VIII HEADACHE

Randolph W. Evans, m.d.

Headaches are a near-universal experience, with a 1-year prevalence of 90% and a lifetime prevalence of 99%. Each year in the United States, 9% of adults see physicians for headaches and 83% self-medicate. Headaches are one of the most common complaints of patients seen by primary care physicians and account for 20% of outpatient visits to neurologists.

The differential diagnosis of headaches is one of the longest in medicine, with over 300 different types and causes. Although most headaches are of benign (and still poorly understood) origin, some headaches can have serious and even potentially life-threatening causes. Thus, it is critical for the physician to diagnose headaches as precisely as possible.

The International Headache Society (IHS) criteria,[1] which were introduced in 1988 and updated in 2004, are the worldwide standard for headache classification. IHS criteria categorize headaches as primary or secondary. Primary headaches—those with no other underlying cause—account for 90% of headaches. This category includes migraine, tension, cluster, and miscellaneous headaches, such as primary exertional headaches. There are a large number of secondary headaches, which are classified according to their causes [*see Table 1*].

A careful history, examination, and, in some cases, diagnostic testing will usually provide the accurate diagnosis of a headache, although a precise diagnosis is not always possible. For example, some benign headaches have both migraine and tension-type features. Chronic daily headaches may also be difficult to classify.

This chapter reviews pain-sensitive structures in the head, the history and examination in patients with headache, and many of the primary and secondary headaches. The interested reader may wish to refer to a headache textbook for more comprehensive information (see the reference list at the end of the chapter).[2-5]

Pain-Sensitive Structures

Similar headaches can have different causes because there are a limited number of pain-sensitive structures in the head. Although all pain is registered in the brain, the brain parenchyma itself is not pain sensitive. The arachnoid, ependyma, and dura (except portions near blood vessels) are also insensitive to pain. The following are sensitive to pain: cranial nerves V, VII, IX, and X; the circle of Willis and proximal continuations; meningeal arteries; large veins in the brain and dura; and structures external to the skull (including scalp and neck muscles, cutaneous nerves and skin, the mucosa of paranasal sinuses, teeth, cervical nerves and roots, and the external carotid arteries and branches).

Headache pain may be felt at its source (e.g., cheek or forehead pain from maxillary or frontal sinusitis) or be referred from another site. For example, supratentorial structures are innervated by the ophthalmic division of the trigeminal nerve, whereas infratentorial and posterior fossa structures are supplied by C_2 and C_3. Thus, a cerebellar hemisphere lesion generally refers pain posteriorly and an occipital lobe lesion refers pain anteriorly. The caudal nucleus of the trigeminal nerve, which is located from the midpons to the third cervical segment, receives pain messages from the upper cervical roots and the trigeminal nerve. Thus, pain from the upper cervical spine or posterior fossa can also be referred to the front of the head.

Headache History

The headache history is usually essential to establishing the diagnosis.[6] Key elements of the history include not only the features of the headache but also the patient's own diagnosis, past history, psychosocial history, and family history [*see Table 2*]. In gathering the key elements, both open-ended ("What are your headaches like?") and closed-ended ("Do you have nausea with the headache?") questions are necessary [*see Table 3*]. Often, it is helpful to ask about a history of mild headaches and bad headaches. Some patients are not able to clearly remember or articulate features of the headache ("It's just a headache, doc."). With patients who have chronic headaches, it may be necessary to provide a headache diary or have them record features of their headaches and then return for a later appointment.

Table 1 Major Categories of Headache Disorders[1]

Primary Headaches
Migraine
Tension-type headache
Cluster headache and chronic paroxysmal hemicrania
Miscellaneous headaches unassociated with structural lesion: idiopathic stabbing, external compression, cold stimulus, benign cough, benign exertional, associated with sexual activity
Secondary Headaches
Headache associated with head trauma
Headache associated with vascular disorder: acute ischemic cerebrovascular disorder, intracranial, hematoma, subarachnoid hemorrhage, unruptured vascular malformation, arteritis, carotid or vertebral artery pain, venous thrombosis, arterial hypertension, associated with other vascular disorder
Headache associated with nonvascular intracranial disorder: high and low cerebrospinal fluid pressure, intracranial infection, intracranial sarcoidosis and other noninfectious inflammatory disease, related to intrathecal injections, intracranial neoplasm, associated with other intracranial disorder
Headache associated with substances or their withdrawal: acute and long-term substance use or exposure, withdrawal after acute and long-term use, associated with substances with uncertain mechanism
Headache associated with noncephalic infection: viral infection, bacterial infection, other infection
Headache associated with metabolic disorder: hypoxia, hypercapnia, mixed hypoxia and hypercapnia, hypoglycemia, dialysis, other metabolic abnormality
Headache or facial pain associated with disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structures
Cranial neuralgias, nerve trunk pain, and deafferentation pain
Persistent pain of cranial nerve origin, trigeminal neuralgia, glossopharyngeal neuralgia, nervus intermedius neuralgia, superior laryngeal neuralgia, occipital neuralgia, central causes of head and facial pain other than tic douloureux

Table 2 Key Elements of the Headache History

Element	*Examples*
Temporal profile	
Age of onset	Migraine, usually ≤ 40 yr; temporal arteritis after age 50
Time to maximum intensity	Gradual in migraine; immediate in thunderclap headache
Frequency	Eight per day with cluster; a few in a lifetime with migraine
Time of day	Cluster or migraine on awakening; tension in the afternoon
Duration	Migraine, 4–72 hr; cluster, 15 min to 3 hr
Recurrence	Migraines recur about 30% of the time after relief with a triptan
Headache features	
Location	Cluster always unilateral; migraine unilateral or bilateral
Quality of pain	Migraine, throbbing; tension, pressure; cluster, boring
Severity of pain	Most severe headaches are migraine or cluster
Associated symptoms and signs	
Before headache	Migraine aura or prodrome, fever before meningitis
During headache	Nausea/vomiting in migraine, eye redness and tearing in cluster
After headache	Mental dullness after migraine
Aggravating or precipitating factors	
Trauma	Migraine, subdural hematoma
Medical conditions	Obesity in pseudotumor cerebri
Triggers	Present in 85% of migraineurs; stress in tension type
Trigger zones	Trigeminal neuralgia
Activity	Exertional headache, benign orgasmic cephalalgia
Pharmacologic	Oral contraceptives, rebound headaches
Relieving factors	
Nonpharmacologic	Sleep for migraine, relaxation for tension type
Pharmacologic	Prescription and over-the-counter drugs, herbs, and vitamins
Previous evaluation and treatment	Obtain medical records as appropriate
Psychosocial history	
Substance use	Rebound headaches from too much caffeine
Occupational and personal life	Stress, occupational toxin exposures
Psychological history	Depression, anxiety
Sleep history	Deprivation causing headaches; sleep apnea
Impact of headache	Missed school, work, family activities
Patient's own diagnosis	May incorrectly self-diagnose as brain tumor, sinus headache, aneurysm
Family history	70% of migraineurs have a first-degree relative with migraine
Complete medical and surgical history	Asthma as a contraindication to beta blockers for migraine

Physical Examination

A directed physical examination may be informative. Examples of significant abnormal findings include hypertension, fever, cervical lymphadenopathy in infectious mononucleosis, cervical trigger points in tension-type headache, and maxillary sinus tenderness in sinusitis. Every patient seen for headaches should have, at the least, a screening neurologic examination; this takes only a few minutes to perform. Although the results of this examination are usually normal, the examination can point to significant underlying disease by revealing abnormalities such as papilledema, a mild lateral rectus paresis, unequal pupils, a mild hemiparesis, or a Babinski sign.

Clinical Classification

In most cases, the findings on history and physical examination will point the clinician toward the diagnosis of primary headache. The three most common primary headaches are migraine, episodic tension type, and cluster headache [*see Table 4*]. Much less often, the clinical features suggest secondary headache [*see Table 5*].

Diagnostic Testing

The vast majority of headaches require no diagnostic testing at all; they can be diagnosed accurately on the basis of a detailed history and a physical examination.[7,8] For example, patients who meet IHS criteria for migraine rarely have abnormal neuroimaging findings to explain the headache. In patients with headache of any type and a normal neurologic examination, the yield of a computed tomographic or magnetic resonance imaging scan is only about 2% or less. However, certain clinical features, patient characteristics, and associated symptoms and signs justify neuroimaging for headaches [*see Table 6*].

Although a CT scan of the head will detect most pathologic conditions that cause headaches and it is the preferred study for acute head trauma and subarachnoid hemorrhage (SAH), an MRI scan is generally preferred for evaluation of headaches. An MRI may demonstrate pathology not seen on a standard CT scan, including abnormalities of the paranasal sinuses, pituitary, posterior fossa, cortical veins (e.g., superior sagittal sinus thrombosis), cervicomedullary junction (e.g., Chiari I malformation), intracranial aneurysms, carotid dissection, infarcts, white-matter abnormalities, congenital abnormalities, and neoplasms.

Electroencephalography (EEG) is not useful for the routine evaluation of patients with headache. However, EEG may be helpful if the patient has headaches and symptoms suggesting a seizure disorder or alteration of consciousness.

Blood tests are generally not helpful for the diagnosis of headaches, but specific tests are indicated when certain conditions are suspected. Such conditions, along with their indicated tests, include arteritis (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP] in temporal arteritis); infection (tests for infectious mononucleosis, Lyme disease, and HIV); and antiphospholipid antibody syndrome, which should be considered in patients with white-matter lesions on MRI. Complete blood counts and metabolic studies are indicated in suspected anemia, renal failure, or hypercalcemia; and endocrine studies are indicated in suspected hypothyroidism or pituitary tumors. Blood studies are also valuable as a baseline for monitoring adverse effects of certain medications for preventing headache (e.g., valproic acid and carbamazepine).

Lumbar puncture can be helpful in diagnosing meningitis, encephalitis, meningeal carcinomatosis, lymphomatosis, SAH, high cerebrospinal fluid pressure (e.g., pseudotumor cerebri), and low CSF pressure. MRI or CT scanning is always performed before a lumbar puncture for the evaluation of headaches, to rule out mass lesions, except in some cases in which acute meningitis is suspected. Lumbar puncture is often indicated for the first or worst headache, to exclude SAH [*see* First or Worst and Thunderclap Headaches, *below*]; headache with fever or other findings that suggest an infectious cause; a subacute or progressive headache in a patient with HIV infection or carcinoma; and an atypical chronic headache (e.g., to rule out pseudotumor cerebri in an obese woman without papilledema).

