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Headache

Guest Editor: Peter J. Goadsby, MD, PhD

992 Editor's Preface
Editor-in-Chief: Steven L. Lewis, MD, FAAN

REVIEW ARTICLES

996 The Migraine Premonitory Phase
Nazia Karsan, MBBS, MRCP; Pyari Bose, MD, MRCP; Peter J. Goadsby, MD, PhD

1009 The Migraine Aura
Andrew Charles, MD

1023 The Migraine Postdrome
Pyari Bose, MD, MRCP; Nazia Karsan, MBBS, MRCP; Peter J. Goadsby, MD, PhD

1032 Acute Treatment of Migraine
Bert B. Vargas, MD, FAAN, FAHS

1052 Preventive Therapy of Migraine
Todd J. Schwedt, MD, FAAN

1066 Headaches Due to Low and High Intracranial Pressure
Deborah I. Friedman, MD, MPH, FAAN

1092 Headache in Pregnancy
Matthew S. Robbins, MD, FAAN, FAHS

1108 Pediatric and Adolescent Headache
Amy A. Gelfand, MD

1137 Cluster Headache and Other Trigeminal Autonomic Cephalalgias
Mark Burish, MD, PhD

DENOTES *CONTINUUM* AUDIO INTERVIEW

DENOTES SUPPLEMENTAL DIGITAL CONTENT

1157 **Cranial Neuralgias**
Stewart J. Tepper, MD, FAHS

1179 **Secondary Headache Syndromes**
Denise E. Chou, MD

1192 **Unusual Headache Disorders**
Amaal Jilani Starling, MD, FAHS

ETHICAL AND MEDICOLEGAL ISSUES

1209 **Common Legal Considerations When Moving to a New Medical Practice**
Joseph S. Kass, MD, JD, FAAN; Rachel V. Rose, JD, MBA

SELF-ASSESSMENT AND CME

984 **Learning Objectives and Core Competencies**

1215 **Instructions for Completing Postreading Self-Assessment and CME Test and Tally Sheet**

1217 **Postreading Self-Assessment and CME Test**

1231 **Postreading Self-Assessment and CME Test—Preferred Responses**

1243 **Erratum**

1244 **Index**

List of Abbreviations (Back Cover)

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EDITOR'S PREFACE

Drome Attacks

This issue of *Continuum* is devoted to the diagnosis and management of our patients with headache. We are truly privileged to have Dr Peter J. Goadsby as the guest editor of this issue, and I am so appreciative that he has brought together such a remarkable group of experts to share their headache expertise with us.

The issue begins with the article by Drs Nazia Karsan, Pyari Bose, and Peter J. Goadsby on the growing topic of the premonitory (prodromal) phase of migraine, the characteristic features of which may be clues to the pathogenesis, and ultimately new treatment strategies, of the disorder. The next phase of migraine is discussed in the article by Dr Andrew Charles, who reviews the unique pathophysiologic, diagnostic, and management issues relevant to the migraine aura. Next, Drs Bose, Karsan, and Goadsby discuss the migraine postdrome, the least recognized and understood component of the migraine attack, which can so affect the quality of life and productivity of our patients.

The following two articles tackle the very practical topic of treatment of our patients with migraine. Drs Bert B. Vargas and Todd J. Schwedt provide their vast clinical experience and knowledge of the evidence-based headache literature (including relevant society guidelines) to review, respectively, the acute and preventive therapy of migraine.

The issue then turns from migraine as a specific cause of headache and disability to other important causes of headache and to specific populations (ie, children or pregnant women) with their own diagnostic and management issues. Dr Deborah I. Friedman discusses the diagnosis and management of headache syndromes that occur due to either low or high intracranial pressure, an article that will be of great benefit to the care of these patients who present with headaches (and other symptoms and signs) due to either of these extremes of intracranial pressure.

Turning to specific populations, Dr Matthew S. Robbins reviews the diagnosis and management of the primary and secondary headache syndromes that can occur in pregnancy and the postpartum state, including discussion of the issues that arise regarding medications and breast-feeding. Dr Amy A. Gelfand then discusses the many diagnostic and management issues related to primary and secondary headache syndromes in pediatric and adolescent patients with headache.

Dr Mark Burish next focuses on the diagnostic criteria and management options for cluster headache and the other trigeminal autonomic cephalalgias to help us provide the most up-to-date and effective management options for these severe headache syndromes. Dr Stewart J. Tepper then discusses the diagnosis and current treatment options for the cranial neuralgias, including a very clear explanation of the current nomenclature that surrounds these syndromes.

Dr Denise E. Chou next focuses on the many causes of secondary headache syndromes that we may encounter in our practices, the diagnosis and management of which may help prevent devastating outcomes. In the final review article of the issue, Dr Amaal Jilani Starling discusses several unusual headache disorders (and even nonheadache disorders such as exploding head syndrome) that need to be on our diagnostic radar.

In the Ethical and Medicolegal Issues article, Dr Joseph S. Kass, associate editor of this section of *Continuum,* and Ms Rachel V. Rose provide a practical review of the common legal considerations readers should keep in mind when moving to a new neurologic practice, a topic of great interest to many, if not all, of our readers in the United States at some point(s) in their careers.

After reading the issue and taking the Postreading Self-Assessment and CME Test written by Drs D. Joanne Lynn and Allison L. Weathers, you may earn up to 20 *AMA PRA Category 1 Credits*™ toward self-assessment and CME or, for Canadian participants, a maximum of 20 hours toward the Self-Assessment Program (Section 3) of the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada. Additional credit can be obtained by listening to *Continuum* Audio interviews associated with this and other *Continuum* issues, available to all subscribers, and completing tests on the new *Continuum* Audio web platform or app. *Continuum* Audio is also accredited by the Royal College of Physicians and Surgeons of Canada.

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I would like to extend my deepest gratitude to Dr Goadsby for his stewardship of this issue from its conceptual, or "prodromal," stage to its current stage, where the fruits of his and his expert colleagues' work will be of great benefit in our practices as we diagnose and manage our many patients with primary and secondary headache syndromes.

I would like to extend my deepest gratitude to Dr Goadsby for his stewardship of this issue from its conceptual, or "prodromal," stage to its current stage, where the fruits of his and his expert colleagues' work will be of great benefit in our practices as we diagnose and manage our many patients with primary and secondary headache syndromes.

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

The Migraine Premonitory Phase

By Nazia Karsan, MBBS, MRCP; Pyari Bose, MD, MRCP; Peter J. Goadsby, MD, PhD

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Continued on page 1008

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ABSTRACT

PURPOSE OF REVIEW: The premonitory phase of migraine is defined as the presence of nonpainful symptomatology occurring hours to days before the onset of headache. Symptoms can include neck stiffness, yawning, thirst, and increased frequency of micturition. Clinical recognition of these symptoms is important to ensure early and effective attack management. Further understanding of the clinical phenotype and neurobiological mediation of these symptoms is important in the advancement of therapeutics research in both acute and preventive treatments of migraine.

RECENT FINDINGS: Since 2014, functional imaging studies have been conducted during the premonitory stage of migraine and have provided novel insights into the early neurobiology and anatomy of the earliest stage of the migraine attack. These studies have shown early involvement of subcortical brain areas including the hypothalamus, substantia nigra, dorsal pons, and various limbic cortical areas, including the anterior cingulate cortex during the premonitory phase. More recent work has revealed altered hypothalamic-brainstem functional connectivity during migraine, which starts before the onset of pain. These exciting findings have provided functional correlation of the symptoms experienced by patients and changes seen on functional brain imaging.

SUMMARY: This article focuses on the prevalence, phenotype, and proposed neurobiology of premonitory symptomatology in migraineurs as well as the scope of future research.

INTRODUCTION

Migraine is a brain disorder that is most commonly associated with head pain. However, it has been known for more than a century that migraine can be associated with nonpainful symptomatology, which can be as disabling as the pain itself and can last longer than the pain part of the attack.[1] This symptomatology can include aura, which is defined as the presence of reversible neurologic disturbance that can accompany the migraine attack,[2] but can also include the increasingly recognized premonitory symptomatology. This newly classified prodromal (premonitory) symptomatology is defined as the presence of nonpainful symptomatology, which can start hours to days before the onset of migraine pain[2] and can be predictive of an impending headache.[3] Although

becoming increasingly recognized, premonitory symptomatology, fatigue in particular, has been noted as far back as the 19th century by Gowers.[1] Since then, several studies examining premonitory symptomatology in more detail have spanned the literature over the last 40 years. Generally, these symptoms are reported consistently by patients, both adults and children, and throughout numerous studies in the literature. Premonitory symptoms commonly involve fatigue and cognitive symptoms, alterations in homeostasis including thirst and increased frequency of micturition, and sensory sensitivities such as photophobia.[3–15] These features are highlighted in **CASE 1-1**.

The presence of these early symptoms, their broad heterogeneous phenotype, and their ability to predict an impending headache provide valuable insights into the early neurobiology of the migraine attack and may help identify novel future targeted therapeutics, targeting neurotransmitters that may mediate these premonitory symptoms. If these targets could be successfully identified and treatments developed, these agents could be a huge breakthrough in aborting pain before its onset. Despite recent advances in migraine therapeutics, with the

CASE 1-1

A 34-year-old woman presented for a consultation regarding migraine. She had been diagnosed with episodic migraine without aura at 12 years of age around the time of menarche. She usually experienced one attack per month. Her attacks were effectively treated with 50 mg oral sumatriptan with pain abortion within 20 minutes. About 5 to 6 hours before her attacks, she noted yawning, extreme fatigue, difficulty concentrating in her work as an investment banker, difficulty tolerating the bright lighting in the office, and she would find it very difficult to focus on all the trading computer screens in front of her. Dull head discomfort or retro-orbital eye discomfort could sometimes build at this time, but she only took the sumatriptan once the pain reached a moderate level. She explained that these symptoms occurred reliably before each attack (in particular the yawning, difficulty concentrating, and fatigue), and she always thought these symptoms were a manifestation of migraine triggers in that when she would become particularly busy at work, she would be more tired than usual and find it harder to concentrate, and she felt that looking at bright lights and many computer screens would then trigger an attack. She had also noticed that the difficulty focusing and concentrating and the light sensitivity could persist even once the pain had been treated with sumatriptan. She found it hard to function normally at work after a headache and often the following day as well.

