has been used in place of ergotamine and in many cases represents an improvement over it, with seemingly less propensity to induce nausea and less arterial vasoconstriction. Its poor oral bioavailability, however, has in the past dictated its use in relatively inconvenient parenteral forms. Sarah might benefit from the newly released nasal spray preparation of this drug.

The introduction of **sumatriptan** in the early 1990s represented an attempt to focus therapeutic activity on serotonin receptor sites involved in migraine while limiting effects on other receptor sites. As such, it represented an important breakthrough in migraine treatment and ushered in the era of truly targeted therapy of migraine. The unwanted vascular and gastrointestinal side effects seen with ergotamine compounds were minimized, while efficacy against the entire symptom complex of migraine—headache, nausea, vomiting, photophobia and phonophobia—was retained. Sumatriptan is available as a self-administered, prepackaged subcutaneous injection, nasal spray or tablet. For headaches which are slower in onset, the tablet form offers convenience that most patients prefer.

**Newer triptans** aim to improve on various aspects of sumatriptan. Low oral bioavailability was theorized to account for the sometimes inconsistent relief of headache from one attack to another with sumatriptan, and newer compounds like zolmitriptan and rizatriptan improve on this. The low lipophilicity of sumatriptan was thought to account for the limited penetration of the drug into the central nervous system, and again, newer drugs such as **zolmitriptan**, **rizatriptan**, **naratriptan** and **eletriptan** all show some degree of central penetration. Whether this translates into improved anti-migraine activity remains to be seen, however. There is at least some possibility that central side effects such as sedation may obviate any advantage this provides. Zolmitriptan has been shown to work equally well for headaches associated with menses as for those not associated with menses; given the correlation between Sarah's headaches and her menstrual periods, this is a treatment possibility. If she prefers a discreet, convenient way of taking medication without leaving her kindergarten classroom, she may prefer to use the new orally disintegrating wafer formulation of rizatriptan, the only triptan available in this novel delivery formulation.

Accumulated clinical experience with the triptans, in addition to a wealth of trial data, has demonstrated an excellent record of safety and tolerability. The most common adverse experiences with all triptans are transient side effects such as fatigue, lightheadedness and nausea. However, all triptans can rarely cause chest pressure or pain and are contraindicated in patients with coronary artery disease or risk factors for coronary artery disease. Fortunately, Sarah, like the majority of patients with migraine, is a young healthy women at low risk for cardiac disease.

The advent of truly selective medications for migraine allows us to target treatment to the disorder while reducing unwanted adverse events. It reduces or avoids the potential for medication misuse or dependence and eliminates unwanted side effects such as sedation and nausea. For all of these reasons, the use of specific treatments will increasingly represent the standard of care for acute treatment of migraine.

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The word migraine is derived from *hemicranium*, literally, "half of the head." The modern word *migraine* was first used by the French in the 13th century. Mygrane, Megryne, Meagrim, Migrym and Megrim are just a few of the early terms for migraine.

Migraine has been known for centuries as *sick-headache*, *blind-headache*, *bilious headache* and *cephalgia biliosa*.

The word *aura* is derived from the Greek for "breeze" or "wind." The dictionary definition is a distinctive atmosphere or a subtle emanation.

Julius Caesar, Freud, Lewis Carroll and Hildegard of Bingen all suffered from migraine

The term *migraineur* is often used to describe a person who has migraine and is correct if that person is male. Strictly the term *migraineuse* should be used for a female who has the disorder but the word is not in common usage.

spread during the attack), fairly severe and accompanied by nausea, and the duration (6-12 hours) is in the range typical of migraine. The improvement with sleep is common but not diagnostic.

***How often do you get these headaches? Has their severity or frequency changed?***
Even when the diagnosis seems clear and the headache condition is long-standing, it is important to ask if there has been a change in the headache pattern that might suggest the emergence of secondary headache due to underlying pathology. First consultations for headache are often motivated by worsening headaches.