Migraine

EPIDEMIOLOGY

The 1-year prevalence of migraine is 18% in women, 6% in men, and 5% in children (both boys and girls). In the United States, 28 million persons have migraine each year.[9,10] The lifetime prevalence is 25% for women and 8% for men. Migraine begins before the age of 20 in 50% of cases and after the age of 50 in 2%; the highest prevalence is from 25 to 50 years of age. About 70% of migraineurs have a positive family history in a first-degree relative. The mode of transmission of susceptibility to migraine remains unclear; there is probably genetic heterogeneity. Interestingly, there is a high prevalence in neurologists (lifetime of 47% in males and 63% in females).[11]

The frequency of migraine can range from once in a lifetime to almost daily. The frequency of attacks in migraineurs is as follows: one to 12 a year, 38%; one to three a month, 37%; one a week, 11%; and two to six a week, 14%. Half of migraineurs do not know that they have migraine, with 42% of undiagnosed patients self-diagnosing themselves with so-called sinus headache and 43% having received a diagnosis of sinus headache from a physician.[10]

There are many disorders with a greater-than-coincidental association (comorbidity) with migraine, including stroke, epilepsy, systemic lupus erythematosus, Raynaud syndrome, multiple sclerosis, and essential tremor.[12] Psychiatric disorders comorbid with migraine include bipolar disorder, major depression, generalized anxiety disorder, panic disorder, and simple and social phobia. Migraine may also be associated with hypertension, mitral valve prolapse, and patent foramen ovale.[13]

Table 3 Helpful Questions to Ask for the Headache History[6]

Do you have different types of headaches or just one?
Where does the headache hurt?
When did you first start having these headaches?
What were you doing when the headache started?
How long before the headache reaches maximal intensity?
How long does the headache last?
Does the headache recur? If so, how often?
What is the pain like? Is it a pressure, throbbing, pounding, aching, or stabbing pain?
Is the pain mild, moderate, or severe?
On a scale of 1 to 10, with 10 the worst and 1 the least, how would you rate the headache?
Do you have trouble with your vision before or during the headache?
Do you have other symptoms (e.g., nausea, vomiting, light sensitivity, noise sensitivity, discomfort with eye movement) with the headache?
Are there signs present (e.g., fever, ptosis, miosis)?
Do you have triggers of your headaches (e.g., menses, stress, foods, beverages, lack of sleep, oversleeping, strong odors, trigger zones)?
What makes the headache worse (e.g., coughing, bending over, physical activity)?
What makes the headache better (e.g., sleep, lying down in a quiet room)?
Do your headaches have any impact on your life?
Do you take over-the-counter medications, vitamins, or herbs for your headaches? If so, how much and how often?
Do you drink caffeinated beverages? If so, what types and how many?
What prescription drugs have you tried and with what effect?
What doctors have you seen in the past for your headaches?
What other treatments have you tried and with what success (e.g., acupuncture, chiropractic, biofeedback, stress management, massage)?
Have you been under much stress lately?
Have you been depressed?
Do you have any parents or siblings with a history of migraines or bad headaches?

ETIOLOGY AND PATHOPHYSIOLOGY

Although the mechanism of migraine remains incompletely understood, there is growing evidence that migraine is a neurovascular disorder.[14] The aura that precedes some migraines is a slow march of visual or other neurologic symptoms associated with changes in neuronal activity that result in spreading neural depression from the occipital cortex. Excitatory changes produce increased blood flow, followed by reduced blood flow caused by neuronal inhibition.

The trigeminal nerve and the blood vessels it innervates may constitute the anatomic substrate for migraine pain. Input from the pain-sensitive cranial nerves and dura passes through the ophthalmic division of the trigeminal ganglion to the trigeminocervical complex (the trigeminal nucleus caudalis and dorsal horns of C_1 and C_2) that produces referred pain in the head (especially the ophthalmic division) and upper posterior neck. When the peripheral branches of the trigeminal nerve are activated during migraine, pain results from neurogenic inflammation that is produced by the antidromic release of calcitonin gene–related peptide by trigeminal nerve endings and that is associated with the release of other pain substances from plasma, platelets, and mast cells (e.g., histamine, prostaglandin, and serotonin). These substances induce vasodilatation and extravasation of plasma proteins and the sensitization of trigeminal nociceptive nerve endings. Throbbing pain and exacerbation by activities such as bending over, head movement, coughing, and walking may reflect mechanical hypersensitivity of meningeal C-fiber nociceptors. Nitric oxide released from blood vessels, perivascular nerve endings, or brain tissue can be a trigger for migraine pain.

Pain signals in the trigeminocervical complex undergo central processing, with second-order neurons receiving input and projecting rostrally to the contralateral thalamus (ventrobasal complex and medial nuclei) and then to the activating cortex (anterior cingulate, insular, and frontal), the periaqueductal gray matter (dorsal raphe nuclei), and the locus coeruleus. Aminergic areas in the periaqueductal gray matter and locus coeruleus influence the incoming pain and cortical blood flow. A continuous

Table 4 Features of Selected Primary Headaches[6]

Feature	*Migraine*	*Episodic Tension-Type*	*Episodic Cluster*
Female-to-male ratio	1:1 before puberty, 3:1 after	5:4	1:5
Family history	First-degree relatives affected in 80% of cases	Frequent	Rare
Typical age at onset (yr)	92% before age 40, 2% after age 50	20–40	20–40
Visual aura	20% of cases	No	Occasional
Location	Unilateral 60%, bilateral 40%	Bilateral > unilateral; anywhere on the head, posterior neck, face	Unilateral, especially orbital, periorbital, frontotemporal
Quality	Pulsatile or throbbing in 85%	Pressure, aching, tight, squeezing	Boring, burning, or stabbing
Severity	Mild to severe (moderate to severe [untreated] in 80%)	Mild to moderate	Severe
Triggers	Present in 85%; numerous	Stress, lack of sleep	Alcohol, nitrates
Duration	4–72 hr; duration > 24 hr (untreated) in 62%; may be < 1 hr in children	Hours to days	15 min to 3 hr
Frequency	Rare to frequent	Rare to frequent	1–8 a day during clusters
Periodicity	Menstrual migraine	No	Yes; average bout, 4–8 wk; average 1 or 2 bouts yearly
Associated features	Nausea in 80%, vomiting in 30%, light and noise sensitivity in 80%	Occasional nausea	Ipsilateral conjunctival injection, tearing, and nasal congestion or drainage; ptosis and miosis in 30%
Behavior during headache	Still, quiet, tries to sleep	No change	Often paces, agitated
Awakens patient from sleep	Can occur	Rare	Frequently

discharge in this pain-control system may occur from stimulation from the cortex or hypothalamus caused by stress or by excessive afferent input from the special senses or from cerebral or extracranial vessels. The migraine prodrome may originate in the hypothalamus.

CLINICAL FEATURES

Migraine can occur with or without an aura [*see* Migraine Aura, *below*]. Migraine without aura (formerly referred to as common migraine) occurs in 80% of migraineurs, and migraine with aura (formerly referred to as classic migraine) occurs in 20%. Most patients who have migraine with aura also have migraine without aura.

According to the IHS criteria for migraine without aura, the duration of untreated or unsuccessfully treated episodes ranges from 4 to 72 hours. The headaches are associated with at least two of the following pain characteristics: unilateral location; pulsating quality; moderate or severe intensity; and aggravation by, or resultant avoidance of, routine physical activity (e.g., walking or climbing stairs). The pain is accompanied by nausea, vomiting, or both, as well as by sensitivity to light (photophobia) and sound (phonophobia). Also, the patient has a history of at least five previous attacks that meet these criteria. If there are no indications that other primary etiologies may be responsible for the headaches, a diagnosis of migraine without aura can be reasonably established.[1]

Although the IHS criteria have been very useful for research purposes, most clinicians recognize migraine through familiarity with the general features [*see Table 4*]. Migraine pain is unilateral in 60% of cases and bilateral in 40%. About 15% of migraineurs report so-called side-locked headaches, with migraine always occurring on the same side. The pain will often be more intense in the frontotemporal and ocular regions before spreading to the parietal and occipital areas. Any region of the head or face may be affected, including the parietal region, the upper or lower jaw or teeth, the malar eminence, and the upper anterior neck. Throbbing pain is present in 85% of episodes of migraine, although up to 50% of patients describe nonthrobbing pain during some attacks. Along with having head pain, up to 75% of migraineurs report having unilateral or bilateral tightness, stiffness, or throbbing pain in the posterior neck. The neck pain can occur during the migraine prodrome, the attack itself, or the postdrome and is typically relieved by migraine medication such as a triptan.

Migraine persisting for more than 72 hours is termed status migrainosus. Without treatment, 80% of patients have moderate to severe pain and 20% have mild pain. The pain, which is usually increased by physical activity or movement, is associated with nausea in about 80% of episodes, vomiting in about 30%, photophobia in about 90%, and phonophobia in about 80%.[10] In children, migraine pain is bilateral in 60% and unilateral in 40%. The duration of the untreated headache in children can be 1 hour or more, much shorter than that in adults.

During an attack, 45% of migraineurs have at least one autonomic symptom (i.e., lacrimation, eye redness, ptosis, eyelid edema, nasal congestion, or rhinorrhea). These symptoms are caused by parasympathetic activation of the sphenopalantine ganglion, which innervates the tear ducts and sinuses, and these symptoms can lead to confusion of migraine with so-called sinus headaches.[15] Of patients with autonomic symptoms, 45% have both nasal and ocular symptoms, 21% have nasal symptoms only, and 34% have ocular symptoms only.

Prodromal symptoms (premonitory phenomena) may be present in about 10% of cases and precede the migraine attack by hours or by up to 1 or 2 days. Prodromal symptoms include changes in mental state such as depression, hyperactivity, euphoria, talkativeness, irritability, drowsiness, and restlessness. Neurologic symptoms may include photophobia, difficulty concentrating, phonophobia, dysphasia, hyperosmia, and yawning. General symptoms may include stiff neck, food cravings, feeling cold, anorexia, sluggishness, diarrhea or constipation, thirst, and fluid retention.

Triggers

Migraines are often triggered by environmental or other factors; 85% of migraineurs report triggers. Patients typically have multiple triggers, with a mean of three.[16] Up to 50% of migraineurs report that a change of weather is a trigger. Other environmental triggers are heat, high humidity, and high altitude. There are numerous additional triggers, including stress (reported by about 50% of patients), letdown after stress, vacations, and crying. Missing a meal (40%), lack of sleep, oversleeping, and fatigue are also commonly reported as triggers. Sensory triggers include bright lights, glare, flickering lights, loud noise, and strong smells such as perfume or cigarette

Table 5 Features of Selected Secondary Headaches[6]

Headache Type	*Epidemiology*	*Age of Onset*	*Location*	*Quality and Severity*	*Frequency*	*Associated Features*	*Comments*
Trigeminal neuralgia	4.3/100,000/yr; male-to-female ratio, 1.6:1	Usually > 40 yr; if < 40 yr, consider multiple sclerosis	Unilateral, 96%; second or third trigeminal division more often than first	Stabbing; electrical bursts; burning; lasts few seconds to < 2 min	Few to many a day	Trigger zone present in > 90% of cases	Usually due to vascular compression of CN V; scan needed to exclude occasional tumor
Brain tumor	Persons/yr: 24,000 primary, 170,000 metastatic	Any age	Often bifrontal; unilateral or bilateral; any location	Can be pressure or throbbing, mild to severe	Occasional to daily; usually progressive	Papilledema in 40%; at time of diagnosis, headache present in 30%–70%	Primaries in adults: lung, 64%; breast, 14%; unknown, 8%; melanoma, 4%; colorectal, 3%; hypernephroma, 2%
Pseudotumor cerebri	1/100,000/yr; 90% are female; 90% are obese	Mean of 30 yr	Often bifrontotemporal but can occur in other locations and unilaterally	Pulsatile; moderate to severe	Daily	Papilledema in 95%; transient visual obscurations in 70%; intracranial noises in 60%; CN VI palsy in 20%	MRI scan preferred to better exclude cortical venous thrombosis and posterior fossa lesions
Subarachnoid hemorrhage	30,000/yr caused by saccular aneurysm	Mean of 50 yr	Usually bilateral; any location	Usually severe but can be mild and gradually increasing	Paroxysmal	Often with nausea, vomiting, stiff neck, focal findings, syncope; stiff neck absent in 36%	CT scan abnormal on first day in 95%; third day, 74%; 1 wk, 50%; lumbar puncture may be essential for diagnosis
Temporal arteritis	In age > 50 yr, annual incidence of 18/100,000; male-to-female ratio, 3:1	Rare before 50 yr; mean age of 70 yr	Variable, unilateral, or bilateral; often temporofrontal	Often throbbing; may be sharp, dull, burning, or lancinating; mild to severe	Intermittent to continuous	50% have PMR; jaw claudication in 38%; 50% have absent pulse or tender STA	ESR WNL in up to 36%; CRP usually elevated; STA biopsy false negative in up to 44%
Acute paranasal sinusitis	More common in children (in whom frontal and sphenoid sinusitis are rare) than in adults	Any age	Frontal (forehead), maxillary (cheek), ethmoid (between eyes), sphenoid (variable)	Dull, aching; can be severe	Acute lasts from 1 day to 3 wk	Fever in about 50%; nasal congestion and purulent nasal drainage usually present (less often in sphenoid)	Well visualized on routine MRI but not on routine head CT scan; sinus CT is the best study
Subdural hematoma	Occurs in 1% after mild head injury; in chronic cases, up to 50% without history of head injury	Any age	Unilateral or bilateral	Mild to severe; may be aching, dull, or throbbing	Paroxysmal to constant	Normal neurologic exam in 50%; alteration in consciousness and focal findings may be present	MRI may detect the occasional isodense subdural hematoma, which can be missed on CT scan