COMMENT

This patient had likely wrongly attributed the symptoms that she experienced prior to a migraine attack as triggers, when they are more likely to be manifestations of the premonitory phase of the attack. Despite her migraine headache being effectively treated with an oral triptan, and despite only experiencing one headache a month, her attack was usually associated with 48 hours of other nonpainful cognitive and sensory sensitivity symptoms, which significantly impaired her functioning at work.

identification of drug agents targeting the calcitonin gene-related peptide (CGRP) pathway[16] and the 5-hydroxytryptamine 1F (5-HT_{1F}) receptor,[17] among several other targets under clinical trials, a need always exists for effective abortive and preventive treatments of this disabling condition. An attractive strategy for migraine management is limiting the morbidity of the migraine attack by preventing pain onset and treating nonpainful disabling symptomatology as well as pain. Further understanding about the premonitory phase of migraine and its biological mediation could provide such a strategy.

This article discusses what we know so far about the premonitory phase of migraine by reviewing studies on the human phenotype, prevalence, neurophysiology, and functional imaging.

PREVALENCE OF PREMONITORY SYMPTOMS

Unfortunately, many of the studies that have looked at premonitory symptoms in migraineurs have been conducted in a retrospective fashion, so while the studies can provide an idea about the clinical phenotype of the premonitory phase, they cannot provide a true prediction of the population prevalence of the presence of these symptoms.[7–15] Only two prospective studies have been conducted, but one study preselected patients who reported premonitory

CASE 1-2

A 6-year-old boy presented to a pediatric neurology clinic because of episodic headaches. He had a history of prominent colicky symptoms as a baby. His mother and sister had a history of migraine. At 4 years of age, the patient had begun experiencing headache on the weekends. At the time of presentation, these headache episodes occurred twice a month and were accompanied by vomiting. They usually occurred on a weekend when he was not at school and had woken up later in the morning.

His parents and sister had noticed that he tended to be irritable on the Friday night preceding a Saturday headache, and he would look pale and grouchy and not like his usual happy self. He often did not want to watch television, talk to the family, or play as he usually did. He also went to bed early, whereas usually on a weekday he did not want to abide by bedtime and wanted to stay up late. When he experienced a headache on a Saturday, it usually occurred after waking and then built up and lasted for several hours. After the headache abated, he remained moody for a few hours and was unable to do his homework for the weekend.

COMMENT

Premonitory symptoms can be experienced by young children as well as adolescents and adults. The phenotype can be harder to elicit as mood and behavioral changes are perhaps more common in this age group. This patient seems to experience premonitory symptoms and facial changes before his migraine headache, which tends to occur on the weekend when he relaxes after a week at school and sleeps in. He also has a symptomatic postdrome. These symptoms, along with the head pain, make it difficult for this patient to effectively complete his schoolwork on two weekends a month.

symptoms associated with their typical migraine attacks with the aim of assessing their ability in predicting headache onset,[3] and the other reported premonitory symptomatology in 84% of patients preceding a headache attack.[6] Because of these limitations and the paucity of large prospective studies, it is difficult to reliably predict the population prevalence of premonitory symptoms in both adults and children from the current literature. The numbers quoted in the above studies vary from 9% to 88%. The wide range of prevalence reported in the literature is likely owing to the broad time period in which these studies were conducted (1980 to 2017), the different methods of data collection (retrospective questionnaires versus prospective questionnaire or electronic diary), and different environments from which patients were recruited (clinic versus general practice or the general population). The studies suggest that, with time, the reported prevalence increases, and this is likely related to increasing physician and patient awareness of the presence of this symptomatology and therefore increased reporting.

The prospective studies have yielded interesting results about the reliability of reporting similar premonitory symptomatology across three migraine attacks[6] and the ability of using an electronic diary system to record symptoms (yawning in particular) to predict the onset of impending headache,[3] which make these symptoms an attractive part of the migraine history to include in clinical treatment trials.

Going forward, to elucidate the true population prevalence of these symptoms among migraineurs, it is prudent to include both questioning about the retrospective presence of these symptoms as part of the standard migraine history in the clinic and asking patients to prospectively note if they experience such symptomatology associated with future spontaneous attacks. **CASE 1-2** demonstrates the presence of these symptoms even in young children.[9,10]

Premonitory symptoms are likely to be more common than has been reported in the literature, and if patients are asked specifically about each symptom, many will report several symptoms in association with attacks. Patients may not associate these often nonspecific symptoms with a migraine attack or may wrongfully mistake them as migraine triggers (eg, assuming that bright lights are triggering a headache, while this is actually premonitory photic hypersensitivity, or feeling that chocolate triggers migraine attacks, while this may actually be premonitory sweet cravings).[18] These difficulties are highlighted in **CASE 1-1**. Additionally, when patients are made aware of the possibility of experiencing such symptoms, a prospective method of data collection (eg, recording of these symptoms in a diary and their association with headache, response to treatment, and ability to predict headache onset) is likely to be a more useful way of assessing prevalence going forward. From the authors' experience, a number of patients report no warning symptoms prior to their attacks but experience very similar premonitorylike symptomatology during their headache attacks. These symptoms are likely biologically mediated in the same way, and the differences in onset timing is poorly understood.

CLINICAL PHENOTYPE OF PREMONITORY SYMPTOMS

The clinical phenotype of premonitory symptoms in both adults and children demonstrated across various studies over the last 37 years is largely consistent (**CASE 1-1** and **CASE 1-2**). Symptoms reported can be broadly categorized into three separate groups: fatigue and cognitive changes, homeostatic alterations, and sensory sensitivities (**TABLE 1-1**).

KEY POINTS

- Prospective studies have shown that the presence of symptoms prior to the onset of headache can occur reliably and can predict pain onset in some individuals.
- The premonitory phase of migraine is likely more common than is currently reported in the literature.
- Premonitory symptoms can be experienced in the lead-up to headache or during headache itself, and similar symptoms can present in the postdrome after headache resolution.
- Physicians should ask about the presence of premonitory symptoms as a standard part of the migraine history.
- Premonitory symptoms of migraine can be experienced by adults, adolescents, and children as young as 18 months old.

Throughout all the studies performed to date, the most commonly reported symptoms are tiredness, mood change, and yawning.[3–15] Similar findings have been found in a study conducted by the authors of this article, with tiredness being the most common symptom; however, concentration changes and mood changes were the next most common symptoms reported by patients who were questioned about premonitory symptoms associated with spontaneous migraine attacks using a retrospective questionnaire. When triggered attacks using nitroglycerin were directly observed and premonitory symptomatology in response to the trigger noted prospectively, mood change was less common, but photophobia was more common.[19]

The ability of exogenous substances such as nitroglycerin, CGRP, and pituitary adenylate cyclase-activating polypeptide 38 to reliably trigger these symptoms in migraineurs is a useful experimental tool in studies of these symptoms in experimental human research.[20,21]

BIOLOGICAL MEDIATION OF PREMONITORY SYMPTOMS

The prospect of being able to understand the mediation of the earliest symptoms of a migraine attack before the onset of pain is interesting from both pathophysiologic and therapeutic perspectives. Refer to FIGURE 1-1 for a summary of the likely pathophysiologic pathways involved in migraine. Over recent years, the understanding of how these symptoms may be mediated has widened through both preclinical studies and enhanced methods of functional brain imaging in patients.

Preclinical Studies

Neuropeptide Y is a substance secreted by the hypothalamus that is involved in feeding and appetite regulation, pain, and circadian rhythms.[22–25] A recent study provided evidence about the role of neuropeptide Y in migraine by studying the effect of systemic administration of neuropeptide Y in response to dural trigeminovascular activation in an animal model.[26] The authors of this study found that systemic neuropeptide Y administration inhibited trigeminocervical complex activation through the neuropeptide Y1 receptor. Given the role of neuropeptide Y in appetite regulation, the authors hypothesized that

TABLE 1-1 **Symptoms Displayed During the Premonitory Phase of Migraine and Their Possible Neuroanatomic Correlates**

Symptom Group	Symptoms Commonly Displayed	Possible Brain Area(s) Involved in Mediating Symptoms
Fatigue/cognitive change	Concentration difficulty, fatigue, memory impairment, depression, elation, irritability	Anterior cingulate cortex, amygdala, locus coeruleus, hypothalamus
Homeostatic alterations	Food cravings, thirst, frequency of urination, yawning, sleep disturbance	Hypothalamus, locus coeruleus
Sensory sensitivities/nonpainful migrainous symptoms	Neck stiffness, photophobia, phonophobia, osmophobia, nausea	Hypothalamus, occipital cortex, brainstem