The additional information Sarah volunteers gives us her reason for consultation and her objective for treatment (avoiding missed workdays), as well as the fact that the headaches have hormonal triggers. Women with migraine may find their headaches either improve or worsen with oral contraceptive use. Improvement is commonly noted during pregnancy, usually after the first trimester.

***Does anyone else in your family have a headache problem?***
Migraine often, but not always, affects multiple family members.

***Does anything seem to trigger your headaches? Can you connect them to anything?***
Information on triggers helps with both diagnosis and prevention approaches. Diet and sleep disturbances can trigger tension-type headaches as well as migraine attacks. Visual stimulation such as bright or flashing lights and ovulation/menstruation are common migraine triggers.

***Do you have any warning signs that tell you a headache is coming?***
Sarah does not experience an aura. The additional information that the headache takes an hour to peak will help guide medication selection. Patients with a relatively slow or gradual onset often do well enough with oral formulations, while those with rapid-onset severe headaches do best with parenteral or intranasal administration. Because of the vomiting, oral preparations will only be effective for Sarah if taken early in the attack.

***What do you usually do when a headache comes on? What seems to make them better, or what will make them worse?***
Withdrawal to a quiet, dark room is typical behavior for patients with migraine, who frequently experience phonophobia, photophobia, or both with their attacks. Aggravation with physical activity is also typical. In contrast, patients with cluster headache tend to pace during their attacks or distract themselves by pounding their fists, etc.
We learn also that NSAID-type analgesics are ineffective for Sarah's headache, so these would not be tried.

***Do the headaches have any impact on your social and family activities?***
Patients may not volunteer information on quality-of-life issues, which can be substantially affected by severe or very frequent headaches. Marital or family problems relating to the patient's frequent disability may need to be addressed by referral to a mental health professional or more simply by inviting the patient to bring the spouse to the follow-up visit so the illness and the treatment plan can be discussed with both of them.

***On a scale of one to ten, with one being no pain at all and ten the worst pain imaginable, how would you rate the severity of your head pain during an attack?***
Determining severity of pain and resulting disability are crucial for deciding what class of medication should be first tried. For example, a patient with severe incapacitating pain ought not to be started on a mild analgesic that is almost certain to be ineffective. Physicians often focus on treating the head pain, yet it is not unusual for the associated symptoms (in this case vomiting) to be equally or more disabling, as in Sarah's case.

***So it sounds like it would really be important to you to be able to avoid missing schooldays because of headache. You need something to control the vomiting as well as something for the headache itself. Is that right?***
The patient's goals and preferences must guide the management strategy. The optimal therapy for this patient would be non-sedating and would address the GI symptoms as well as the head pain. Sarah is interested in non-pharmacologic approaches and likely to comply well with them, given her intelligence and her cooperative attitude during the interview. Advice on nutrition and sleep hygiene will validate her own observations and motivate her to avoid these sorts of triggers. Whether she will need or want a referral for biofeedback or relaxation training for stress management can be considered on follow-up.

# EPIDEMIOLOGY OF MIGRAINE

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Results of the American Migraine Study indicate that over 23 million people in the U.S. have migraine, with prevalence rates of 17.6% in females and 5.7% in males between 12 and 80 years of age.[1] Prevalence rises in both males and females from the age of 12 years to about age 40, peaking between ages 35 and 40.

Migraine accounts for 64% of all severe headaches in females and 43% of all severe headaches in males.[1] Most migraine sufferers have never received a medical diagnosis of migraine—about 59% of female and 71% of male migraineurs have not been correctly diagnosed.[2] About half of migraine sufferers realize that they have migraine. Others may mistakenly call their headache "sinus" or "stress" headache. Among those who have consulted, the majority are initially seen by general practitioners or family physicians.[2] Of those who have never consulted a physician, 61% report severe pain and 67% report severe disability or need for bed rest with their headaches.[2]

Prevalence of migraine is higher among lower socioeconomic groups, possibly due to increased exposure to stressors that may exacerbate the disorder.[1] For more severely affected individuals, there may be a "downward drift" phenomenon; the unemployment rate among those with severe migraine is higher than that of the general population.[3]