CN—cranial nerve CRP—C-reactive protein ESR—erythrocyte sedimentation rate MRI—magnetic resonance imaging PMR—polymyalgia rheumatica STA—superficial temporal artery WNL—within normal limits

Table 6 Reasons to Consider Neuroimaging for Headaches[6]

Temporal and clinical features	First or worst headache Subacute headaches with increasing frequency or severity A progressive or new daily persistent headache Chronic daily headache Headaches always on the same side Headaches not responding to treatment
Patient characteristics	New-onset headaches in patients with cancer or HIV infection New-onset headaches after age 50
Associated symptoms and signs	Fever, stiff neck, nausea, and vomiting Aura and focal neurologic symptoms or signs in nonmigraine headache Papilledema, cognitive impairment, or personality change Seizures

smoke. Up to 50% of patients report alcohol as a trigger; this can be all forms of alcohol or only one type, such as red wine or beer. Up to 45% report food triggers such as chocolate, dairy products (particularly cheese), citrus fruits, fried foods, and nitrates and nitrites in cured meats or fish (e.g., frankfurters, bacon, and smoked salmon). Other triggers include minor head trauma, exertion, and nitroglycerin.

There are triggers unique to women. Half of women with migraine report menses as a trigger, and 14% have migraines associated only with their menses. During pregnancy, the frequency of migraines decreases (especially during the second and third trimesters) in 60%, remains the same in 20%, and increases in 20%. Migraines may occur for the first time when women start using oral contraceptives (OCs). Low-estrogen OCs usually have no effect on migraine or may even improve it, although frequency can increase. Of patients with new-onset migraine or increased frequency of migraine associated with OCs, 30% to 40% may improve when OCs are discontinued, although improvement may not occur for up to 1 year. Two thirds of women with prior migraine improve with physiologic menopause. Surgical menopause results in worsening of migraine in two thirds of cases.

Migraine Aura

The migraine aura has a total duration of usually less than 1 hour and frequently less than 30 minutes. An aura lasting more than 1 hour but less than 1 week is termed migraine with prolonged aura, or complicated migraine. The most common aura is a vision-related one, which is present in 99% of cases. There are two types: (1) positive visual phenomena, with hallucinations, and (2) negative visual phenomona, or scotomas, with either an incomplete or a complete loss of vision in a portion or all of the visual field. Most visual auras have a hemianoptic distribution. Photopsias consist of small spots, dots, stars, unformed flashes or streaks of light, or simple geometric forms and patterns that typically flicker or sparkle.

A scintillating scotoma, also called a fortification spectrum (because of its resemblance to a medieval fortified town as viewed from above) or teichopsia (seeing fortifications), is present in about 10% of cases. The scotoma, which is frequently semicircular or horseshoe shaped, usually begins in the center of the visual field and then slowly extends laterally. The scotomatous arc or band is a shimmering or glittering, bright, zigzag border. Most visual auras consist of flickering, colored or uncolored, unilateral or bilateral zigzag lines or patterns, semicircular or arcuate patterns, wavy lines, or irregular patterns. Rare visual auras include metamorphopsia (objects appear to change in size and shape), macropsia, micropsia, telescopic vision (objects appear larger than normal), teleopsia (objects appear to be far away), mosaic vision, Alice in Wonderland syndrome (distorted body image), and multiple images. Headaches, when unilateral, usually occur on the side contralateral to the visual symptoms but can occasionally be ipsilateral.

A sensory aura, which is present in about 30% of episodes of migraine with aura, consists of numbness, tingling, or a pins-and-needles sensation. The aura, which is usually unilateral, commonly affects the hand and then the face, or it may affect either one alone. Paresthesias of one side of the tongue is typical. Less often, the leg and trunk may be involved. A true motor aura is rare, but sensory ataxia or a heavy feeling is often misinterpreted as weakness.

Speech and language disturbances may occur in up to 20% of cases. Patients often report a speech disturbance when the spreading paresthesias reach the face or tongue. Slurred speech may be present. With involvement of the dominant hemisphere, paraphasic errors and other types of impaired language production and comprehension may occur. Rarely, other aura symptoms may be described, including déjà vu and olfactory and gustatory hallucinations.

Although visual symptoms frequently occur by themselves, combinations of aura symptoms can occur. Sensory, speech, and motor symptoms are usually associated with visual symptoms or with one or more other symptoms. When two or more aura symptoms are present, they almost always occur in succession rather than simultaneously.

Migraine aura can occur without headache (acephalgic migraine), often in patients whose migraine episodes typically involve headache (with or without aura). A visual aura is the most common in such cases. Another type of acephalgic migraine is episodic vertigo without a headache, auditory disturbances, or other neurologic symptoms, lasting minutes to days.[17] In older persons, the aura—termed late-life migraine accompaniment—can be confused with a transient ischemic attack [*see* Geriatric Headache, *below*]. Rarely, migraineurs have persistent visual aura. This usually consists of simple, unformed hallucinations in the entire visual field of both eyes, including innumerable dots, television static, clouds, heat waves, flashing or flickering lights, lines of ants, a rainlike or snowlike pattern, squiggles, bubbles, and grainy vision. Occasionally, palinopsia (the persistence of visual images), micropsia, or formed hallucinations occur.

Migraine Variants

Migraine variants include familial hemiplegic; basilar-type; benign paroxysmal vertigo of childhood; abdominal; confusional; so-called footballer's; benign episodic mydriasis; and retinal. Familial hemiplegic migraine is a rare variant of migraine with aura accompanied by hemiplegia or hemiparesis. Attacks may occur on the same side as previous episodes or on another side and typically feature a slow spread of paresis involving the face, arm, and leg. Alteration of consciousness, ranging from confusion to coma and aphasia, may be present. Familial hemiplegic migraine type I is caused by an autosomal dominant mutation in a brain-specific P/Q-type calcium channel subunit on chromosome 19.

Basilar-type migraine is a rare disorder that most often occurs in children and rarely occurs in patients older than 50 years.[18] According to IHS criteria, attacks are marked by two or more of the following fully reversible aura symptoms: dysarthria, vertigo, tinnitus, hypacusia, diplopia, visual symptoms simultaneously in the temporal and nasal fields of the two eyes, ataxia, decreased level of consciousness, and simultaneous bilateral paresthesias. These symptoms, which originate from the brain stem or both occipital lobes, are not accompanied by motor weakness. There is also at least one of the following: bilateral paresthesias; gradual development of at least one aura symptom over 5 minutes or longer, the occurrence of different aura symptoms in succession over 5 minutes or longer, or both; or persistence of each aura symptom for 5 to 60 minutes. Patients with basilar-type migraine may also have other types of migraine. Visual symptoms—which usually take the form of blurred vision, shimmering colored lights accompanied by blank spots in the visual field, scintillating scotoma, and graying of vision—may start in one visual field and then spread to become bilateral. Diplopia occurs in up to 16% of cases. Vertigo may be present, either alone or accompanied by various combinations of tinnitus, dysarthria, gait ataxia, and paresthesias (usually bilateral but sometimes affecting alternate sides in successive episodes). Impairment of consciousness is common and may include obtundation, amnesia, syncope, and, rarely, prolonged coma. A severe throbbing headache, typically with a bilateral occipital location, is present in 96% of cases. Nausea and vomiting typically occur, with light and noise sensitivity in up to 50% of cases.

Benign paroxysmal vertigo of childhood presents as episodes of vertigo without headache. Abdominal migraine also occurs in children and features recurring episodes of abdominal pain without headache that may be associated with nausea, vomiting, pallor, and flushing. Confusional migraine presents with a headache, which can be minimal, associated with a confusional state that can last from 10 minutes to 2 days. Agitation and impaired memory may be present. The patient may exhibit inattention, distractibility, and difficulty maintaining coherent speech or action. So-called footballer's migraine (originally described in soccer players) refers to the triggering of migraine by acute minor head trauma in children or adolescents.

Benign episodic mydriasis is a transient, isolated mydriasis. This disorder typically occurs in young adults or children. Patients have normal vision and pupillary reactivity to light that may occasionally accompany migraine headaches. The episodes last 15 minutes to 24 hours, are often associated with blurred vision, and can average two or three a month. Eyelid or ocular motility abnormalities are absent. Angle-closure glaucoma should be excluded. Dilatation of the pupil is secondary either to parasympathetic insufficiency of the iris sphincter or to sympathetic hyperactivity of the iris dilator. Retinal migraine, a rare diagnosis of exclusion, produces episodes of transient monocular visual loss lasting minutes to hours, which may or may not be associated with headache.

ACUTE TREATMENT

Certain general principles apply to the use of medications for acute (symptomatic) treatment of migraine. Early treatment, when the headache is mild, is much more effective than later treatment, when the migraine is moderate or severe in intensity. Frequent use of acute-treatment medications can lead to rebound headache; for that reason, acute therapy should be restricted to a maximum of 2 or 3 days a week. Different patients may respond to different medications at different times. Patients benefit from stratified care.[19] Treatment is based on characteristics of the patient's episodes (including peak intensity, time to peak intensity, associated symptoms, and disability) and is tailored to specific patient needs. Nasal, parenteral, or rectal administration of medication should be used in patients with significant nausea or vomiting or gastroparesis. Antinausea medications such as promethazine and prochlorperazine may help in such cases. Many migraineurs respond to over-the-counter medications for acute symptoms [*see Table 7*]. Over-the-counter drugs are often more effective if taken when the pain is mild rather than when it has become more intense.

Patients who do not respond or who respond incompletely to over-the-counter medications may require a prescription medication. The combination of isometheptene mucate, dichloralphenazone, and acetaminophen (Midrin) can be highly effective, especially for mild to moderate headache.[20] Combination medications that include butalbital (e.g., Fiorinal) may also be effective. Surprisingly, despite their common use, the butalbital combinations have not been studied in a placebo-controlled trial.[21] Oral and intranasal opiates may also be effective. Butorphanol nasal spray (Stadol) may be very effective for some patients who have severe migraine with nausea or vomiting and cannot keep an oral medication down, do not respond to triptans, or require a rescue medication when the usual medication is ineffective. Side effects include dizziness, nausea, vomiting, and drowsiness. However, frequent use of medications such as

Table 7 Efficacy of Selected Over-the-Counter Medications for Relief of Moderate to Severe Migraine Pain[75-78]

Medication and Dose	*Percentage of Responders at 2 Hr (Percentage Placebo)*		*Percentage of Responders at 6 Hr (Percentage Placebo)*	
	Mild or No Pain	*No Pain*	*Mild or No Pain*	*No Pain*
Ibuprofen, 400 mg	42 (28)	15 (8)	49 (32)	31 (20)
Acetaminophen, 1,000 mg	58 (39)	22 (11)	77 (46)	46 (28)
Acetaminophen, 500 mg, plus aspirin, 500 mg, plus caffeine, 130 mg	59 (33)	22 (7)	79 (52)	51 (23)
Aspirin, effervescent, 1,000 mg	55 (37)	29 (17)	Not assessed	

Note: Percentages are rounded.

butalbital and opiates can lead to rebound headaches and habituation.