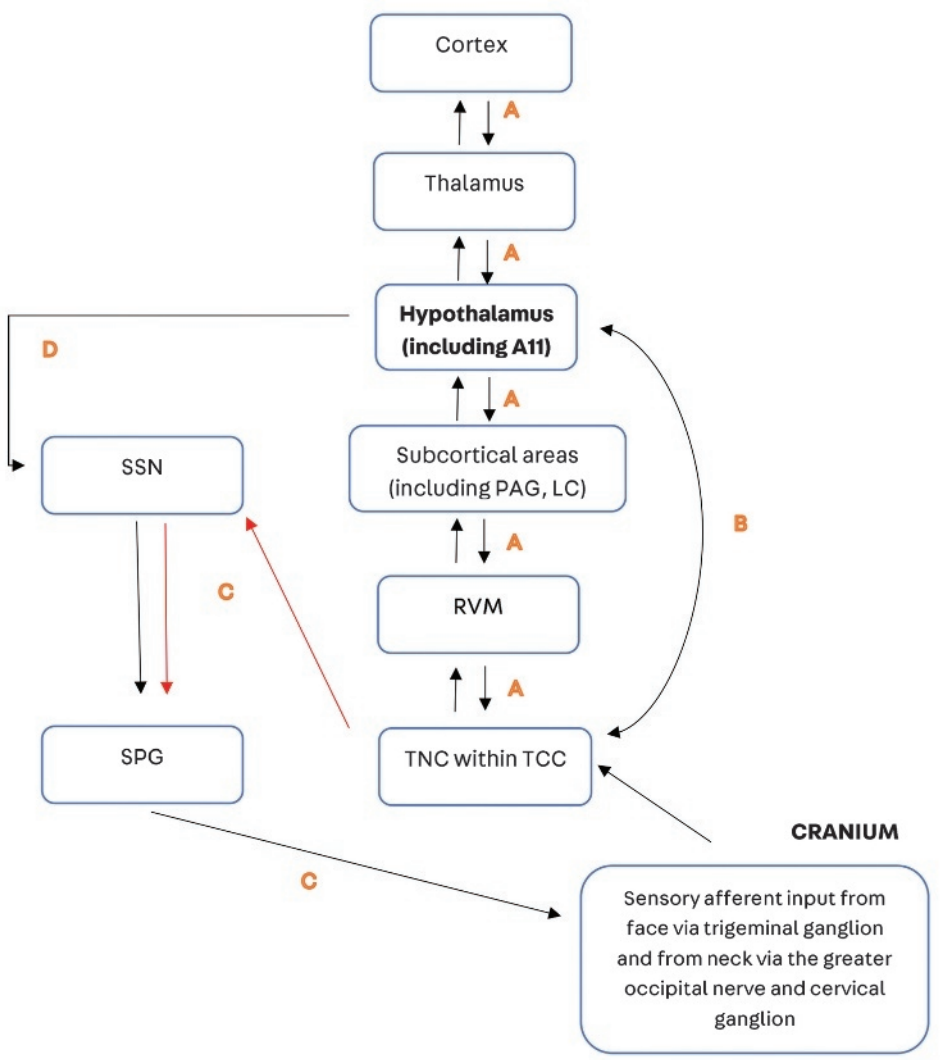

FIGURE 1-1

A depiction of the pathways believed to be involved in the pathophysiology of migraine. Sensory afferent input from the cranium travels to the brain via the greater occipital nerve, trigeminal ganglion, and cervical ganglion and converges in the trigeminal nucleus caudalis (TNC) within the trigeminocervical complex (TCC). From here, second-order neurons project to several brain areas including the periaqueductal gray (PAG) and locus coeruleus (LC) via the rostroventral medulla (RVM). Further ascending projections occur via the hypothalamus and thalamus to the cortex. Reciprocal descending connections are present between these brain structures, highlighted by *A*. A descending modulatory pathway also exists between the hypothalamus and its nuclei, including the A11, to the TCC via the RVM, highlighted by *B*. A reflex connection is present between TCC neurons and the superior salivatory nucleus (SSN) in the pons and from here to the sphenopalatine ganglion in the face (SPG), which provides the parasympathetic outflow to the cranium, highlighted by *C* and *red arrows*; this reflex is likely responsible for mediating the cranial autonomic symptoms associated with many of the primary headache disorders. A descending connection is present between the hypothalamus and the parasympathetic pathway via the SSN, highlighted by *D*. Several of the brain areas shown in this figure have been implicated in the neurobiological mediation of premonitory symptoms, and their early engagement prior to the onset of headache suggests that trigeminonociceptive signaling occurs later during the migraine attack, possibly in response to activation of this system during the premonitory phase.

KEY POINTS

- Common premonitory symptoms of migraine are fatigue, yawning, neck discomfort, and concentration difficulty.
- Pharmacologic triggering models in human experimental research and functional neuroimaging have enabled the neurobiology of the premonitory phase of migraine to be studied and have provided functional correlation between the clinical phenotype and areas of brain seen to be activated on imaging.

neuropeptide Y may be involved in both pain and the appetite changes that occur in migraine. The same authors also studied insulin, glucagon, and leptin in migraine and found that all these could alter trigeminal nociceptive input transmission.[27] This study suggested the link between migraine and impaired appetite, blood glucose levels, and the potential role of the hypothalamus in mediating this.

Other preclinical studies have demonstrated the role of the hypothalamic-orexinergic pathway in migraine as well as the role of the hypothalamus and its connections in migraine and their potential role in mediating some of the symptoms such as sleep disruption, food aversion, and mood change and emotionality.[28,29] Previous evidence supports the role of the hypothalamus in migraine, including demonstration that stimulation of the A11 nucleus of the hypothalamus reduces pain-evoked trigeminocervical complex firing, and that this can be reversed by a D2 receptor antagonist.[30] Yawning is a partially dopamine-mediated symptom,[31] and apomorphine, a dopamine agonist, can induce yawning, which can be reversed by hypophysectomy, suggesting a hypothalamus-pituitary axis site of symptom mediation through dopamine receptors.[32] Interestingly, small studies using domperidone in the premonitory stage were effective at preventing headache onset,[33,34] reinforcing the likely role of dopamine in the premonitory stage of migraine. Additionally, the substantia nigra, an important area of dopamine receptors within the brain, was found to be active during the premonitory stage in a functional imaging study, suggesting another site where it could be exerting its action.[35] Research has also implicated somatostatin as another hypothalamic hormone that may be involved in the primary headache conditions.[36] A somatostatin analogue, octreotide, has been shown to be helpful in cluster headache in humans but not in migraine.[37] Additionally, cholecystokinin expression is increased in the ventromedial thalamus following noxious trigeminal stimulation,[38] suggesting a hypothalamic role for the mediation of feeding and appetite changes associated with migraine (**TABLE 1-2**).

These studies suggest the role of neuropeptide Y and dopamine (as well as perhaps orexins, somatostatin, and cholecystokinin), all secreted through the hypothalamus, in mediating some of the premonitory symptoms associated with migraine and that these substances may also have roles in trigeminal nociception.

Human Neurophysiology Studies

An electrophysiologic study was conducted in 1998 looking at brain changes before the onset of migraine pain.[39] The authors of that study demonstrated a high contingent negative variation (a measure of slow cortical potential) amplitude the day before a migraine headache, suggesting that maximum negativity contingent negative variations are associated with the increased likelihood of migraine the following day and are likely to represent a loss of cortical habituation. A 1999 study looked at measuring visually evoked event–related potentials in migraineurs during the attack and interictally.[40] P3 (a particular waveform of a cognitive event-related potential) intervals were studied to look at cognitive habituation. The authors of the study found that a progressive increase in cognitive habituation occurred leading up to the attack (with maximum increase during the days leading up to headache) with subsequent rapid normalization during the attack, suggesting that objective cognitive changes occur prior to a headache attack. Symptoms such as concentration difficulty, fatigue, and emotional change during the premonitory

phase are likely mediated by frontal cortical areas and their limbic connections. In 2008, another study demonstrated that a component of the visual evoked potential is increased in migraineurs 72 hours prior to the onset of headache, suggesting increased visual cortex responsiveness preictally compared to interictally.[41] These studies provide electrophysiologic support in humans for abnormal brain physiology preceding a migraine headache attack.

Human Functional Imaging Studies

Over recent years, functional neuroimaging in humans has allowed valuable insights in the neurobiology and cerebral representation of many human

Summary of the Hypothalamic Neurotransmitters Implicated to Date in Migraine Neurobiology, Their Possible Roles, and Therapeutic Contributions to Migraine TABLE 1-2

Hypothalamic Neurotransmitter/ Hormone	Hypothalamic Area Involved	Potential Role in Migraine	Therapeutic Implications
Orexins (A and B)	Lateral hypothalamus	Circadian rhythm and sleep-wake cycle, feeding, arousal, autonomic symptoms	Targeting these receptors may have therapeutic use in migraine (seen in animal models but not effectively demonstrated in humans)
Cholecystokinin	Ventromedial nucleus	Feeding regulation and appetite suppression in response to trigeminal pain	Cholecystokinin may be involved in the associations between appetite and feeding (cravings and anorexia) in migraine
Dopamine	A11 nucleus	Inhibits neuronal firing in the trigeminocervical complex via descending inhibition through dopamine receptors, yawning, nausea	Dopamine antagonists are helpful antiemetics in migraine and may also have a further antinociceptive and antipremonitory role
Somatostatin	Posterior hypothalamus	Descending modulation of trigeminovascular pain signaling	Somatostatin antagonists may have a useful effect in primary headache conditions
Antidiuretic hormone (vasopressin)	Paraventricular and supraoptic nuclei	Thirst, polyuria, and circadian rhythm regulation in response to light	No clear therapeutic advances at this time
Melatonin	Released from the pineal gland in response to hypothalamus suprachiasmatic nucleus neuronal input; melatonin receptors are present in the suprachiasmatic nucleus	Sleep-wake regulation, may also have an antinociceptive role	Melatonin has some therapeutic efficacy in migraine

symptoms and disorders. The hours to days preceding a migraine headache attack have been studied with functional brain imaging since 2011, when it was shown using functional MRI (fMRI) that activity within the trigeminal nucleus caudalis, an area of convergence of sensory afferent input from the head and neck within the brainstem, changed following trigeminal pain stimulation and could predict the next headache attack with the highest level of activity in the preictal period.[42] This study again supported alterations in brain networks before the onset of migraine headache.

The first imaging studies studying the premonitory stage of migraine in particular were reported in 2014, with a positron emission tomography (PET) study demonstrating early activation of the hypothalamus, dorsolateral pons, and several cortical areas during the premonitory phase of triggered attacks.[35] This study for the first time demonstrated a neural basis to these symptoms and a functional correlation between the symptomatology displayed and the changes seen on the imaging, with anterior cingulate cortex activation likely mediating mood and cognitive change and hypothalamic activation mediating yawning, thirst, frequency of micturition, and neck discomfort.

Further PET studies provided additional functional correlation between symptoms and imaging when subjects with premonitory photophobia who were imaged during the premonitory phase showed occipital cortex activation,[43] and those with nausea showed activation in a brainstem area likely to be in the region of the nucleus tractus solitarius.[44]

Since then, further imaging studies have also been conducted using fMRI. When one subject with migraine was scanned every day for 30 days, spontaneous premonitory periods and headaches were captured throughout the month, and altered hypothalamic activity in response to trigeminal nociceptive stimulation using intranasal ammonia was observed and increased up to 24 hours prior to the onset of migraine headache.[45] The authors also demonstrated altered functional coupling of the hypothalamus with the spinal trigeminal nuclei and the dorsal pons the day before spontaneous headache.[45] These findings suggested a role of altered hypothalamus and brainstem connectivity before the onset of migraine pain, again suggesting a role of the hypothalamus early during the course of an attack. The most recent study used fMRI to image migraineurs in the preictal, postictal, and interictal phases of migraine and compared the imaging findings to healthy controls,[46] again demonstrating increased midbrain and hypothalamic connectivity in the lead-up to a headache attack.