The indirect costs of migraine far exceed the direct costs. In terms of lost productivity, migraine-related disability costs the U.S. economy about $13 billion annually.[4] In lost work day equivalents, which take into account reduced efficiency when continuing at work during an attack, women lose an average of 8.3 workdays per year, while men lose an average of 3.8 workdays per year due to migraine.[5] In the National Health Interview Survey data, 10% of children with migraine missed at least one day of school over a 2-week period due to migraine.[6] It was estimated that male migraineurs were bedridden for 20 million days and female migraineurs were bedridden for 92 million days in the U.S. in 1998.[4] The economic burden of migraine to society is thus substantial, quite apart from the burden of pain and disability experienced by the individual.

### U.S. Prevalence and Patterns

- 23 million migraineurs in U.S.
- 3:1 ratio of females/males: 18% of U.S. women and 6% of U.S. men have migraine
- 59% of females report ≥ 1 severe headache per month
- 50% of males report ≥ 1 severe headache per month

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# THE DIAGNOSIS OF MIGRAINE

*Lawrence C. Newman, MD. The Headache Institute. New York, NY*

Migraine is characterized by recurrent attacks of headache in combination with a variety of associated features affecting multiple systems. In fact, although head pain is the feature of migraine most investigated, migraine is actually a constellation of symptoms. These symptoms range from mild to totally incapacitating, varying not only between patients but between individual attacks as well.

Most migraine sufferers experience their first attack during their teenage years or early twenties and may suffer from recurrent headaches for many years. Migraine often subsides in the fifth and sixth decades. Migraine may begin in childhood; however, its appearance for the first time after age 40 is uncommon enough to prompt a work-up for an underlying cause. Migraine is approximately three times more common in women than in men.

As reported by Sarah, migraine often is a familial disorder, but the exact mode of transmission remains unknown. It is therefore very useful to ask patients if others in their families suffer from similar headaches.

The typical migraine attack can be divided into five phases. These phases need not all be present, nor is any one phase necessary for establishing the diagnosis of migraine. Rather, these phases represent a continuum in a chain of events that characterizes a migraine attack.

The first phase or **prodrome** is experienced by approximately 60% of migraine sufferers and consists of a variety of vague complaints often not recognized by the patient, yet nearly always observed by those close to the sufferer. These premonitory symptoms begin hours to days before the headache itself, and usually involve alterations in the patient's mood, appetite or energy level. Typical prodromal symptoms include irritability, depression, fatigue, anorexia, food cravings, impairment in concentration, yawning, increased urination, and a heightened sensory awareness. As these features of the prodrome are often overlooked by the patient, careful questioning during the history may help reveal their presence.

The second phase of migraine, the **aura**, is experienced by only 10%-15% of all migraine sufferers. Many physicians mistakenly believe that migraine cannot be diagnosed in its absence. When aura is not present, as in the case of our patient Sarah, the diagnosis of *migraine without aura* is given. The migrainous aura represents a transient disturbance in neurologic function. Although the aura is usually characterized by visual phenomena such as scotomata (blind spots), photopsia (similar to the blue lights that persist following a flash-bulb photograph), or fortification spectra (a zig-zag pattern reminiscent of walled fortresses), an aura may also consist of paresthesias, weakness, or rarely aphasia. The most common visual aura, the scintillating scotoma, consists of a region of flickering lights surrounding a blind spot. By definition the migraine aura is transient; the International Headache Society (IHS) diagnostic criteria state that the aura should last less than 1 hour.

The third phase of migraine is the **headache**. The pain of migraine is usually one-sided, although attacks may alternate sides. The site of maximal pain is usually temporo-orbital, but the pain often radiates into the ipsilateral occiput and neck and in some cases may spread to the opposite side of the head.