Triptans

The introduction of the triptans has dramatically improved the acute treatment of migraine. Triptan medications are selective 5-hydroxytryptamine ($5\text{-}HT_{1B/1D}$) receptor agonists that share a basic indole ring structure with different side chains. Triptans have three potential mechanisms of action: cranial vasoconstriction, peripheral neuronal inhibition, and inhibition of transmission through second-order neurons of the trigeminocervical complex. These mechanisms inhibit the effects of activated nociceptive trigeminal afferents and control acute migraine attacks.[14]

Over the past decade, seven triptans have become available in the United States: sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, frovatriptan, and eletriptan [*see Table 8*].[22] In migraineurs who take oral triptans when their pain is moderate to severe in intensity, the 2-hour response rate (i.e., no pain or mild pain) is about 45% for naratriptan and frovatriptan and about 65% to 70% for the others. With all of the triptans, the 2-hour pain-free response rates are much higher if the drug is taken when the headache is mild; depending on the drug, the response rate may exceed 70%.

The oral triptans may not be equally effective for all patients. If a patient has an unsatisfactory or inconsistent response, unpleasant side effects, or tachyphylaxis with one triptan, a different triptan may prove to be effective and tolerable. Patients who have prominent vomiting or nausea or who desire the quickest relief may benefit from subcutaneous sumatriptan (at 2 hours, 79% of patients show a response and 60% are pain free) or intranasal sumatriptan or zolmitriptan.

Patients may experience a recurrence, which is defined as the return of headache (usually of moderate or severe intensity) within 24 hours after an initial response to acute treatment. When taken for moderate to severe pain, naratriptan, frovatriptan, almotriptan, and eletriptan have the lowest recurrence rates (about 20% to 25%). The recurrence rates for the other triptans are about 31% with zolmitriptan, 33% with sumatriptan, and 40% with rizatriptan. The time to recurrence is generally about 12 hours.[23]

Triptans can stimulate $5\text{-}HT_{1B}$ receptors on coronary arteries and result in constriction, which may become clinically significant in patients with coronary artery stenosis or vasospastic disease.[24] For example, in a study of patients undergoing cardiac catheterization, 6 mg of subcutaneously administered sumatriptan resulted in a 14% reduction in coronary artery diameter.[25] Consequently, triptans as a class are contraindicated in patients with known or suspected ischemic heart disease, Prinzmetal angina, or uncontrolled hypertension. Data on cardiac risk have been derived from the use of sumatriptan because sumatriptan has been the most widely used triptan and has the largest reported studies; however, all the triptans have a similar cardiac risk. The common triptan side effects—tightness, heaviness, pressure, or pain in the chest, neck, or throat—are not associated with electrocardiogram changes and are not caused by coronary vasoconstriction.[26]

The estimated chance of a myocardial infarction occurring within 24 hours of oral or subcutaneous use of sumatriptan is small but not negligible. Between 1991 and December 1996, 19 cardiac-related deaths occurring within 24 hours after the last sumatriptan dose were reported worldwide in five million migraineurs treating more than 100 million attacks.[26] In addition, there have been seven reported cases of atrial fibrillation triggered by sumatriptan,[27] possibly caused by transient elevations in atrial pressure.[28] In a prospective study of 23,339 migraineurs who used 6 mg of sumatriptan subcutaneously for up to 12 months, a total of 185,579 migraine attacks occurred.[29] There were a total of 13 cardiac events (three myocardial infarctions, six anginal episodes, and four cases of dysrhythmia) occurring 24 hours or more after the administration of sumatriptan. Subcutaneously administered sumatriptan is eliminated from the body within 10 hours, so the late cardiac events were probably unrelated to the drug. However, only about 15% of the patients in this study were older than 50 years and only a small percentage were older than 60 years.

In view of the potential adverse cardiovascular events associated with triptans, a cardiac evaluation is recommended for patients at risk for unrecognized coronary artery disease. The evaluation can be done before or during the use of triptans. Patients at risk include men older than 40 years, women older than 50 years, and those with cardiac risk factors. There is no consensus, however, on what constitutes an appropriate cardiac evaluation.[30]

INTRACTABLE MIGRAINE AND MIGRAINE STATUS

Intravenous fluids and electrolyte replacement may be necessary for patients with intractable vomiting associated with migraine. Medication options include the following:

1. Sumatriptan, 6 mg subcutaneously.
2. Dihydroergotamine (DHE), 0.5 to 1 mg by slow intravenous push, perhaps combined with an antiemetic such as metoclopramide, because DHE may cause nausea (DHE and triptans should not be used within 24 hours of each other).
3. Prochlorperazine, 5 to 10 mg intravenously.
4. Ketorolac, 30 to 60 mg intramuscularly.
5. Corticosteroids (a single or rapidly tapering dose of prednisone, starting at 80 mg a day, or dexamethasone, 6 mg orally or I.V.).

Table 8 Triptans Available in the United States

Drug (Brand Name)	*Formulation*	*Strengths (mg)*
Almotriptan (Axert)	Tablets	12.5
Eletriptan (Relpax)	Tablets	20, 40
Frovatriptan (Frova)	Tablets	2.5
Naratriptan (Amerge)	Tablets	1, 2.5
Rizatriptan (Maxalt)	Tablets Orally disintegrating preparation* (Maxalt MLT)	5, 10
Sumatriptan (Imitrex)	Subcutaneous injection Tablets Nasal spray	6 25, 50, 100 5, 20
Zolmitriptan (Zomig)	Tablets Orally disintegrating preparation* (Zomig ZMT)	2.5, 5

*Dissolves on the tongue; can be taken without water (efficacy similar to that of tablet form).

Table 9 Preventive Medications for Migraine

Drug Class	*Agent*	*Dosage*	*Typical Side Effects*
Beta blockers	Propranolol*	40–120 mg b.i.d.	Hypotension, tiredness, exacerbation of asthma
	Propranolol long acting*	60–160 mg/day	
	Metoprolol	50–200 mg/day	
	Nadolol	40–160 mg/day	
	Atenolol	50–100 mg/day	
	Timolol	10–30 mg/day	
Antidepressants	Amitriptyline*	25–150 mg h.s.	Drowsiness, dry mouth, weight gain, constipation
	Nortriptyline	25–150 mg h.s.	
	Venlafaxine	37.5–225 mg/day	Nausea and vomiting
Anticonvulsants	Divalproex sodium*	500–1,000 mg/day	Nausea, tremor, drowsiness, weight gain, alopecia, hematologic and liver abnormalities, fetal abnormalities
	Topiramate*	25–300 mg h.s.	Weight loss, paresthesias, cognitive disturbances, kidney stones
	Gabapentin	300–800 mg t.i.d.	Dizziness, fatigue, drowsiness

*Class I evidence indicates that these are the most effective medications for migraine prevention.

6. Parenteral narcotics such as meperidine, which may be combined with promethazine.
7. Valproate sodium (500 mg diluted in 50 ml of saline, administered intravenously over 5 to 10 minutes and repeated every 8 hours, if necessary).
8. Droperidol (2.5 mg I.M. or I.V.).
9. Intravenous metoclopramide.

There is a very small risk of torsade de pointes with the use of neuroleptics such as prochlorperazine and droperidol.

PREVENTIVE TREATMENT

A number of factors may justify daily preventive medication for patients with migraines [*see Table 9*].[31] Indications for preventive treatment are as follows:

1. The headaches significantly interfere with the patient's daily routine, despite acute treatment.
2. Acute medications are contraindicated, ineffective, or overused or have intolerable side effects.
3. Frequent migraines (two or more attacks a week).
4. Uncommon migraine types (hemiplegic, basilar, prolonged aura, or migrainous infarction).
5. The cost of acute medications is significantly greater than the cost of preventive medication.
6. Patient preference (i.e., the patient is willing to risk the possibility of side effects from the preventive medication to reduce the frequency of headaches).

Several general principles apply to the use of preventive medications[31]:

1. The clinician should start with a low dose of medication and increase it slowly, depending on the response and whether side effects occur.
2. Each medication should be given a trial of 2 to 3 months at adequate doses.
3. Overused medications that may be causing rebound headache and may decrease the efficacy of preventive treatment should be discontinued or tapered (depending on the drug).
4. The patient should keep a headache diary to monitor his or her headaches.
5. The clinician should educate the patient about the rationale for treatment and possible side effects and should address the patient's expectations for treatment. Many patients want a complete cure, and although this is certainly understandable, it is usually not possible.

Coexistent or comorbid conditions should be considered. Some medications may be effective against both migraine and another disorder. Other disorders, along with the migraine medications that may be effective against them, include epilepsy (divalproex sodium, topiramate, and gabapentin), hypertension (beta blockers), depression (tricyclic antidepressants), bipolar disorder (divalproex sodium or topiramate), insomnia (tricyclic antidepressants), essential tremor (beta blockers and topirimate), and overweight or obesity (topiramate). On the other hand, coexistent diseases such as depression or asthma may be relative contraindications to the use of beta blockers. In a woman who is pregnant or may become pregnant, the potential for teratogenesis should be considered. Patients who have mild responses to one preventive agent may benefit from the addition of a second agent. Finally, if a medication does not work or has significant side effects, withdrawal of the agent may need to be done slowly, especially if the patient has been receiving moderate or high doses of the drug. This is particularly true of tricyclic antidepressants and beta blockers.

Class I evidence indicates that the beta blocker propranolol, the tricyclic antidepressant amitriptyline, and the antiseizure medications divalproex sodium and topiramate are the most effective preventive medications, reducing the frequency of migraines by more than 50% in about 50% of patients. In general, preventive medications are more effective when patients are placed on a titration schedule with a minimum target dose. Titration schedules and minimum target doses are as follows:

propranolol (either regular or long acting), 40 mg daily, increased weekly by 40 mg to a maximum daily dose of 120 to 160 mg; amitriptyline, 10 mg at bedtime, increased weekly by 10 mg to a maximum daily dose of 50 mg; divalproex sodium (either regular or extended release), 500 mg daily for 1 week and then 1,000 mg daily; and topiramate, 25 mg daily for the first week, increased by 25 mg/wk in divided doses, to a maximum daily dose of 100 mg administered at a dosage of 50 mg twice daily.[32]

In addition to propranolol, other beta blockers may be effective [*see Table 9*]. Regarding the tricyclic antidepressants, the quality of evidence for nortriptyline is not as good as that for amitriptyline, but nortriptyline has been shown to have similar efficacy with less sedation. Venlafaxine may be as effective as amitriptyline with fewer side effects.[33,34] Selective serotonin reuptake inhibitors (SSRIs) are probably not effective for migraine prevention, and verapamil and gabapentin are only modestly effective.[31]

There are natural products that may be beneficial for migraine prevention, including the herb feverfew (*Tanacetum parthenium*); extract from the butterbur plant, *Petasites hybridus* (Petadolex, 75 mg twice daily); riboflavin (400 mg a day); coenzyme Q10 (100 mg three times daily[35]); and oral magnesium supplements. Botulinum toxin injections may also be of benefit, especially in intractable cases. The relative benefit of these treatments may become clearer with additional studies, but for now, some migraineurs may prefer them because they have few if any side effects.

For many migraineurs, the avoidance of triggers may be useful. Examples include adequate sleep at set hours, routine exercise, regular meals, avoiding triggering foods and beverages, and wearing sunglasses in bright sunlight or glare. Some patients may benefit from biofeedback, relaxation training, and psychotherapy.