FUNCTIONAL CORRELATION OF FINDINGS

The unifying themes from all the work that has been conducted in this field over the last several decades are as follows:

- **The phenotype of premonitory symptomatology largely withstands several different studies across different populations, different age ranges (adults versus children and adolescents), over several years, and with various methods of data collection. The most common symptoms consistently described are listed in TABLE 1-1.**
- **Clinical evidence shows that the brain behaves abnormally preictally prior to a headache in migraine, with alterations in cognition and cortical responsiveness, alterations in hypothalamic-brainstem connectivity, and increased regional cerebral blood flow in the region of the hypothalamus, dorsal pons, and cortical areas including the anterior cingulate cortex.**

- Preclinical evidence supports the role of the hypothalamus in migraine, both in nociception and in mediating some premonitory symptomatology. These symptoms may be mediated by neurotransmitters including neuropeptide Y and dopamine (FIGURE 1-1).
- Certain neurotransmitters potentially involved in the mediation of premonitory symptoms may make attractive therapeutic targets (TABLE 1-2).

THERAPEUTIC AVENUES

A large reason for the ever-increasing interest in the premonitory stage of migraine includes the insights that understanding the phase can provide into potential therapeutic targets, including the development of agents that could work prior to the onset of pain or to treat nonpainful symptomatology associated with the migraine attack.

The following are the trials of agents targeting the premonitory phase and the potential targets that have emerged from studies of such symptoms.

Domperidone and a triptan were trialed historically during the premonitory phase with the aim of assessing their ability to prevent pain onset.[33,34,47] These studies have been small yet have yielded interesting and encouraging results. Varying doses of domperidone (between 10 mg and 40 mg) taken during the premonitory phase were able to abort pain onset in 30% to 63% of attacks,[34] and 30 mg could prevent headache onset in 66% of attacks compared to 5% with placebo.[33] Naratriptan 2.5 mg was found to prevent 60% of migraine headaches when dosed in the premonitory phase in an open-label study.[47]

Despite the encouraging results, large-scale, placebo-controlled, double-blind, randomized studies are needed in the future to answer the question as to whether longer-acting triptans taken during the premonitory phase can prevent pain onset (given that previous studies have shown a more favorable triptan response when triptans are taken once mild pain has started,[48] and conflicting literature exists about the use of triptans in preventing headache onset when dosed during aura[49–52]) and whether domperidone may be a useful agent during the premonitory phase.

More recently, the orexins have emerged as hypothalamic neurotransmitters of interest given their role in sleep and the strong association between sleep and migraine.[53] Despite increasing preclinical evidence for the role of orexinergic mechanisms in migraine,[54,55] a human trial of the orexin receptor antagonist filorexant for treating migraine was unsuccessful.[56]

Somatostatin is a substance secreted by the hypothalamus, and evidence exists for its descending role in modulation of trigeminovascular pain signaling.[36] However, both preclinical[57] and clinical studies[58,59] have failed to demonstrate efficacy of somatostatin analogues in migraine. Octreotide, however, does seem to have a beneficial role in cluster headache.[37]

Melatonin is released from the pineal gland in response to hypothalamic input, but melatonin receptors are present in the suprachiasmatic nucleus within the hypothalamus.[60,61] Melatonin has been historically linked to headache disorders, mainly because of the strong association of some of the primary headache disorders with sleep and circadian rhythm.[62] Melatonin is more commonly used in cluster headache,[63] where better evidence exists for its efficacy, but some conflicting evidence exists for its efficacy for prevention in both adult and pediatric migraine.[64–68]

The results of all these treatment avenues that have been trialed in migraine suggest that larger population-based, double-blind, randomized controlled studies are required to better understand the effect, if any, of these agents in migraine. Hopefully, with increased understanding of how and through which

KEY POINTS

- The engagement of limbic and subcortical brain areas prior to the onset of headache in migraine is, to date, unique to this as an acute pain condition and provides interesting insights into how the migraine attack starts and progresses to pain.
- Increasing evidence exists for the role of the hypothalamus and its connections in mediating the premonitory symptoms of migraine, as well as the role of these connections in trigeminal nociceptive signaling.
- Understanding of the brain areas and pathways involved in the premonitory phase of migraine, including the dopaminergic pathway, provide novel insights into targeted neurochemical therapeutic targets.
- Understanding the mechanisms behind the mediation of premonitory symptoms within the brain may lead to therapeutic advances for effective abortive migraine agents, as well as for agents that may treat disabling nonpainful symptomatology as well as headache.

neurotransmitters various brain areas may be involved in the premonitory phase, targeted therapeutics research can be extended in the future.

CONCLUSION

Past research and recent advances have confirmed a neural basis to migraine and its acceptance as primarily a disorder of the brain. It is clear that the disorder involves much more than just pain, and this wide and varied heterogeneous phenotype is likely mediated through various complex brain pathways, with the involvement of several neurotransmitters and brain areas.

Further understanding of the possible neurochemical pathways at play and the biological basis for premonitory symptoms may lead to the development of targeted acute therapy for this condition in an era where, despite recent advances, no specific effective migraine abortive medications have gained a license for clinical use since the triptans in 1991.[69] Pharmaceutical agents that could abort pain before its onset if taken during the premonitory stage, as well as potentially treat premonitory symptoms, would be an attractive option for patients.

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DISCLOSURE

Continued from page 966

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The Migraine Aura

By Andrew Charles, MD

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

ABSTRACT

PURPOSE OF REVIEW: This article discusses the basic mechanisms of migraine aura and its clinical significance based upon evidence from human studies and animal models.

RECENT FINDINGS: Prospective clinical studies have reinforced the understanding that migraine aura is highly variable from one individual to the next as well as from attack to attack in an individual. While migraine with aura clearly has a higher heritability than migraine without aura, population studies have not identified specific genes that underlie this heritability for typical migraine with aura. Imaging studies reveal hypoperfusion associated with migraine aura, although the timing and distribution of this hypoperfusion is not strictly correlated with migraine symptoms. Mapping of migraine visual aura symptoms onto the visual cortex suggests that the mechanisms underlying the aura propagate in a linear fashion along gyri or sulci rather than as a concentric wave and also suggests that aura may propagate in the absence of clinical symptoms. Cortical spreading depression in animal models continues to be a translational model for migraine, and the study of spreading depolarizations in the injured human brain has provided new insight into potential mechanisms of cortical spreading depression in migraine. Migraine with aura has multiple comorbidities including patent foramen ovale, stroke, and psychiatric disorders; the shared mechanisms underlying these comorbidities remains a topic of active investigation.

SUMMARY: Although it occurs in the minority of patients with migraine, aura may have much to teach us about basic mechanisms of migraine. In addition, its occurrence may influence clinical management regarding comorbid conditions and acute and preventive therapy.

INTRODUCTION

The aura is a remarkably complex and variable feature of migraine that has significant implications regarding pathophysiology, comorbidities, and therapy. While it has been recorded in detail for centuries, the understanding of migraine aura continues to evolve. This article describes the classification of migraine aura, its clinical features, its basic mechanisms, and its relevance to clinical management.

Migraine aura is described in the *International Classification of Headache Disorders, Third Edition* (*ICHD-3*) as "recurrent attacks, lasting minutes, of unilateral fully reversible visual, sensory, or other central nervous system symptoms that usually develop gradually and are usually followed by headache

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Dr Charles receives personal compensation for serving on the advisory boards of Alder BioPharmaceuticals, Inc; Biohaven Pharmaceutical; Eli Lilly and Company; and eNeura Inc. Dr Charles receives personal compensation for serving as associate editor of *Cephalalgia*; as CME program speaker of Medicom and Medlearning Group; and as a consultant for Amgen Inc. Dr Charles has served as an expert witness in legal proceedings for Milano & Wanat LLC.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Charles discusses the unlabeled/investigational use of ketamine for the treatment for migraine aura.

and associated migraine symptoms."[1] Refer to TABLE 2-1 for detailed *ICHD-3* diagnostic criteria of migraine with aura.

CLINICAL FEATURES OF MIGRAINE AURA

A key point regarding the definition of migraine aura is its gradual onset and progression in contrast to the abrupt onset of symptoms that is typical of brain ischemia or hemorrhage. Also, unlike with ischemia, positive visual and sensory symptoms (eg, flashing lights, paresthesia) are more common than negative ones.[2,3] These symptoms reflect an underlying physiologic phenomenon that begins slowly and spreads slowly (CASE 2-1).

The clinical features of migraine aura are remarkably variable both from one individual to the next as well as from attack to attack in an individual.[2,3] Visual aura symptoms are by far the most common, occurring in 90% or more of patients, followed by sensory, language, and motor symptoms.[3] When sensory, language, or motor aura symptoms do occur, they most commonly occur in conjunction with visual symptoms, although nonvisual aura symptoms occasionally occur in isolation.[2,3] In some but not all patients, a consistent temporal progression from visual symptoms to other aura symptoms occurs.[3] The basis for the propensity of migraine aura to involve the visual cortex remains unclear. It has been speculated that the higher neuron-to-astrocyte ratio in the

TABLE 2-1 ***ICHD-3* Diagnostic Criteria for Migraine With Aura**[a]

A At least two attacks fulfilling criteria B and C

B One or more of the following fully reversible aura symptoms

1 Visual
2 Sensory
3 Speech and/or language
4 Motor
5 Brainstem
6 Retinal

C At least three of the following six characteristics

1 At least one aura symptom spreads gradually over ≥5 minutes
2 Two or more aura symptoms occur in succession
3 Each individual aura symptom lasts 5 to 60 minutes
4 At least one aura symptom is unilateral
5 At least one aura symptom is positive
6 The aura is accompanied, or followed within 60 minutes, by headache

D Not better accounted for by another *ICHD-3* diagnosis

ICHD-3 = International Classification of Headache Disorders, Third Edition.