When obtaining a headache history, the patient should be specifically asked about the location of pain and whether the pain ever shifts sides. The presence of side-shift implies a benign process, since unilateral headaches without side alteration may be due to an underlying cause such as an arteriovenous malformation (AVM) or tumor. Migraine pain is usually described as throbbing or pounding, is of moderate to severe intensity, and is made worse by routine activity such as climbing stairs. Although the headache of migraine usually causes the most disability, accompanying symptoms may be the source of disability for many patients (like Sarah), and should not go untreated. Typical associated symptoms include nausea, vomiting, photophobia, phonophobia, osmophobia (sensitivity to odors), poor concentration and irritability. These features, together with the head pain, result in the patient preferring to retire to a darkened, quiet room.

Untreated or poorly treated attacks of migraine last between 4-72 hours and then spontaneously resolve. This is the fourth stage known as **resolution**.

The last phase, the **postdrome**, consists of body aches, decreased appetite and concentration, fatigue and weakness, and may persist for 24 hours following the resolution of the headache.

While these phases describe features common to a single migraine attack, there can be significant variation from attack to attack even in the same individual. For example, hormonally associated migraine may have a clinical presentation distinct from an early morning attack of migraine. Patients are generally aware if they have more than one kind of headache, and it is sometimes helpful to offer these patients additional management options.

Additionally, in many patients migraine is a chronic disorder with a natural history. Initial migraine attacks may be characterized by more vascular and gastrointestinal symptomatology but progress to headaches associated with more myogenic and psychological symptoms, especially with excessive analgesic use. This process has been called **transformation**.

Attacks of migraine occur sporadically and at varying intervals. These headache episodes can occur as infrequently as once a year or less, to as often as several times per week. In U.S. population studies, most sufferers reported 1-3 attacks per month.

Migraines may begin spontaneously or may be precipitated by certain triggers. Common triggers include changes in sleep patterns, weather changes (falling barometric pressure), emotional stress, missing meals, menstruation, use of oral contraceptives or estrogen replacement therapy. Many patients as well as physicians are convinced that a number of foods function as triggers, such as chocolate, aged cheeses, red wine, MSG and nitrate-containing foods, and citrus fruits. Most studies have failed to validate these suspected triggers. As most triggers are not consistent, it is often useful to ask patients to track their headaches with a diary in an attempt to uncover putative trigger factors that can be minimized or avoided.

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### Diagnosis: Migraine Without Aura

- Headache attacks last 4-72 hours.
- Headache has at least **two** of the following characteristics
  - Unilateral location
  - Pulsating quality
  - Moderate or severe intensity
  - Aggravation by routine physical activity
- Headache is accompanied by at least **one** of the following:
  - Nausea and/or vomiting
  - Photophobia and phonophobia
- History, physical and neurological exams do not suggest underlying causes such as head trauma, vascular disorders, intracranial neoplasm or infection, etc., or these causes have been ruled out by subsequent investigation.

### Menstrual Migraine

- No standard definition exists, but it is recognized that some women have migraine that occurs **only** immediately before, during or after the menstrual period; the attacks may be frequent or infrequent.
- More commonly, women may have *menstrually associated migraine*, meaning that they are more likely to have attacks perimenstrually or at the time of ovulation, but have them at other times as well.
- Migraine attacks that are associated with the menstrual cycle are often more severe or protracted and may sometimes require additional treatment options.

# PATHOPHYSIOLOGY OF MIGRAINE

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Whether migraine is a vascular or neuronal phenomenon has been debated for centuries. Innovative experimental work by Wolff in the 1930s supported the vascular theory.[1] In this model migraine was initiated by a period of vasoconstriction followed by vasodilatation, resulting in vascular extravasation and pain. If the period of vasoconstriction produced significant oligemia, neuronal disruption occurred, giving rise to the aura. This theory provided little explanation for clinical observations such as why migraine without aura is the more common form of migraine and why headaches may continue after vasodilation has resolved, nor can prodromes, photophobia or phonophobia be explained by this theory.