WOMEN AND MIGRAINE

There are issues specific to treatment of female migraineurs.[36] Menstrual migraine is treated with the same acute-treatment medications as other migraines (see above). Interval or short-term preventive treatment of menstrual migraine, starting 2 or 3 days before menses and continuing during the menses, may be helpful for some women with regular menses and migraines that are poorly responsive to symptomatic medications. Potentially effective medications include the following: amitriptyline or nortriptyline, 25 mg at bedtime; long-acting propranolol, 60 to 80 mg daily, or nadolol, 40 mg daily; nonsteroidal anti-inflammatory drugs (NSAIDS) such as naproxen sodium, 550 mg twice daily; ergotamine, 1 mg once or twice a day, or DHE, 1 mg subcutaneously or intramuscularly; naratriptan, 1 mg orally twice daily, or frovatriptan, 2.5 mg twice daily, for 6 days perimenstrually; transdermal estradiol, 100 µg applied 3 days before the expected start of menses and replaced after 3 days; continuous combined OC use, with a lower estrogen dose given during the menses; and extended-duration OC use.

Although there is controversy regarding whether low-estrogen OCs increase the risk of stroke, most women who have migraine without aura can safely take low-estrogen OCs if they have no other contraindications or risk factors. When taking low-estrogen OCs, women younger than 35 years who have migraine with aura (e.g., visual symptoms lasting less than 1 hour) have a risk of ischemic stroke of about 30 per 100,000 annually, which is twice the risk of those women who have migraine without aura.[37] An IHS task force concluded that OCs may be contraindicated in women with migraine who have additional risk factors that cannot easily be controlled, including migraine with aura, because of a possible increase in the risk of ischemic stroke, and that these risks must be assessed and evaluated on an individual basis.[38] Women with aura symptoms such as hemiparesis or aphasia or prolonged focal neurologic symptoms and signs lasting more than 1 hour should avoid starting low-estrogen OCs and should stop the medication if they are already taking it. Progestin-only OCs and the many other contraceptive options can be considered, as appropriate. Cigarette smoking should be strongly discouraged, because female migraineurs who smoke one or more packs of cigarettes a day raise their risk of ischemic stroke by a factor of about 10.

Estrogen replacement therapy has a variable effect on migraine: 45% of patients show improvement, 46% show worsening of migraine, and 9% show no effect. If migraines increase when a patient starts estrogen replacement, the following strategies may be beneficial:

1. Reduce the estrogen dose.
2. Change the estrogen type to one less likely to promote migraine. From most to least likely to promote migraine, these are, in order, conjugated estrogens (Premarin), pure estradiol (Estrace), synthetic estrogen (Estinyl), and pure estrogen (Ogen).
3. Convert from interrupted to continuous dosing in the case of estrogen-withdrawal migraine.
4. Convert from oral to parenteral administration (e.g., a transdermal patch).
5. Add androgens.

Management of migraine during pregnancy and breastfeeding[39] is beyond the scope of this chapter.

Tension-Type Headaches

The 1-year prevalence of tension-type headaches has been variably reported as being from 30% to 90%. The lifetime prevalence is 78% (63% in males and 86% in females; the male-to-female ratio is about 1:1.3). The prevalence peaks in the fourth decade of life.

CLINICAL FEATURES

Tension-type headache may be episodic or chronic. The IHS criteria for episodic tension-type headache are as follows: at least 10 previous headache episodes fulfilling the criteria; number of days with the headache being less than 180 a year or 15 a month; and headache lasting from 30 minutes to 7 days. At least two of the following pain characteristics should be present: pressing/tightening (nonpulsating quality); mild or moderate severity; bilateral location; and no aggravation of headache by walking up and down stairs or performing similar types of routine physical activity. There should be no nausea or vomiting (anorexia may occur); and either photophobia or phonophobia may be present, but not both.

The pain is variably described as pressure, soreness, tightness, a band or cap on the head, or a weight on the head. During severe episodes, a pulsating sensation is occasionally present. Although 90% of episodic tension-type headaches are bilateral, these headaches can be unilateral in patients with trigger points or oromandibular dysfunction.

In chronic tension-type headache, according to IHS criteria,

the average headache frequency is 15 days or more a month for at least 6 months, or 180 days or more a year. The pain characteristics are the same as for episodic tension-type. There should be no concomitant vomiting, and no more than one of the following features should be present: nausea, photophobia, or phonophobia. Some patients may have continuous headaches for years. Secondary causes of episodic and chronic tension-type headaches should be excluded, as appropriate.

TREATMENT

Acute headaches may respond to the following: aspirin or acetaminophen, alone or in combination with caffeine; NSAIDs; isometheptene in combination with other agents; and butalbital with other agents. Overuse of any of these medications, however, may lead to rebound headaches. Frequent butalbital use can also result in dependency. The muscle relaxants baclofen and tizanidine may also be effective and are not habituating, whereas the muscle relaxant carisoprodol can be habituating. Tizanidine is an α_2-adrenergic agonist that inhibits the release and effectiveness of norepinephrine both at central sites (e.g., the locus coeruleus) and at the spinal cord. It has central muscle relaxant and antinociceptive effects. Tizanidine can be given at a dosage of 2 mg three times a day, or it can be started as 2 mg at bedtime and titrated upward to the maximum tolerated dose or a maximum dosage of 18 mg in three divided doses daily, depending on the response. Because about 5% of patients on tizanidine develop abnormally elevated transaminase levels, which reverse after discontinuance of the drug, baseline measures and periodic monitoring of liver function for the first 6 months are recommended. Tizanidine may be effective for chronic tension-type and chronic daily headaches.

Frequent headaches may require preventive medications. Tricyclic antidepressants are generally more effective than SSRIs. Other migraine preventive agents (see above) may be helpful, especially when tension-type headache and migraine are both present.

Chronic Daily Headache

Chronic daily headache (CDH) has a frequency of 15 or more days a month. The 1-year prevalence of CDH in adults is about 3% in males and 5% in females; it is about 1% in adolescents of both sexes. Severe CHD affects 0.5% of the population of the United States.

HEADACHE TYPES IN CDH

CDH includes four different headache types: chronic, or transformed, migraine (35% of patients with CDH); chronic tension-type headache, occurring in more than 50% of patients with CDH; hemicrania continua; and new daily persistent headache.

Chronic migraine, or transformed migraine, is a complication of intermittent migraine that usually occurs by 20 to 30 years of age. It may occur with or without medication overuse. In 70% of patients, there is a gradual transformation from episodic migraine to CDH that may be associated with analgesic overuse, psychological factors (e.g., depression, anxiety, abnormal personality profile, and home or work stress), and obesity. In 30% of patients, there is a sudden transformation that may be triggered by head or neck trauma, flulike illness, aseptic meningitis, surgery, or medical illness. Migraine characteristics are present to a significant degree, intermittently or continuously.

Chronic tension-type headache, with or without medication overuse, occurs 15 days a month for at least 6 months or occurs at least 180 days a year [*see* Tension-Type Headaches, *above*]. Hemicrania continua, with or without medication overuse, is a rare entity with constant, unilateral pain of variable intensity that responds dramatically to indomethacin. Painful exacerbations are associated with ptosis, lacrimation, and nasal congestion. New daily persistent headache, with or without medication overuse, involves a fairly rapid onset of a daily persistent headache in a patient with no past history of increasingly frequent migraine or tension-type headache.[40] This is probably a heterogeneous disorder of uncertain cause, which in some cases may be triggered by a viral infection.

TREATMENT

If medication-overuse or rebound headaches (see below) are a possibility, medications that may be responsible should be tapered. Some acute-treatment medications that may be effective are longer-acting NSAIDs (e.g., naproxen sodium), baclofen, tizanidine, and hydroxyzine (50 mg p.o., t.i.d., p.r.n.), which are not associated with rebound. Triptans may be used as appropriate but should be limited to 2 or 3 days a week because of the risk of rebound.

For prevention of CDH, the same medications are used as for chronic tension-type headache and migraine. Combination therapy may be helpful in some cases. The effect of treatment may not be apparent for weeks. Treatment may not be effective until rebound is eliminated.

For detoxification or if there is significant medical or psychiatric comorbidity, inpatient treatment may be indicated if outpatient therapy fails. Options include intravenous DHE (0.5 to 1.0 mg I.V.), usually given with an antiemetic (e.g., metoclopramide, 5 to 10 mg I.V.) every 8 hours. DHE may be combined with other medications, such as NSAIDs, oral or intravenous corticosteroids, intravenous prochlorperazine, and intravenous valproate sodium [*see* Intractable Migraine and Migraine Status, *above*]. One or more of these treatments can be used in patients who cannot tolerate DHE or patients in whom DHE is contraindicated.

Behavioral therapy and psychological or psychiatric referral may be beneficial. Physical therapy may be useful if there is a myofascial contribution to the headaches. Trigger-point injections and occipital nerve blocks may be worthwhile in some cases.

Even with optimal therapy, about one third of patients who show improvement will experience recurrence of their daily headache and medication-overuse pattern. Some patients have intractable CDH that is resistant to all treatments.

Medication-Overuse Headaches

Migraineurs are particularly susceptible to medication-overuse or rebound headaches, which can occur with frequent use of symptomatic medications, including acetaminophen, aspirin, caffeine, NSAIDs with short half-lives (e.g., ibuprofen), butalbital, ergotamine, opiate agonists, and triptans.[41] Frequent use of symptomatic medications may also result in tolerance (the decreased effectiveness of the same dose of an analgesic, often leading to the use of higher doses to achieve the same degree of effectiveness) and in habituation and dependence (respectively, the psychological and physical need to repeatedly use drugs).

Rebound headache is a retrospective diagnosis made when headache frequency decreases after the patient stops or reduces

the medication suspected of causing the headache. The best evidence is from a prospective study of caffeine-withdrawal headache in persons with low to moderate caffeine intake (the equivalent of about 2.5 cups of coffee daily). In this study, 50% of persons given placebo had a headache by day 2, compared with 6% of those given caffeine.[42] Withdrawal was also associated with nausea, depression, and flulike symptoms.

Because it would be unethical to conduct prospective studies on rebound headache from medication withdrawal, only limited information is available regarding the percentage of migraineurs who are susceptible to rebound, the dosage limits, and the time required for rebound to develop. Medication overuse may occur when simple analgesics are taken 15 or more days a month for 3 months; when triptans are taken 10 or more days a month; when combination analgesics containing simple analgesics plus opioids, butalbital, or caffeine (alone or together) are taken for 10 or more days a month for 3 months; and when opioids are used 10 or more days a month.[43]

In the treatment of suspected rebound headache, the medications acetaminophen, aspirin, NSAIDs with short half-lives, and triptans can be stopped abruptly. Caffeine use should be tapered off, to avoid withdrawal symptoms. Opiates and butalbital should be tapered because of the risk of a serious withdrawal syndrome. If butalbital is abruptly discontinued, phenobarbital can be substituted to prevent withdrawal; the phenobarbital is tapered down from 60 mg to 15 mg at night over 1 week.[44] After medication withdrawal, the duration of rebound headaches from triptans is about 4 days and from other analgesics is about 9 days.[45] A migraine preventive medication can also be started, but it may not be effective when patients are overusing symptomatic medications.

Two outpatient transitional strategies have been suggested to reduce the headaches during the withdrawal period. One approach is the use of prednisone: 60 mg/day for 2 days, 40 mg/day for 2 days, and then 20 mg/day for 2 days.[46] Alternatively, the combination of tizanidine and a long-acting NSAID such as naproxen may be effective.[47] Inpatient treatment is the same as for CDH (see above).