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visual cortex could be involved or that the distinct columnar organization of the cortex could play a role.

Although the scintillating scotoma is the classically described visual aura phenomenon, flashing lights is a more commonly reported visual disturbance.[2] Isolated scotomas and other distortions of vision are also common. When the scintillating scotoma of migraine does occur, it typically begins at the center of the visual field and expands outward, but it can also begin peripherally and propagate toward the center. Individual patients may have multiple sites of migraine aura initiation in the visual cortex. The visual aura percept may propagate throughout an entire visual field or may remain spatially limited.[4] Some patients may simply report blurred vision, but no consensus exists about whether blurred vision should be considered an aura symptom. Sensory symptoms are typically paresthesia of the hand and face, although numbness may also occur, and the distribution may spread to involve the trunk and lower extremity in some patients.[3] The most common language symptom is

CASE 2-1

A 27-year-old woman with a history of episodic headache presented for evaluation of new transient visual, sensory, and language symptoms. She reported that 2 days ago she had an episode consisting of "flashing lights" that gradually spread to involve most of the right side of her vision. She had difficulty focusing her vision while this occurred. While the visual symptoms were occurring, she noticed a mild global headache and light sensitivity. About 5 minutes after the visual disturbance began, she experienced a tingling sensation on the right side of her face and her right hand, and at some point after this, she noticed that she was having difficulty speaking. She also noticed that her right arm felt "clumsy." The visual symptoms and difficulty speaking resolved after approximately 30 minutes, but she continued to feel some tingling of her face and had mild impairment of coordination of her right hand for several hours. She had moderate bilateral headache for the next 24 hours, after which all her symptoms had resolved completely. She had not been taking any medications until 2 weeks prior to this episode, when she had started on an oral contraceptive preparation. Her neurologic examination was entirely normal.

COMMENT

This case describes a typical presentation of a migraine aura. The gradual onset and progression of symptoms is reassuring, indicating that her symptoms are likely not due to cerebral ischemia. Although visual symptoms are most common, sensory, language, and motor symptoms may occur. "Flashing lights" are a common migraine visual aura description; aura symptoms may vary from attack to attack in a given individual. Typically, but not always, visual symptoms precede other aura symptoms. Other migraine symptoms including headache and light sensitivity may accompany rather than follow aura or may not occur at all. New onset of aura may happen in patients with migraine in times of hormonal change, particularly during pregnancy or following the initiation of hormonal therapies.

word-finding difficulty, but a variety of dysphasic language disturbances may occur.[3] The typical duration of aura is 30 minutes; however, in some cases, the aura may last only a few minutes and, in others, it may last more than 4 hours.[3]

Dizziness and vertigo during migraine attacks may be more commonly associated with migraine with aura, although these symptoms may also occur in migraine without aura.[5] Symptoms including vertigo, dysarthria, tinnitus, hypacusis, diplopia, ataxia, and decreased level of consciousness are now included as part of the diagnosis of migraine with brainstem aura (TABLE 2-2).[1] The diagnosis of migraine with brainstem aura has replaced the diagnosis of basilar migraine in the *ICHD-3*, reflecting an understanding that the symptoms included in this diagnosis do not necessarily reflect changes in perfusion through the basilar artery. The evidence that these symptoms arise from aura mechanisms involving the brainstem is not strong, and peripheral vestibular or cochlear dysfunction could also be involved in producing symptoms of dizziness, vertigo, tinnitus, and hearing impairment.

The duration and severity of the headache of migraine with aura has been reported to be less than with those without aura, but the severity of pain associated with aura varies widely. Migraine aura without headache is common, whereas, conversely, some patients report that their attacks that include aura are associated with their most severe headache.[3] As discussed below, the variable relationship between migraine aura and headache occurrence and severity raises questions regarding the relationship between the mechanisms of aura and those that cause pain.

INCIDENCE AND PREVALENCE OF MIGRAINE AURA

In population studies, the prevalence of migraine with aura among individuals with migraine has been reported to range from approximately 20% to 40%.[6] The

TABLE 2-2 ***ICHD-3* Diagnostic Criteria for Migraine With Brainstem Aura**[a]

A Attacks fulfilling criteria for migraine with aura and criterion B below

B Aura with both of the following:

1 At least two of the following fully reversible brainstem symptoms:

- a Dysarthria
- b Vertigo
- c Tinnitus
- d Hypacusis
- e Diplopia
- f Ataxia not attributable to sensory deficit
- g Decreased level of consciousness (Glasgow Coma Scale ≤13)

2 No motor or retinal symptoms

ICHD-3 = International Classification of Headache Disorders, Third Edition.

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relative prevalence of migraine with aura compared with migraine without aura is approximately the same in women and men.[6] Of those who have attacks of migraine with aura, the majority also have attacks of migraine without aura.[3] This variability is a potential confounding factor in clinical studies, in which patients are commonly binned in a binary fashion as having either migraine with or without aura when, in fact, many have both.

GENETICS OF MIGRAINE AURA

Migraine commonly runs in families, and the heritability of migraine with aura is significantly greater than that of migraine without aura. First-degree relatives of those with migraine with aura have been reported to have a nearly fourfold risk of migraine with aura but no increased risk of migraine without aura.[7] By contrast, first-degree relatives of those with migraine without aura have been reported to have a nearly twofold risk of migraine without aura and 1.4 times risk of migraine with aura.[7] Twin studies indicate heritability of 65% in patients with migraine with aura compared with 52% in patients with migraine without aura.[8] Genome-wide association population studies, however, have not revealed any clearly increased association of the verified migraine gene polymorphisms with migraine with aura as compared to migraine without aura.[9] A population study of genetic risk found a higher genetic risk for migraine in general and migraine without aura but not in migraine with aura.[9] The reasons for this apparent discrepancy between heritability studies and genome-wide association studies are unclear.

The familial hemiplegic migraine syndromes are monogenic disorders in which migraine aura is severe and often prolonged. An open question regarding the gene mutations responsible for familial hemiplegic migraine is whether their effects modulate migraine in general or rather are more specifically "aura genes," whose effects transform typical aura into more severe and widespread clinical symptoms. The frequency of migraine attacks is not necessarily higher in patients with familial hemiplegic migraine as compared with patients with typical migraine, and those with familial hemiplegic migraine may also have attacks of typical migraine.[10] Thus, familial hemiplegic migraine genes may not change the susceptibility to migraine in general but rather may change the clinical phenotype of migraine when it does occur. A mutation in the gene encoding the TRESK potassium channel (*KCNK18*), causing reduced function of the channel, was reported in a family with migraine with aura.[11] One of the two mutations in casein kinase 1 delta (*CSNK1D*) found in families with migraine and familial advanced sleep phase syndrome was associated primarily with migraine aura, although some carriers of the mutation only experienced migraine without aura.[12]

VASCULAR CHANGES WITH MIGRAINE AURA

During migraine aura, brain hypoperfusion may occur in a distribution correlated with aura symptoms as indicated by positron emission tomography (PET), MRI perfusion, and arterial spin labeling studies.[13–15] Hypoperfusion may also extend to regions of the brain beyond those related to aura symptoms or occur in patients without clinical symptoms of aura.[16] Hyperperfusion has also been reported in some cases during aura and in other cases following aura symptoms.[17,18] Neither the hypoperfusion nor the hyperperfusion are strictly correlated temporally or spatially with either aura symptoms or headache, indicating that the blood flow changes are not primarily responsible for aura

KEY POINTS

- Migraine aura symptoms include visual, sensory, language, motor, or brainstem symptoms that begin and progress gradually, which reflect a slowly propagating physiologic phenomenon in the brain.
- The symptoms of migraine aura are highly variable from person to person and may vary significantly from attack to attack in a given individual.
- Characteristics of the visual percept of the migraine aura indicate that the brain activity underlying aura can begin in different parts of the visual cortex in the same individual and that the activity spreads in a linear fashion along a sulcus or gyrus rather than as a concentric wave.
- The diagnosis of migraine with brainstem aura has replaced the diagnosis of basilar migraine in the most recent version of the *International Classification of Headache Disorders, Third Edition*, reflecting an understanding that the symptoms included in this diagnosis are not necessarily produced by changes in perfusion through the basilar artery.
- Migraine with aura has greater heritability than migraine without aura, but thus far the only genes that have been identified in association with migraine are those responsible for monogenic familial hemiplegic migraine disorders.

symptoms.[13] It is extremely rare for the hypoperfusion associated with migraine aura to reach the threshold for ischemia, which is consistent with the rarity of migrainous infarction. Interestingly, however, patients with migraine aura have been reported to have increased recruitment of ischemic tissue into the infarct with acute stroke and possibly a larger infarct size.[19] Thus, it appears that while migraine aura itself does not result in stroke, migraine aura mechanisms may worsen stroke when it occurs because of causes other than migraine (see the discussion of spreading depolarizations below). Changes in vascular permeability have also been reported with migraine with prolonged aura and hemiplegic migraine,[20] although such changes may not occur with typical aura.[18]

CORTICAL SPREADING DEPRESSION IN ANIMAL MODELS

The phenomenon of cortical spreading depression, originally described by Leão in the 1940s, is generally assumed to be the physiologic mechanism responsible for the migraine aura. Leão described a slowly propagated depolarization, followed by suppression of electrographic activity, that spreads from a focal site of initiation to involve the majority of one hemisphere of the lissencephalic (lacking sulci or gyri) cortex in different animal models. Cortical spreading depression in animals can be triggered by mechanical perturbation of the cortex, local application of potassium, excessive electrical stimulation, administration of endothelin (which may cause local ischemia), and application of the sodium-potassium ATPase inhibitor ouabain.[21] Cortical spreading depression results in the massive release of neurotransmitters including glutamate, dopamine, and ATP, as well as large changes in the concentrations of extracellular and intracellular ions including sodium, potassium, chloride, and calcium.[21]

Cortical spreading depression in animal models also results in dramatic changes in the vasculature. In mice, the propagating cortical spreading depression wave is accompanied by the marked constriction of cortical surface arteries followed by recovery and, in some cases, transient slight vasodilation.[22] In the 60 minutes following a single cortical spreading depression event, sustained vasoconstriction occurs in the face of ongoing depolarization and neuronal firing, consistent with an uncoupling of the normal relationship between brain activity and blood flow.[22] It is possible that this sustained neurovascular uncoupling could play a role in the consequences of cortical spreading depression, including pain, via release of nociceptive messengers such as ATP and calcitonin gene-related peptide (CGRP).