In response to this debate, Lance and others proposed the "unifying theory," which suggested that migraine was initiated by neuronal events producing vascular changes and headache.[2-4] Work by Moskowitz demonstrated the existence of a cerebrovascular system controlled by the trigeminal nerve, disturbance of which caused a sterile inflammatory process, resulting in vasodilation and protein extravasation, particularly from meningeal vessels.[5]

Antidromic impulses (ie, those traveling in the direction opposite to normal) in the trigeminal nerve cause the release of neuropeptides at the perivascular nerve endings—neurokinins, calcitonin gene-related peptide (CGRP) and possibly substance P—that produce vasodilation and a neuroinflammatory reaction in the meninges and scalp. Thus the trigeminovascular pathway may be involved in the pain, but thus far it has not been possible to determine what initiates the antidromic impulses in the trigeminal nerve, nor how to relate them to the presumed changes in cerebral perfusion that have been documented by Olesen and others over many years and by several different techniques.[3]

Also uncertain at present is whether "spreading cortical depression (SCD) of Leao" really occurs in humans and whether it is involved in the genesis of migraine. There will be further discussion of SCD in subsequent issues of *AASH Headache Profiles*. Briefly, in lower animals such as the rat and rabbit, stimulation of the exposed cerebral cortex, especially in the occipital area, can initiate a wave of electrical suppression that migrates anteriorly at about 2-3mm/minute, crossing the territories of several cerebral arteries. The wave of electrical silence is preceded by a zone of hyperemia and is followed by a phase of oligemia. The rate of progression of Leao's phenomenon is reminiscent of the rate of progression of the visual symptoms of a migrainous aura. This has led to intense speculation as to the possible involvement of SCD in migraine. Studies employing PET scanning and magnetoencephalography have provided some evidence in favor of the theory that SCD is involved.

The cascade of events responsible for an attack of migraine appears yet more complex in light of the PET studies of Diener and his colleagues in Essen showing that a region in the brainstem is metabolically activated during the migraine attack.[6] This region has been dubbed "the migraine generator," although it is premature to believe that migraine invariably starts in the brainstem in view of the well-described cognitive, visual and other symptoms that must originate in higher regions of the nervous system.

## POSTTEST—TRUE OR FALSE

1. Migraine without aura is relatively uncommon compared to migraine with aura.
2. Associated symptoms (eg, nausea, vomiting) can be as severe or disabling as the head pain itself.
3. Pain intensity and time to peak pain should be considered in selecting medication and route of administration.
4. Women with migraine usually report improvement in their headaches with oral contraceptive use.
5. Onset after age 40 is uncommon and should prompt additional work-up to rule out underlying disorders.

The role of serotonin as a critical neurochemical regulator for this trigeminovascular system gained acceptance with the advent of sumatriptan, although its role is still incompletely understood.[7] The triptans relieve the pain of migraine rapidly and reduce the severity of associated symptoms such as nausea, photophobia and phonophobia, presumably by their actions on 5-$HT_{1B/1D}$ receptors. Experimentally, the triptans and the ergots reduce protein extravasation and the inflammatory changes produced by electrical stimulation of the trigeminal nerve in anesthetized animals. Whether this is their mode of action in relieving the symptoms of migraine is not yet certain.

More recently, efforts have been undertaken to define the genetic basis of migraine. Even though results are inconclusive, most accept the concept of an important genetic component to migraine.

Though the pathophysiology of migraine remains incomplete, several important concepts are emerging. These include:

1. Migraine as an inherited neuronal vulnerability.
2. A "migraine threshold" may exist which reflects the capacity of the nervous system to adjust to change. If demands exceed the capacity to adjust, there is disruption of neuronal function, resulting in a wide constellation of symptomatology.
3. The trigeminovascular mechanisms that may underlie the pain of migraine are possible defense mechanisms not dissimilar from those proposed mechanisms protecting other portals of body entry in disorders such as in asthma or urticaria.

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### Suggested Reading

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### Answers—Pretest

1. Migraine without aura.
2. The diagnosis can be made on the basis of b, d, e, g, i, and j; a, h, k, l, and m are typical of migraine and provide additional support for the diagnosis.
3. Any of the triptans would be reasonable choices, or intranasal DHE.
4. Sedation, given her wish to continue working; nausea, since vomiting is already a prominent feature of her attacks.

### Answers—Posttest

1. False
2. True
3. True
4. False
5. True

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