Drug-Induced Headache

Many drugs can induce acute headache, including nitroglycerin, antihypertensive agents (beta blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and methyldopa), dipyridamole, hydralazine, phosphodiesterase-5 inhibitors (e.g., sildenafil), histamine receptor antagonists (e.g., cimetidine and ranitidine), NSAIDs (especially indomethacin), cyclosporine, and antibiotics (especially amphotericin, griseofulvin, tetracycline, and sulfonamides).

Drug-induced aseptic meningitis, a rare occurrence, has numerous possible causes, including NSAIDs, antibiotics (e.g., trimethoprim-sulfamethoxazole, sulfasalazine, cephalosporins, ciprofloxacin, isoniazid, and penicillin), intrathecal drugs and diagnostics (e.g., antineoplastic agents such as methotrexate and cytarabine; gentamicin; corticosteroids; spinal anesthesia; baclofen; repeated iophendylate for myelography; and radiolabeled albumin); intraventricular chemotherapy; intravenous immunoglobulin; vaccines (polio; measles, mumps, and rubella; and hepatitis B); and other drugs, such as carbamazepine, muromonab-CD3, and ranitidine.[48]

The clinical presentation of drug-induced aseptic meningitis is the same as that of viral meningitis. CSF findings are the same as those in viral meningitis, except for a neutrophil predominance; however, in cases induced by intravenous immunoglobulin, eosinophils are present.

Cluster Headaches

Cluster headaches are an uncommon headache type, occurring in only about 0.4% of the general population. Cluster headaches are five times more common in men than in women. The headaches can occur at any age, including childhood and adolescence (although they are rare in children younger than 10 years), but usually begin in the third or fourth decade of life. As the name denotes, this condition is marked by periods of recurrent headaches (one to eight a day) interspersed with periods of remission. In 90% of patients, the clusters occur episodically. In the remaining 10%, the clusters are chronic, with cluster periods lasting for more than 1 year without remission or with remission lasting less than 14 days.

CLINICAL FEATURES

Cluster headaches are one sided and severe. The most common types of pain, in order of decreasing frequency, are orbital, retro-orbital, temporal, supraorbital, and infraorbital. The headache may alternate sides between cluster periods or, rarely, within the same period. The pain is described as constant, boring, pressing, burning, or stabbing; about 30% of patients describe throbbing or pulsating pain. Cluster headaches have a rapid onset, with peak intensity in 5 to 10 minutes, and usually a short duration of 30 to 45 minutes, although a minority of patients may have pain persisting up to 3 hours (rarely longer). During attacks, most patients prefer to walk, sit, kneel, stand, or jog in place. Many find it difficult to lie down, and they feel restless and agitated.

Autonomic symptoms are present in over 97% of cases. Lacrimation and conjunctival injection are each present in about 80% of cases, and ipsilateral nasal congestion or clear drainage is present in 75%.[49] A partial Horner syndrome with a slight ipsilateral ptosis or miosis or a combination of both is present in about 65% of cases and, in some patients, may persist between attacks in later stages of the disorder. Increased forehead sweating may occur in some patients during attacks. Erythema of the eyelid or a circumscribed area of the face or forehead may be present. Nausea and sensitivity to light and noise accompany the headache in some patients. An aura, usually visual, occasionally precedes the headache. Small quantities of alcohol, nitroglycerin, and histamine can trigger attacks during cluster periods but not during remission.

DIAGNOSTIC TESTING

Cluster headaches can usually be diagnosed on the basis of the clinical criteria alone. Neuroimaging, preferably MRI, may be considered in cases with the following features: a pattern of clusterlike headache that does not conform to the clinical criteria; onset of cluster headache after age 40; a progressive pattern of headaches; chronic cluster headache; and any focal neurologic deficit other than Horner syndrome.

Symptomatic or secondary cluster headache can result from head trauma or iatrogenic trauma (e.g., orbital enucleation or dental extraction). A variety of pathologic conditions have been associated with clusterlike headaches, including arteriovenous malformations, aneurysms, sphenoid sinusitis, parasellar tumors, upper cervical cord meningioma and infarction, subdur-

al hematoma, cerebral metastases, and temporal arteritis. These headaches are usually atypical in their lack of periodicity or response to medications or their accompaniment with abnormal neurologic signs.

TREATMENT

For acute attacks of cluster headache, inhalation of 100% oxygen at a rate of 7 to 10 L/min for 15 to 20 minutes with a nonrebreathing face mask is effective in about 60% of cases.[50] Sumatriptan, 6 mg subcutaneously, is effective in about 75% of all cluster headache patients, with no tachyphylaxis or rebound effect in most patients. Intranasal sumatriptan or oral triptans are less efficacious. Intravenous DHE, 1 mg, may provide relief in less than 10 minutes; onset is slower with intramuscular or intranasal administration. Triptans and DHE should not be used within 24 hours of each other. Ergotamine may also be effective. Topical lidocaine 4%, administered as nosedrops, may be effective in at least one third of patients. To administer the drops, the patient lies supine with the head tilted backward 30° and turned to the side of the headache. A nasal dropper may be used. The dose (1 ml) may be repeated once after 15 minutes. Butorphanol nasal spray may be tried if other treatments are not effective or are contraindicated, but this medication has a significant potential for habituation and addiction.[51]

Transitional treatments are medications that may induce rapid suppression of attacks before a preventive medication takes effect. Transitional treatments include prednisone, 60 mg daily for 3 days, followed by 10 mg decrements every 3 days (the drug is given in the morning to prevent interference with sleep); ergotamine tartrate, 1 mg orally twice a day, including a bedtime dose if nocturnal attacks occur (the drug is contraindicated in patients with peripheral vascular and cardiovascular disease; ergotamine and triptans should not be used within 24 hours of each other); DHE, 0.5 to 1.0 mg subcutaneously or intramuscularly every 8 to 12 hours; and a greater occipital nerve block on the side ipsilateral to the attacks, using 120 mg of methylprednisolone and 3 ml of 1% lidocaine.

A number of medications may be effective for prevention of cluster headaches. Verapamil is the drug of choice for both episodic and chronic types. It is started at 120 to 240 mg a day and slowly increased (up to 80 mg increase every 3 days) to 480 mg if necessary.[50] The drug can be given in both a regular formulation three times daily and an extended-release formulation once a day. In some cases of chronic cluster headache, a daily dose of more than 720 mg may be necessary. With daily doses of 240 mg or higher, baseline and serial electrocardiograms are indicated to monitor for the development of heart block. Methysergide may be effective for younger patients with episodic cluster headache who have no contraindications for its use. Methysergide is started at 2 mg three times a day and increased to 12 mg daily if necessary. It may be best to avoid combining methysergide with ergotamine, DHE, or triptans because of the potential for additive vasoconstrictor effect. However, methysergide has limited availability in the United States. Other medications that may be effective include topiramate (50 to 125 mg daily); divalproex sodium (500 to 2,000 mg daily); lithium carbonate (150 to 300 mg t.i.d. with monitoring of blood levels), especially for chronic rather than episodic cluster; baclofen (10 mg t.i.d.); and melatonin, 10 mg at bedtime. Topical capsaicin cream 0.025% may be effective; it is applied with a cotton-tipped applicator 0.5 in. up the nostril on the same side as the headache three times daily for 7 days. For chronic or intractable cases, combination therapy can be used.

Surgical treatment may be useful for patients with total resistance to medical treatment and strictly unilateral pain. Options include percutaneous radiofrequency retrogasserian rhizotomy, gamma-knife radiosurgery to ablate the trigeminal nerve root, and percutaneous retrogasserian glycerol rhizolysis.

Geriatric Headache

Older persons have fewer headaches than younger ones. The prevalence of headaches at different ages in women and men, respectively, is as follows: 21 to 34 years, 92% and 74%; 55 to 74 years, 66% and 53%; and after age 75, 55% and 22%.[52] Although 90% of headaches in younger patients are of the primary type, only 66% of headaches in the elderly are primary.[53] There is a decreasing prevalence of migraine with older age. Past the age of 70 years, only 5% of women and 2% of men still have migraine. There are many causes of new-onset headaches in the elderly, some of which can be particularly worrisome.[54] The risk of serious secondary disorders in persons older than 65 years is 10 times higher than that in younger persons.[55]

LATE-LIFE MIGRAINE ACCOMPANIMENTS

Late-life migraine accompaniments are transient visual, sensory, motor, or behavioral neurologic manifestations that are similar or identical to migraine aura.[56] Headache is associated with only 50% of cases and may be mild. These accompaniments occur more often in men than in women. From most to least common, migraine accompaniments consist of visual symptoms (transient blindness, homonymous hemianopsia, and blurring of vision); paresthesias (numbness, tingling, pins-and-needles sensation, or a heavy feeling of an extremity); brain stem and cerebellar dysfunction (ataxia, clumsiness, hearing loss, tinnitus, vertigo, and syncope); and disturbances of speech (dysarthria or dysphasia).

Other causes of transient cerebral ischemia should be considered, especially when the patient is seen after the first episode or if the case has unusual aspects. The usual diagnostic evaluation for transient ischemic attacks (TIAs) or seizures is performed [*see 11:IV Cerebrovascular Disorders and 11:XII Epilepsy*].

Features that help distinguish migraine accompaniments from TIAs include a gradual buildup of sensory symptoms; a march of sensory paresthesias; serial progression from one accompaniment to another; longer duration (90% of TIAs last for less than 15 minutes); and multiple stereotypical episodes.

If the episodes are frequent, preventive treatment can be considered with medications such as verapamil, topiramate, divalproex sodium, and aspirin. Beta blockers should be avoided because of the potential for worsening of vasospasm. For acute treatment, ergotamine, DHE, and triptans should be avoided because of the risk of increasing cerebral vasospasm.

CEREBROVASCULAR DISEASE

Headaches commonly accompany stroke. In a prospective study of 163 patients with stroke, headache occurred in 29% with bland infarcts, 57% with parenchymal hemorrhage, 36% with TIAs, and 17% with lacunar infarcts.[57] Women and patients with a history of recurrent throbbing headaches were more likely to have headaches associated with stroke. The headache began before the stroke in 60% of cases and at its onset in 25%. The quality, onset, and duration of stroke-associated headaches vary widely. The headaches are equally likely to be abrupt and to be gradual in onset. In patients presenting with

what they consider to be the worst headaches of their lives, SAH should be excluded.

Headache accompanying stroke is usually unilateral, focal, and of mild to moderate severity, although up to 46% of patients may have an incapacitating headache. The headache may be throbbing or nonthrobbing and, in rare cases, may be stabbing. The headache is more often ipsilateral than contralateral to the side of the cerebral ischemia. Headache is more common in ischemia of the posterior circulation than of the anterior circulation and more common in cortical than in subcortical events. The headache is of longest duration in cardioembolic infarcts and thrombotic infarcts, of medium duration in lacunar infarction, and of shortest duration in TIAs.

HEAD TRAUMA

Although there are numerous causes of head trauma, falls are of particular concern in the elderly. Approximately 30% of all persons older than 65 years fall at least once a year. Subdural hematomas follow approximately 1% of mild head injuries, even those involving no loss of consciousness, such as a bump on the head or riding a roller coaster. Chronic subdural hematomas occur more often in the elderly because of brain atrophy that causes stretching of the parasagittal bridging veins and a predisposition to tearing. The atrophy in an older person also permits hematomas to accumulate without symptoms for a longer period of time than it does in a younger person. Other risk factors include use of aspirin or warfarin[58] and alcoholism.

Headaches are present in up to 90% of patients with head trauma. The headaches are nonspecific; they can range from mild to severe and from paroxysmal to constant and can be bilateral or unilateral. They may be exacerbated by coughing, straining, or exercise and may be associated with vomiting or nausea. About 50% of patients with chronic subdural hematomas will have altered mental status. A strokelike presentation with a transient or persistent hemiparesis can also occur. Only about 50% of patients with a chronic subdural hematoma will have a history of a head injury. The history may also be inaccurate in patients with dementia.