Studies in rodent models indicate that cortical spreading depression activates peripheral and central trigeminal pain pathways. This may occur via trigeminal afferents that innervate the dura[23] or via direct descending central pathways.[24] Potential nociceptive messengers include glutamate, ATP, and high mobility group box 1 (HMGB1).[25,26] A recent study found that monoclonal antibodies targeting CGRP inhibited the firing of nociceptive neurons in the brainstem, consistent with CGRP as a mechanism by which cortical spreading depression could cause pain.[27]

Mice expressing migraine-associated genes have a higher susceptibility to cortical spreading depression.[21] Female mice have also been reported to have a higher susceptibility to cortical spreading depression.[28] Estrogen has been found to increase the susceptibility to cortical spreading depression, whereas testosterone has been reported to have the opposite effect.[29] Migraine preventive medications with known efficacy in humans (including those that treat migraine

with and without aura) generally inhibit cortical spreading depression in rodents, such that this model has been used to predict the efficacy of medications in development for migraine.[30] Acute and preventive neuromodulation approaches including transcranial magnetic stimulation also inhibit cortical spreading depression.[31] Thus, cortical spreading depression in animal models appears to be a reasonable translational model for studying migraine.

CORTICAL SPREADING DEPRESSION IN HUMAN BRAIN INJURY

Spreading depolarizations that are very similar in nearly all characteristics to cortical spreading depression in animal models have been described in detail in humans with brain injury. Repetitive spreading depolarizations emanating from sites of injury have been characterized with electrocorticography in patients with traumatic brain injury and ischemic and hemorrhagic stroke.[32] These events typically propagate along a single sulcus or gyrus and can be associated with either vasodilation or paradoxical vasoconstriction, similar to what is observed in mice. In some cases, spreading depression events are believed to exacerbate underlying brain injury.[32]

CORTICAL SPREADING DEPRESSION AND MIGRAINE AURA

Despite its nearly universal acceptance as the pathophysiologic mechanism underlying the migraine aura, cortical spreading depression has, in fact, never been definitively demonstrated in conjunction with aura in humans. This may be, in part, because most EEG recordings are not configured to measure direct current changes such as those that occur in conjunction with the cortical spreading depression wave, or they may not have the spatial resolution to detect an event that may occur in a relatively small area of cortex. Slowly propagated waves of reduced blood flow over broad areas of the cortex have been reported in both migraine with and without aura, and it has been widely assumed that this propagated hypoperfusion is related to cortical spreading depression.[13,16] Indeed, the occurrence of cortical spreading depression related to migraine aura is commonly depicted as a broad concentric wave traversing multiple gyri and sulci. However, mapping of the percept of the migraine aura onto the visual cortex suggests that the mechanism underlying aura travels in a much more spatially restricted manner along a single gyrus or sulcus,[4] similar to what has been observed in humans in the setting of brain injury. It is therefore possible that most surface EEG recordings have not had the resolution to detect such a spatially restricted event.

If the pathophysiologic mechanism of the migraine aura is indeed traveling in a more linear fashion along a gyrus or sulcus, this raises multiple other interesting issues. First, it is not clear by what path it could travel from the occipital cortex to the sensory cortex to the motor cortex. Second, the blood flow changes that have been observed in migraine may be much more extensive than changes in brain parenchymal activity that are responsible for aura symptoms. Finally, if migraine aura mechanisms do indeed contribute to pain, then it is clear that the distribution of headache is not correlated with the spatially limited location of the changes in brain activity that cause aura.

MIGRAINE AURA AND HEADACHE

Because migraine aura typically occurs at the beginning of the headache phase of an attack, and because cortical spreading depression has been shown to

KEY POINTS

- Although migrainous infarction is rare, migraine aura mechanisms occurring in response to ischemia may worsen stroke when it does occur.
- Cortical spreading depression has long been assumed to be the physiologic phenomenon underlying the migraine aura, and cortical spreading depression in animal models appears to be a valid translational model for migraine, but it has never been definitively demonstrated with migraine aura in humans.

activate trigeminal nociceptive pathways in animal models, it has been hypothesized that migraine aura contributes to headache. One problem with this hypothesis is the clinical observation that migraine aura commonly occurs without headache, and the majority of migraine attacks are not associated with aura. Further, in attacks in which aura and headache both occur, the headache may accompany aura rather than follow it, and occasionally migraine aura occurs well after headache begins. Thus, an obligate relationship does not exist between the occurrence of aura and the occurrence of headache, nor does a completely consistent temporal relationship exist between the two.[3,33]

THE CONCEPT OF SILENT AURA

Proponents of the hypothesis that aura plays a primary role in a migraine attack have suggested that aura mechanisms could be occurring in patients who do not have symptoms of aura—the so-called "silent aura." As with other migraine mechanisms, it is certainly possible that clinically silent changes may occur in the nervous system during migraine. In the case of a single patient who carefully recorded symptoms of visual aura, there were multiple minutes of recording when he did not experience symptoms, despite the apparent propagation of the aura mechanism in the visual cortex based on retinotopic extrapolation of the aura percept on to the cortex.[4] These observations reinforce the possibility that propagation of aura mechanisms through noneloquent cortex could be occurring in migraine, even in the absence of correlated clinical symptoms.

SEX HORMONE EFFECTS ON MIGRAINE AURA

Migraine with aura is not more prevalent relative to migraine without aura in women as compared to men. Nonetheless, the menstrual cycle and female sex hormones may have significant effects on migraine aura. Migraine associated with the menstrual period is more common without aura, and peak estrogen levels have been reported to be higher in women with a diagnosis of migraine with aura as compared to those without aura.[34] These observations have led to the hypothesis that the occurrence of aura is associated with higher levels of endogenous estrogen. In support of this hypothesis, new onset of migraine aura or worsening of migraine with aura may occur with initiation of oral contraceptive or hormone-replacement therapy or with pregnancy.[34] On the other hand, low-dose continuous estrogen therapy has been reported to reduce aura in a small retrospective case series, possibly because of suppression of normal fluctuations in estrogen or other hormone levels.[35]

PATENT FORAMEN OVALE AND MIGRAINE AURA

Numerous studies have reported an association between migraine with aura and patent foramen ovale, particularly large patent foramen ovale with significant right-to-left shunt.[36] In a randomized controlled trial, closure of patent foramen ovale did not result in a significant difference compared with sham control (with regard to the primary end point of a 50% reduction in migraine attacks), but exploratory analysis revealed that patients for whom aura occurred with a majority of attacks had significant benefit from patent foramen ovale closure.[37] A study of patent foramen ovale closure in patients with migraine

with aura found that patent foramen ovale closure did not meet the primary end point of significant reduction in the number of migraine days, but a secondary analysis of these results found that days with migraine with aura were significantly reduced.[38] These findings, while not supporting patent foramen ovale closure as a therapy for migraine, do raise the possibility of a causative role for right-to-left shunt in migraine aura. Other circumstantial evidence supporting such a causal role comes from observations of patients with hereditary hemorrhagic telangiectasia, a syndrome associated with pulmonary arteriovenous malformations that may cause significant right-to-left shunt. These patients have a higher prevalence of migraine with aura, and ablation of pulmonary arteriovenous malformations has been reported to reduce migraine attacks.[39] Microemboli have been reported to trigger cortical spreading depression in rodent models[40]; paradoxical emboli via right-to-left shunt could therefore be a mechanism for triggering mechanisms of aura. Alternatively, migraine aura might be triggered by deoxygenated blood traveling via right-to-left shunt. Migraine aura has been reported to be triggered by hypoxia in human studies, suggesting this as a possible mechanism underlying the association of patent foramen ovale and migraine with aura.[41]

MIGRAINE AURA AND STROKE

Several population studies have found an association between stroke and migraine with aura but not without aura and specifically in women as compared to men.[42] A hospital registry study examining the incidence of perioperative stroke found that patients with migraine were at increased risk of perioperative ischemic stroke, with the highest risk being for those with a diagnosis of migraine with aura.[43] Investigation of patients on an inpatient stroke unit found that patients with migraine with aura were overrepresented relative to migraine without aura, and those with migraine, in general, were younger and more likely to have patent foramen ovale.[44] A study of a US health care claims database from 2006 to 2012 found that there was a cumulative incidence of 11 strokes per 100,000 females aged 15 to 49 years.[45] An increased odds ratio was found for ischemic stroke among those with migraine with or without aura not using combined hormonal contraceptives (odds ratios of 2.7 and 2.2, respectively). In patients with aura, combined hormonal contraceptive use was associated with a further increase in the association with ischemic stroke (odds ratio 6.1), but this was not the case for migraine without aura (odds ratio 1.8). Issues regarding this study include the small numbers and the reliance upon diagnostic codes. A 2002 study of the relationship between stroke and migraine in women aged 20 to 44 years of age reported that among 86 cases of ischemic stroke and 214 controls, an increased risk of stroke was found in patients both with and without aura and particularly in those who had more than 12 attacks of aura per year at migraine onset, but the study found that correcting for oral contraceptive use had no effect on this association.[46]

While substantial evidence clearly exists for the association between migraine with aura and stroke, the mechanism(s) for this association remains unclear. It is often presumed that this association is because of migrainous infarction that occurs in the setting of a migraine aura, possibly related to cortical spreading depression. No evidence supports this presumption,

KEY POINTS

- Cortical spreading depression can activate trigeminal pain pathways in animal models, but the variable relationship between migraine aura and headache does not support aura as a mechanism that triggers headache.
- Migraine with aura is associated with patent foramen ovale and increased risk of stroke; patent foramen ovale could play a significant role in the increased stroke risk associated with migraine with aura.
- No evidence supports a contraindication to triptans as acute therapies in attacks of migraine that include aura.

however, and an alternative explanation is that migraine aura and stroke share a predisposition or mechanism. Patent foramen ovale is an example of such a possible predisposition; patent foramen ovale could represent a factor that is independently associated with migraine aura and stroke.