TEMPORAL ARTERITIS

Temporal (giant cell) arteritis (TA) is a systemic panarteritis that selectively involves arterial walls with significant amounts of elastin. Approximately 50% of patients with TA have polymyalgia rheumatica, and about 15% of patients with polymyalgia rheumatica have TA. Both conditions occur almost exclusively in patients older than 50 years, with a mean age of onset of about 70. The ratio of women to men with TA is 3 to 1. The annual incidence is about 18 per 100,000 population in persons older than 50 years.

Headaches are the most common symptom of TA, reported by 60% to 90% of TA patients.[59] The pain is most often throbbing, although many patients describe a sharp, dull, burning, or lancinating pain. The pain may be intermittent or continuous and is more often severe than moderate or slight. For some patients, the pain may be worse at night when lying on a pillow, while combing the hair, or when washing the face. Tenderness or decreased pulsation of the superficial temporal arteries is present on physical examination in about half of all patients with TA. The location of the headache is variable and may be unilateral or bilateral. Intermittent jaw claudication occurs in 38% of cases.

The diagnosis of TA is based on clinical suspicion, which is usually but not always confirmed by laboratory testing.[60] The three best tests are the Westergren ESR, the CRP level, and temporal artery biopsy. For elderly patients, the ESR range of normal may vary from less than 20 mm/hr to 40 mm/hr. Elevation of the ESR is not specific for TA; elevation of the ESR can be seen in any infectious, inflammatory, or rheumatic disease. TA with a normal ESR has been reported in 10% to 36% of patients. When abnormal, the ESR averages 70 to 80 mm/hr and may reach 120 or even 130 mm/hr. If the ESR is elevated at the time of diagnosis, it can be followed to help guide the corticosteroid dosage.

CRP is an acute-phase plasma protein from the liver. As with the ESR, elevation of CRP levels is nonspecific and can be seen with numerous disorders. The CRP level is not influenced by various hematologic factors or age and is more sensitive than the ESR for the detection of TA. The combination of ESR and CRP levels gives the best specificity (97%).

The diagnosis of TA is made with certainty when a superficial temporal artery biopsy demonstrates necrotizing arteritis characterized by a predominance of mononuclear cell infiltrates or a granulomatous process with multinucleated giant cells. The false negative rate of temporal artery biopsies ranges from 5% to 44%.

In patients without contraindications, treatment of TA is typically started with prednisone at a dosage of 40 to 80 mg a day. The headache will often improve within 24 hours. The initial dose is maintained for about 4 weeks and then slowly reduced over many months, depending on the clinical effect, the ESR, and the occurrence of side effects. Long-term treatment is often required.

TRIGEMINAL NEURALGIA

Trigeminal neuralgia begins after the age of 40 in 90% of cases. About 80% of cases result from vascular compression of the trigeminal nerve at the root entry zone; most commonly, such compression is caused by a branch of the superior cerebellar artery. About 5% of cases are caused by tumors. The pain is a severe, sharp, shooting, or electric shock–like sensation lasting seconds to 2 minutes. It is usually in a unilateral maxillary or mandibular trigeminal distribution and uncommonly in the ophthalmic division.[61]

In about 90% of cases of trigeminal neuralgia, the patient has trigger zones, usually in the central part of the face around the nose and lips. Normally nonpainful stimuli in these zones can trigger pain. Stimuli can include talking, chewing, washing the face, brushing the teeth, shaving, facial movement, and cold air. After a paroxysm of pain, there is a refractory period lasting up to several minutes during which stimulation of the trigger zone will not trigger pain. Facial grimacing or spasm may accompany the pain (tic douloureux). Between painful paroxysms, the patient is usually pain free, although dull aching may persist for a few minutes after attacks of long duration or multiple clustered attacks. Multiple attacks may occur for weeks or months. About 50% of patients with trigeminal neuralgia will have spontaneous remissions for at least 6 months. Physical examination is usually normal except for trigger zones, although up to 25% of patients will have sensory loss.

Medications that may be effective against trigeminal neuralgia, alone or sometimes in combination, include carbamazepine, oxcarbazepine, baclofen, phenytoin, clonazepam, divalproex sodium, topiramate, lamotrigine, gabapentin, and pimozide. About 30% of patients do not respond to medical treatment but may respond to one of the many surgical approaches available.

POSTHERPETIC NEURALGIA

Although herpes zoster most commonly occurs in the thoracic region, the second most commonly involved area is a trigeminal distribution, usually in the ophthalmic division (herpes zoster ophthalmicus), which occurs in 23% of cases. The zoster is almost always unilateral. The incidence of postherpetic neuralgia (PHN) (i.e., the persistence of pain for more than 1 month after the initial outbreak) greatly increases with older age, to about 1,000 per 100,000 population for those who are 80 years of age or older. PHN develops in 50% of persons older than 50 years and in 80% of those older than 80 years. Zoster involving the face nearly doubles the risk of developing facial PHN, which lasts longer than PHN in other locations.

Typically, the vesicles crust, the skin heals, and the pain resolves within 3 to 4 weeks after the onset of the rash of herpes zoster. PHN involves three types of pain: a constant burning or deep aching; an intermittent spontaneous pain with a jabbing or lancinating quality; and a superficial, sharp, or radiating pain or itching provoked by light touch (allodynia), which is present in 90% of persons with PHN and often interferes with sleep.[62] The type of pain experienced varies from patient to patient.

Treatment with oral corticosteroids (e.g., prednisone, starting at 60 mg/day and tapering off over 2 weeks) may reduce acute pain in herpes zoster but does not lower the risk of PHN. One week of therapy with famciclovir (500 mg every 8 hours) or valacyclovir (1,000 mg every 8 hours), ideally started within 72 hours after onset of acute zoster, mildly reduces the risk and duration of PHN.[63] Numerous treatments of varying efficacy are available for PHN, including tricyclic antidepressants (amitriptyline, nortriptyline, and desipramine), duloxetine, gabapentin, pregabalin, topical agents (capsaicin, lidocaine, aspirin, and NSAIDs), opioids, and tramadol. Unfortunately, PHN persists for 1 year or more in over 20% of patients.

CARDIAC ISCHEMIA

In rare cases, cardiac ischemia can cause a unilateral or bilateral headache brought on by exercise and relieved by rest.[64] The headache can occur alone or can be accompanied by chest pain. Angina is generally believed to be caused by afferent impulses that traverse cervicothoracic sympathetic ganglia, enter the spinal cord via the first to the fifth thoracic dorsal roots, and produce the characteristic pain in the chest or inner aspects of the arms. Cardiac vagal afferents, which mediate anginal pain in a minority of patients, join the tractus solitarius. A potential pathway for referral of cardiac pain to the head would be convergence with craniovascular afferents.[65]

HYPNIC HEADACHE

Hypnic headache is a rare disorder that occurs more often in the elderly (but with a range of 36 to 83 years of age) and predominantly in women.[66] The headache occurs only during sleep and awakens the sufferer at a consistent time. Nausea is infrequent, and autonomic symptoms are rare. The headache can be unilateral or bilateral, throbbing or nonthrobbing, and mild to severe in intensity. The headaches can last 15 minutes to 3 hours and can occur frequently, as often as nightly, for many years. Medications reported to be effective include caffeine (one or two cups of caffeinated coffee or a 40 to 60 mg caffeine tablet before bedtime), lithium carbonate (300 mg at bedtime), indomethacin, atenolol, melatonin, cyclobenzaprine, prednisone, and flunarizine (not available in the United States).

The diagnosis of hypnic headache is one of exclusion. Secondary causes of nocturnal headaches that must be ruled out include drug withdrawal, temporal arteritis, sleep apnea, oxygen desaturation, pheochromocytoma, primary and secondary neoplasms, communicating hydrocephalus, subdural hematoma, and vascular lesions.[67] Migraine, cluster, and chronic paroxysmal hemicrania are other primary headaches that can cause awakening from sleep. Migraine typically has associated symptoms and very uncommonly occurs only during sleep. Cluster headaches have autonomic symptoms and may occur during the day as well as during sleep. Chronic paroxysmal hemicrania occurs both during the day and at night, lasts for less than 30 minutes, and occurs 10 to 30 times a day.

Other Headaches

Numerous other types of headache have been identified. The more common of these are briefly discussed.

FIRST OR WORST AND THUNDERCLAP HEADACHES

The term first or worst refers to severe headache of a type the patient has never experienced before, which may be the first episode of a primary headache such as migraine or cluster, or to the worst headache the patient has ever had, which can be caused by numerous primary and secondary disorders [*see Table 10*].[6]

Headache in Subarachnoid Hemorrhage

Headache is present in 90% of cases of subarachnoid hemorrhage, or SAH.[68] The classic headache is sudden, severe, and continuous, often with nausea, vomiting, meningismus, focal neurologic findings, and loss of consciousness [*see 11:IV Cerebrovascular Disorders*].

Thunderclap Headache

A sudden severe headache with maximal onset within 1 minute without evidence of SAH is termed a thunderclap headache.[69] A small percentage of patients with thunderclap headache will have unruptured aneurysms, cerebral vasospasm, cerebral venous thrombosis, carotid artery or vertebral artery dissections, pituitary apoplexy, occipital neuralgia, and possibly Erve virus infection. Most cases of thunderclap headache are primary disorders: primary thunderclap headache, so-called crash migraine, and primary orgasmic headache.

COUGH, EXERTIONAL, AND SEXUAL HEADACHES

Primary cough, exertional, and sexual headache have lifetime prevalence rates of 1% each. All three types occur more often in men.[70]

Primary cough headache is a bilateral headache of sudden onset that is precipitated by coughing and lasts less than 1 minute. About 25% of patients have the onset after a respiratory infection with cough. This is an infrequent type of headache, with patients having a mean age of onset of 55 years. The diagnosis is one of exclusion. Patients should undergo neuroimaging to exclude pathology such as Chiari malformation, platybasia, basilar impression, brain tumors, cerebral aneurysm, carotid stenosis, and vertebrobasilar disease. Treatments that may be effective include indomethacin, a single lumbar puncture, and methysergide. Some patients have an abrupt recovery after extraction of abscessed teeth.

Table 10 Differential Diagnosis of the Acute, Severe New-Onset Headache

- Primary headache disorders
  - Migraine
  - Cluster
  - Primary exertional headache
  - Primary orgasmic cephalalgia
- Posttraumatic
  - Associated with vascular disorders
    - Acute ischemic cerebrovascular disease
    - Subdural and epidural hematomas
    - Parenchymal hemorrhage
    - Unruptured saccular aneurysm
    - Subarachnoid hemorrhage
    - Systemic lupus erythematosus
    - Temporal arteritis
    - Internal carotid and vertebral artery dissection
    - Cerebral venous thrombosis
    - Acute hypertension
      - Pressor response
      - Pheochromocytoma
      - Preeclampsia
  - Associated with nonvascular intracranial disorders
    - Intermittent hydrocephalus
    - Benign intracranial hypertension
    - Post–lumbar puncture
    - Related to intrathecal injections
    - Intracranial neoplasm
    - Pituitary apoplexy
  - Acute intoxications
  - Associated with noncephalic infection
    - Acute febrile illness
    - Acute pyelonephritis
  - Cephalic infection
    - Meningoencephalitis
    - Acute sinusitis
  - Acute mountain sickness
  - Disorders of eyes
    - Acute optic neuritis
    - Acute glaucoma
  - Cervicogenic
    - Greater occipital neuralgia
    - Cervical myositis
  - Trigeminal neuralgia

Primary cough headache also includes headache brought on by sneezing, blowing the nose, laughing, crying, weightlifting, bending, stooping, or straining with a bowel movement. Weightlifting can also produce a benign acute bilateral nuchal-occipital or nuchal-occipital-parietal headache that can persist as a residual ache for days or weeks. SAH should be considered as a cause with the initial presentation.

Primary exertional headache is a bilateral, usually throbbing, headache brought on by physical activity and lasting from 5 minutes to 24 hours. Some of the activities that can cause this headache are running, rowing, tennis, and swimming. In some persons, the headache may be precipitated by one activity but not others. Exercise can trigger a migraine in migraineurs. Depending on the clinical scenario and number of headaches, secondary causes may need to be excluded, such as SAH, sinusitis, brain tumors, pheochromocytoma, cardiac ischemia (anginal headache), and intracranial arterial dissection. The headaches may be prevented by a warm-up period or by avoiding particular activities. Indomethacin may be preventive. Migraineurs with exertional headache may respond to migraine preventive medications.

The IHS criteria describe two types of primary headache precipitated by sexual activity in the absence of any intracranial disorder. Both are usually bilateral and may be prevented or eased by stopping sexual activity before orgasm. The preorgasmic type is a dull ache in the head or neck that intensifies as sexual excitement increases and is probably caused by muscle contraction. The orgasmic type is a sudden severe headache occurring at orgasm; the headache may remain severe for minutes to 4 hours and then fade to a milder headache lasting up to 48 hours. Forty percent of patients with the explosive type of headache also have exertional headache. A postural headache similar to a post–lumbar puncture headache can occur after sexual activity, presumably because of a dural tear and CSF leak triggered by the activity.

Sexual headache occurs more often when a person tries to have repeated orgasms in close succession. A personal or family history of migraine is common. SAH should be excluded, especially when patients present with their first sexual headache, because sexual activity is a precipitant of up to 12% of ruptured saccular aneurysms. Rarely, pheochromocytoma is a cause. Phosphodiesterase-5 inhibitors for erectile dysfunction can cause headaches in about 15% of users.

In some patients, primary orgasmic headaches can be prevented by weight loss, an exercise program, a more passive role during intercourse, variation in posture, and limitation of additional sexual activity on a single day. The headache may also be prevented by taking medication (e.g., indomethacin, ergotamine, or a triptan) 30 to 60 minutes before engaging in sexual activity.[71] Patients with frequent sexual headaches may respond to migraine preventive medications, such as a beta blocker or verapamil.

HEADACHE IN PSEUDOTUMOR CEREBRI

Pseudotumor cerebri, also known as idiopathic intracranial hypertension, is a disorder of unknown etiology, with an incidence of one per 100,000 population and an onset usually in persons between the ages of 11 and 58 (mean age, 31 years). Ninety percent of patients are young, obese women. Headache is present in 75% or more of patients, papilledema in 95%, a cranial nerve VI palsy in 25%, transient visual obscurations in 70%, visual loss in 30%, and roaring noises in 70%. The headaches, which are usually pulsatile, daily, and continuous, can be unilateral or bilateral, with a bifrontotemporal location being the most common. Nausea is present in about 60% of cases, and vomiting is present in 40%.

The diagnosis of pseudotumor cerebri is one of exclusion, because there are many other causes of papilledema [*see Table 11*]. Testing includes a scan of the brain. MRI is more sensitive than CT, and magnetic resonance venography will exclude cerebral venous thrombosis. If the brain scan is negative, a lumbar puncture should be done. The opening pressure is usually elevated and the CSF analysis is normal, except for a low CSF protein level in some cases.

Treatments include weight loss and diuretics to decrease CSF production. Diuretics used in pseudotumor cerebri include acetazolamide, starting with a dosage of 500 mg twice daily and increasing to as much as 1 g twice daily, if necessary, and furosemide, starting at 20 mg twice daily and increasing to as much as 40 mg three times daily. Patients taking furosemide

should also receive potassium supplementation. Migraine preventive medications can be useful for persistent headache. Topiramate is especially useful because weight loss is a side effect.[72] Funduscopic exam, visual acuity, and visual fields should be closely monitored to help prevent visual loss. Corticosteroids can be used for emergency treatment of impending visual loss. Surgery may be considered for patients who do not respond to medical treatment and are experiencing progressive visual loss. Surgical options are optic nerve sheath fenestration and lumboperitoneal shunting.

HEADACHE IN BRAIN TUMORS

Up to 70% of persons with brain tumors report headaches.[73] The headaches are usually similar to tension-type headaches but can mimic migraine and cluster headaches. The headaches are usually bilateral but can be unilateral. The neurologic examination can be normal. Suspicion of a brain tumor should be raised when a patient has new-onset or progressive headaches or headaches associated with other problems, such as a seizure, confusion, prolonged nausea and vomiting, hemiparesis, or other focal findings. Headaches that are worst on arising in the morning account for less than 20% of brain tumor headaches.

HEADACHE IN PARANASAL SINUSITIS

Acute sinusitis lasts from 1 day to 4 weeks, and subacute sinusitis lasts from 4 to 12 weeks. Nasal congestion, purulent nasal drainage, and facial tenderness and pain are common. Fever is present in 50% of patients. Anosmia, pain on mastication, and halitosis may also be present. Maxillary sinusitis usually causes pain in the cheek, gums, and maxillary teeth; less often, it causes pain in the periorbital, supraorbital, or temporal areas. The pain decreases when the patient is supine and increases when the head is upright. The maxillary sinus is tender to palpation. Frontal sinusitis causes severe frontal headaches with tenderness to percussion or palpation over the frontal sinus. The pain is less when the head is upright and worse when the patient is supine. Complications include brain abscess, meningitis, subdural or epidural abscess, osteomyelitis, subperiosteal abscess, orbital edema, orbital cellulitis, and orbital abscess.[74]

The headache of sphenoid sinusitis, which accounts for 3% of all cases of acute sinusitis and is usually associated with pansinusitis, may be frontal, occipital, or temporal (alone or in combination) and periorbital. The pain is less when the person is upright and increases when the person is supine, standing, walking, bending, or coughing. Nausea and vomiting are common. Photophobia and eye tearing may be present. Nasal discharge and drainage are present in 30% of cases, and fever occurs in more than 50%. Sphenoid sinusitis may be misdiagnosed as migraine, meningitis, trigeminal neuralgia, or brain tumor. Complications include bacterial meningitis, cavernous sinus thrombosis, subdural abscess, cortical vein thrombosis, ophthalmoplegia, and pituitary insufficiency. A parameningeal focus may cause an aseptic meningitis.

Ethmoid sinusitis produces pain in the periorbital, retro-orbital, temporal, or inner canthal area or between the eyes, and it is usually associated with rhinitis. Coughing, straining, or lying supine can worsen the pain, whereas keeping the head upright lessens it. Complications include meningitis, orbital cellulitis, cavernous sinus thrombosis, and cortical vein thrombosis.

Chronic sinusitis has a duration longer than 12 weeks and can produce a usually low-grade and diffuse headache often accompanied by nasal obstruction, congestion, and fullness. The symptoms often increase during the day.

Plain sinus radiographs can be used to diagnose acute maxillary or frontal sinusitis but are often inadequate for ethmoid or sphenoid disease. CT of the sinuses in the coronal plane is highly sensitive for the detection of nasal and paranasal sinus disease. However, a routine CT scan of the head may inadequately cover these areas. An MRI scan of the brain routinely visualizes the paranasal sinuses. Radiographic evidence of sinusitis is present as an incidental finding in 40% of adults without symptoms.

Treatment of paranasal sinusitis is discussed in detail elsewhere [*see 7:XIX Bacterial Infections of the Upper Respiratory Tract*].

HYPERTENSION

Although mild or moderate hypertension does not usually cause headache, severe hypertension from the following conditions can cause headache: acute pressor response to exogenous agents; pheochromocytoma; malignant hypertension; and preeclampsia and eclampsia. Headaches from severe hypertension are usually bioccipital and throbbing but can be generalized or involve frontal throbbing. The headache is often present on awakening in the morning. The diastolic blood pressure is usually elevated to 120 mm Hg or higher. Hypertensive encephalopathy can present as headache, nausea, and vomiting, which may be associated with visual symptoms. Papilledema, focal neurologic deficits, seizures, and decreased levels of consciousness may be present.

Table 11 Etiologies of Papilledema and Headache[79]

- Intracranial mass
- Obstruction or deformity of the ventricular system
- Cerebral venous thrombosis
- Extracranial venous obstruction
  - Radical neck dissection
  - Cardiac failure
  - Chronic respiratory disease
- Hypertensive encephalopathy
- Preeclampsia and eclampsia
- Meningitis/encephalitis
- Meningeal carcinomatosis
- Elevated CSF protein concentration
  - Guillain-Barré syndrome
  - Systemic lupus erythematosus
  - Spinal tumors, especially oligodendroglioma
- Large arteriovenous malformations
- Optic neuritis (usually unilateral)
- Central retinal venous thrombosis (usually unilateral)
- Lead toxicity (in children)
- Lyme disease (in children)
- Parameningeal infection (in children)
- Head trauma
- Medications
  - Vitamin A and derivatives (isotretinoin, etretinate)
  - Minocycline and tetracycline
  - Anabolic steroids
  - Steroid withdrawal
  - Nalidixic acid
- Other medical conditions
  - Renal disease
  - Hypoparathyroidism
  - Hypercoagulable states

A sudden severe headache can reflect an acute pressor response caused when patients receiving monoamine oxidase inhibitors ingest wine or foods with a high tyramine level. Illicit drugs with sympathomimetic actions, such as cocaine, methamphetamine, and methylenedioxymethamphetamine (ecstasy), can also cause acute hypertension and stroke [*see 8:I Management of Poisoning and Drug Overdose*].

OCCIPITAL NEURALGIA

The term occipital neuralgia is in some ways a misnomer, because the pain is not necessarily from the occipital nerve and does not usually have a neuralgic quality. Greater occipital neuralgia is a common type of posttraumatic headache but frequently is also seen in patients without injury. The aching, pressure, stabbing, or throbbing pain may be in a nuchal-occipital, parietal, temporal, frontal, periorbital, or retro-orbital distribution. Occasionally, a true neuralgia may be present, with paroxysmal shooting pain. The headache may last for minutes or hours to days and can be unilateral or bilateral. Lesser occipital neuralgia tends to be similar but with pain generally referred more laterally over the head.

The headache may result from an entrapment of the greater occipital nerve in the aponeurosis of the superior trapezius or semispinalis capitis muscle or may instead be referred pain without nerve compression from trigger points in these or other suboccipital muscles. Digital pressure over the greater occipital nerve at the midsuperior nuchal line (halfway between the posterior mastoid and the occipital protuberance) reproduces the headache. However, pain referred from the C2-C3 facet joint or other area of the upper cervical spine and posterior fossa pathology may produce a similar headache.

Occipital neuralgia may improve with local anesthetic nerve blocks, which can be combined with an injectable corticosteroid (e.g., 3 ml of 1% lidocaine or 2.5 ml of 1% lidocaine and 3 mg of betamethasone). Before giving the injection, the physician should perform aspiration to avoid inadvertent injection into the occipital or vertebral artery. NSAIDs and muscle relaxants may also be of benefit. If the patient has a true occipital neuralgia with paroxysmal lancinating pain, treatment with baclofen, carbamazepine, or gabapentin may help. Physical therapy and transcutaneous nerve stimulators may help some patients.

The author is a consultant or a member of the speakers' bureaus of GlaxoSmithKline, AstraZeneca, Merck & Co., Inc., Pfizer, Inc., UCB Pharma, Inc., Eisai Inc., and Ortho-McNeil Neurologics.

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