PSYCHIATRIC COMORBIDITIES ASSOCIATED WITH MIGRAINE AURA

Migraine with aura has been reported to be associated with a number of psychiatric comorbidities including depression, bipolar disorder, panic disorder, and suicidality.[47] Interestingly, however, patients with migraine aura without headache were reported to have reduced affective disorder and suicidality compared to those with headache.[48] The mechanisms underlying these associations remain unclear but could include shared pathophysiology regarding neurochemical function or cortical excitability.

IMPLICATIONS OF MIGRAINE AURA FOR CLINICAL MANAGEMENT

Attacks of migraine with aura may be less responsive to triptans than those without aura.[49] Currently, the only treatment specifically indicated for the acute treatment of migraine with aura is single-pulse transcranial magnetic stimulation.[50] This treatment is now approved for use in the United States by the US Food and Drug Administration (FDA) for the acute treatment of migraine with aura and for the prevention of migraine. Studies have provided evidence that ketamine may be helpful for migraine with prolonged aura,[51] but this approach has not been widely adopted. No treatments are specifically indicated for the prevention of migraine with aura (CASE 2-2).

Although multiple organizations including the World Health Organization and the American College of Obstetricians and Gynecologists recommend against the use of estrogen-containing oral contraceptives in women with migraine with aura because of increased risk of stroke, the evidence supporting this recommendation is mixed and has many confounding factors.[52,53] Many of the studies indicating increased stroke risk were based on use of estrogen doses that are significantly higher than those used presently. Further, aura diagnosis was not consistent, nor was the diagnosis of stroke consistently definitive with imaging verification, which can be problematic when aura can present with strokelike symptoms and therefore be misdiagnosed as stroke. Also, most studies did not subclassify patients based on the frequency of aura; age may be a significant factor, and correction for other stroke risk factors was inconsistent and subject to different interpretations. While multiple studies report a higher relative risk of stroke in women with migraine with aura using estrogen-containing oral contraceptives, all studies agree that the absolute risk of stroke is small.[52,53] Although clearly still a controversial issue, at this point in time, it is this author's view that compelling evidence does not support recommendations regarding the use of oral contraceptives in women with migraine with aura, except to suggest that low-dose estrogen preparations should be used whenever possible. Also, some neurologists hesitate to prescribe triptans in patients with aura based upon concerns regarding possible vasoconstrictive effects of these medications, but magnetic resonance angiography (MRA) studies indicate that triptans do not, in fact, constrict intracranial blood vessels,[54] and no evidence supports a contraindication to triptans as acute therapies in attacks of migraine with aura.

CASE 2-2

A 24-year-old woman presented for a second neurologic opinion regarding management of migraine. She had a history of episodic migraine with and without visual aura since age 13. Her attacks occurred once per month and, if treated effectively with a triptan, lasted 1 hour. If she was not able to use a triptan as acute therapy, the attacks lasted for 24 hours. She experienced aura with approximately 30% of her attacks, consisting of a slowly expanding arc of jagged lines that propagated throughout one visual field over approximately 30 minutes. On two occasions that she could remember, she experienced numbness of her face associated with the visual symptoms. On one occasion, she experienced difficulty speaking as the visual symptoms were resolving. If the aura occurred, approximately 10 minutes after the aura began, she experienced pain that started in the neck then spread to the occipital region and eventually to the retro-orbital region. The pain increased in intensity as it spread and eventually became incapacitating in severity. She had nausea with some of her attacks and consistently experienced light sensitivity. Oral sumatriptan, which was prescribed by a neurologist, was effective in relieving headache and associated symptoms for approximately 90% of attacks.

She was interested in starting an oral contraceptive, so she had asked her primary care provider about this. She had never smoked tobacco. She was told by her primary care provider that she could not take an oral contraceptive because an increased risk of stroke existed in women with migraine aura. She was also told that she should not take sumatriptan, because this could cause stroke in patients with migraine with aura. She was confused about why her neurologist would have prescribed sumatriptan if it was risky and was concerned about the risk of stroke.

COMMENT

While multiple studies indicate that oral contraceptive use is associated with an increased risk of stroke in women with migraine with aura, the evidence is mixed, and studies regarding this question have multiple confounding factors, including estrogen dose, age, the frequency of aura, definitive confirmation of stroke, and other stroke risk factors.[52,53] This is a complex issue that remains controversial, but some neurologists (including this author) believe that the evidence is not sufficient to support guidelines recommending against use of all estrogen-containing oral contraceptives (especially low-dose estrogen preparations) in women with migraine with aura. Regarding triptan use, the misconception that triptans cause significant intracranial vasoconstriction commonly leads practitioners to avoid these medications for fear of migrainous infarction. In fact, good evidence now suggests that sumatriptan does not constrict intracranial vessels, and no evidence exists whatsoever to contraindicate triptan use in patients with migraine with aura. This author would, despite contrary guidelines, endorse the use of low-dose estrogen contraception in this patient, as well as the use of sumatriptan as an acute therapy.

CONCLUSION

The migraine aura is a dramatic neurologic event with complex neural and vascular mechanisms and has potentially important implications regarding diagnostic and therapeutic management. Refined understanding of its clinical features, comorbidities, patterns of propagation in the human brain, and specific responses to therapy can add important new insight into the pathophysiology of migraine and its optimal therapy.

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The Migraine Postdrome

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

ABSTRACT

PURPOSE OF REVIEW: **The migraine postdrome is the least studied and least understood phase of migraine. This article covers the salient features of the migraine postdrome and provides insight into the history, clinical symptoms, and future implications of this phase of migraine.**

RECENT FINDINGS: **Prospective electronic diary studies have shown that patients are left disabled with various nonheadache symptoms in the migraine postdrome, and 81% of patients report at least one nonheadache symptom in the postdrome. Hence, it is important to understand this phase better and ensure that more effective treatments become available in the future to lessen the morbidity associated with this phase. Functional imaging shows widespread reduction in brain-blood flow in the postdrome, which explains the multitudes of symptoms experienced by patients.**

SUMMARY: **The disability related to migraine is not exclusive to the headache phase but extends into the postdrome phase and is associated with several nonheadache symptoms that prolong the symptoms experienced by patients with migraine. Further research into the postdrome is crucial to improve our overall understanding of migraine mechanisms. This knowledge may also help to treat the concurrent nonheadache symptoms better in the future. Novel neuroimaging techniques provide a valuable noninvasive tool to push the frontiers in the understanding of migraine pathophysiology. These methods may help shed further light onto the possible links between key brain structures and networks that could be implicated in the pathophysiology of the various migraine phases.**

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Continued on page 1031

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INTRODUCTION

Migraine is a leading cause of disability worldwide,[1] extracting a huge economic burden on global economies.[2,3] Knowing more about the key neural networks and neurotransmitters involved during the various phases of migraine may improve our understanding and management of the condition, which may also open doors to focused therapeutic options. Four main phases of migraine have been described[4]: the migraine aura, premonitory phase, headache phase, and the postdrome. Of these phases, the postdrome is relatively newly described. The postdrome is the period between resolution of the throbbing headache and when the patient feels completely back to normal.[5] During the postdrome phase, patients experience numerous nonheadache symptoms that

KEY POINTS

- Tiredness, concentration difficulty, and neck stiffness are the most typically reported postdrome symptoms of migraine.
- Postdrome symptoms appear to be common, with 81% to 94% of patients with migraine reporting these symptoms.
- Treatment with triptans does not appear to alter the underlying diencephalic and brainstem mechanisms involved in migraine pathophysiology, and persistent activation of these networks may explain some of the symptoms in the migraine postdrome.
- Comorbidities such as anxiety and depression do not appear to influence the presence or absence of the migraine postdrome.
- Assigning postdrome symptoms into four main groups (neuropsychiatric, sensory, gastrointestinal, and general symptoms) gives clarity in classifying and assessing the symptoms.

can significantly limit the return to normal function in a proportion of patients.[6–8] A prospective daily electronic diary study showed that about 81% of subjects with migraine reported at least one nonheadache symptom in the postdrome (TABLE 3-1).[5] Some data also show the presence of postdrome in a pediatric population.[9] While common and disabling, the postdrome phase is not yet defined in the *International Classification of Headache Disorders, Third Edition (ICHD-3)*.[10] Defining the phase and incorporating it into the headache classification is needed so that vital research can be pursued and standardized.

HISTORY

Research into the postdrome phase is scant. Liveing[11] documented in his 1872 book *Observations on Megrim or Sick-Headache* that sleep resolved migraine attacks. Selby[12] was among the few neurologists who described the postdrome as a characteristic feature of migraine. Selby described the postheadache phase as the anticlimactic act of the migraine drama in which pain and nausea has settled down but patients are left with a difficult to describe prostration and malaise yet typical of migraine. Blau[13] suggested that the postdrome may be due to a slow decline in migraine processes and also hypothesized that it could be the converse process of the premonitory phase.

CLINICAL FEATURES

Patients report various nonheadache symptoms in the postdrome phase (TABLE 3-2). The symptoms can broadly be grouped into neuropsychiatric, sensory, gastrointestinal, and general systemic symptoms.[14,15] Tiredness, concentration difficulty, and neck stiffness are the most typically reported postdrome symptoms.[5] The average duration of the postdrome reported in different studies varies from 18 to 25.2 hours.[6,13]

Postdrome symptoms also appear to be common, with 81% to 94% of patients reporting these symptoms in various studies.[5,7] Although treatment with triptans can be helpful in managing the headache phase, no fundamental alteration appears to occur in the underlying diencephalic and brainstem mechanisms involved in migraine pathophysiology, and this may explain some of the symptoms in the postdrome.[5,16,17] Also, no dominant role appears to exist for comorbidities such as anxiety and depression in the occurrence or absence of the postdrome (CASE 3-1).[6]

In one study involving 40 subjects, patients described 255 nonheadache symptoms in the postdrome.[13] However, several of the symptoms in this cohort were very hard to distinguish between. For example, it is not easy to know the clinical criteria used to distinguish between a subdued mood, depressed mood, bad mood, and introverted mood. Quintela and colleagues[15] strategically addressed this by assigning postdrome symptoms into four main groups: neuropsychiatric, sensory, gastrointestinal (digestive as per the authors of the study), and general symptoms. This gave clarity in classifying and assessing the symptoms. Future research may tell us if it is possible to localize some of these symptoms.

POTENTIAL KEY ANATOMIC STRUCTURES

The key structures involved in the perception of headache include the large intracranial vessels and dura mater[18]; the peripheral terminals of the trigeminovascular system that innervate these structures; the caudal portion of

Relative Frequency of Postdromal Migraine Symptoms Reported at Baseline and Recorded Prospectively in an Electronic Diary Study[a]

TABLE 3-1

Nonheadache Feature	Percent of Patients Who Recalled Each Postdromal Symptom at Baseline (n = 83)	Percent of Attacks in Which Postdromal Symptoms Were Prospectively Reported During the Electronic Diary Study (n = 425)
Tired/weary	75%	88%
Difficulty with concentration	67%	56%
Stiff neck	16%	42%
Light sensitive	13%	36%
Intolerant/irritable	22%	29%
Dizziness	10%	19%
Yawning	15%	14%
Pale face	18%	21%
Noise sensitive	12%	32%
Hunger/food craving	15%	15%
Thirst	13%	32%
Emotional	13%	24%
Difficulty with thoughts	15%	33%
Constipation	4%	7%
Frequent urination	7%	21%
Nausea/vomiting	6%	15%
Difficulty reading or writing	10%	17%
Difficulty with speech	5%	9%
Other	32%	44%

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the trigeminal nucleus, which extends into the dorsal horns of the upper cervical spinal cord and receives input from the first and second cervical nerve roots (the trigeminocervical complex); and the pain modulatory systems in the brain that receive input from trigeminal nociceptors.[16]

The first direct clinical evidence that showed involvement of brainstem structures in migraine generation was reported by Raskin and colleagues.[19] Patients (n = 175) underwent implantation of an electric pain stimulation system that was developed for controlling pain (usually intractable low backache). The electrodes were implanted in the somatosensory area of the thalamus or the periaqueductal gray region. Of these 175 patients, 15 who had not typically previously experienced headaches developed headache with what the authors described as "florid migrainous" features. Of these subjects, 13 had electrodes inserted into the periaqueductal gray region, and the headaches persisted following explantation of the electrodes. Subsequently, activation of the ventrolateral periaqueductal gray was shown by positron emission tomography (PET) during a spontaneous migraine attack.[17] Activation of the periaqueductal gray has also been shown using PET imaging in nitroglycerin-triggered migraine attacks.[20]

The dysfunction of neuromodulatory structures in the brainstem is thought to be a core component in the pathophysiology of migraine.[16] As the major noradrenergic nucleus, the locus coeruleus has a vital role in the regulation of cortical function and is known to modulate responses to afferent traffic.[21] This area has been shown to be activated during acute migraine attacks in PET studies[17,22] and could play a dominant role in the postdrome.

Evidence supports the view that the brain in patients with migraine is hyperexcitable to a variety of stimuli. This suggests that neuronal depolarization, which is the presumed initiating event in migraine aura and possibly in migraine without aura, is more easily triggered.[23–25] Because of the hyperexcitability, a lower level of transcranial magnetic stimulation of the occipital cortex is required to produce visual phosphenes in patients with migraine compared with patients without migraine.[26–28] Genetic mutations can increase neuronal excitability through a variety of mechanisms.[29–31] The cortical excitability may indicate the chronicity process in the disease.[32]

TABLE 3-2 **Migraine Postdrome Symptoms**[a]

Category	Symptoms
Neuropsychiatric symptoms	Mood changes, concentration trouble, sleep disturbance (insomnia and hypersomnolence)
Sensory symptoms	Head soreness, photophobia, phonophobia, speech disturbance
Gastrointestinal symptoms	Nausea, flatulence, constipation, vomiting, anorexia, food craving, abdominal pain, diarrhea
General systemic symptoms	Tiredness, urination, fluid retention

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Previous functional imaging studies have shown activations of the posterolateral hypothalamus, midbrain tegmental area, periaqueductal gray, dorsal pons, and various cortical areas such as the frontal, temporal, and occipital regions in the premonitory phase.[20] The symptoms that patients report are broadly similar in the premonitory and postdromal phases.[5,33] Based on the similarity of symptoms, one can hypothesize that a shared neural network may be active in the postdrome and premonitory phases.

Another potential neuroanatomic explanation for postdrome symptoms is diffuse cortical and subcortical involvement given the multitude of symptoms patients describe in the postdrome.[5,6,14,15,34] After evaluating postdrome symptoms within his cohort of subjects, Blau[13] suggested involvement of the whole brain in the pathophysiology of the postdrome but especially the frontal lobes and the hypothalamus as vital structures in this phase. Interestingly, widespread reduction in brain blood flow in the postdrome has been demonstrated in a functional imaging study using arterial spin labeling MRI, which can explain the clinical presentation very well. This study suggests involvement of the various cortical and brainstem areas such as the superior frontal gyrus, medial frontal gyrus, middle frontal gyrus, putamen, superior temporal gyrus, middle temporal gyrus, inferior temporal gyrus, posterior

CASE 3-1

A 33-year-old woman presented for a consultation regarding her history of episodic migraine. She described getting between one to two headache episodes per month. Her throbbing headaches would respond well to oral sumatriptan, which had been prescribed by her primary care provider. Following the cessation of her throbbing headache, she reported a mixed feeling of relief and mental exhaustion. She felt like her head was "sore and bruised." She also reported tiredness and concentration difficulty. These nonheadache symptoms could last several days and would limit her return to normal function.

The patient was a neurosciences PhD student, and the symptoms were having a profound impact on her ability to write her PhD thesis. Not knowing what these symptoms represented and not being given a diagnosis for these symptoms was making her more anxious. The symptoms were profoundly affecting her quality of life. She had seen several neurologists and had undergone several investigations including several normal brain MRIs. Her neurologic examination was normal.

COMMENT

This case illustrates some of the clinical symptoms patients experience in the postdrome of migraine. This patient had seen various providers who had not given her an explanation for her symptoms, and she ended up having extensive investigations. She was seen eventually in a tertiary headache clinic at the time of her current presentation, following a referral by her primary care provider, and was given the diagnosis of migraine postdrome. Once she was reassured that her symptoms were related to a migraine postdrome, she could better focus on her PhD studies.

KEY POINTS

- Based on the similarity of symptoms, one can hypothesize that a shared neural network may be active in the postdrome and premonitory phases of migraine.
- Not recognizing the typical postdrome symptoms may lead to patients undergoing unnecessary investigations and hospital visits, and recognition and reassurance regarding postdrome symptoms may alleviate the patient's concerns.
- The role of brainstem noradrenergic mechanisms and cortical spreading depression in the postdrome pathophysiology needs to be explored further. Functional neuroimaging may hold the key.
- The lack of literature surrounding the postdrome phase of migraine and its significant burden for patients in terms of returning to normal function indicate a vital need to understand it better.

cingulate, anterior cingulate, thalamus, hypothalamus, and midbrain in the neurobiology of the postdrome.[35]

PATHOPHYSIOLOGIC MECHANISMS OF THE POSTDROME

The locus coeruleus is a brainstem noradrenergic nucleus located in the dorsal pontine tegmentum. This nucleus provides the major source of norepinephrine to the cerebrum, brainstem, cerebellum, and spinal cord. The existence of reciprocal circuits between this nucleus, the neocortex, diencephalon, limbic system, and spinal cord emphasize its widespread impact within the neuraxis.[36] The locus coeruleus noradrenergic system is one of the first systems that becomes involved during a stressful event. It is involved in a broad range of physiologic and psychological events such as pain processing, behavioral modification, and stress reactivity.[37] Functional imaging studies have shown activation of the dorsal pons in premonitory and migraine headache phases.[17,20,22,38] This activation might include the locus coeruleus,[20] leading to widespread vasoconstriction mediated by an α_2-adrenoceptor mechanism.[39–41] The near global reductions in regional cerebral blood flow seen in the postdrome[35] can potentially be explained by widespread vasoconstriction via α_2-adrenoceptor mechanism through activation of brainstem nuclei. This may serve as a pain modulatory mechanism but, as a consequence, may lead to the protean postdromal symptoms that result from a near global reduction in regional cerebral blood flow.

Another mechanism that can potentially explain the reductions in regional cerebral blood flow in the postdrome is the phenomenon of cortical spreading depression. This bioelectric phenomenon was first described by Leão,[42,43] who demonstrated a wave of spreading suppression of spontaneous EEG activity when electrically stimulating the rabbit cortex. Cortical spreading depression usually silences spontaneous and evoked electric activity for 5 to 15 minutes. However, in certain pathophysiologic states, such as hypoglycemia, hypoxia, and ischemia, cortical spreading depression can occur spontaneously and can be prolonged in nature.[44] Increased susceptibility to cortical spreading depression occurs when astroglial function is hampered.[45] Electrophysiologic studies demonstrate that in patients with migraine a cortical and possibly subcortical dysfunction may explain increased susceptibility to cortical spreading depression.[46,47] Cortical spreading depression is preceded by a fast network of oscillations, suggesting brief hyperexcitability.[43] This is followed by complete suppression of neuronal activity, lasting several minutes, followed by complete recovery.[42] Hadjikhani and colleagues[27] used functional imaging to support cortical spreading depression as the generator of migraine aura. Persistent hypoperfusion following cortical spreading depression has been demonstrated and hence corroborates the notion that the perfusion changes of migraine may be pathophysiologically related to spreading depression.[48]

Functional imaging, including functional MRI (fMRI) and PET, has been increasingly used in migraine and other pain states and has alluded to areas of brain activation that are thought to be key structures in the initiation and propagation of the headache and pain states.[20,49,50] Functional imaging has also helped improve our understanding of the nonpain phases of migraine including the postdrome.[35,51] The paucity of literature surrounding the postdrome phase

and its significant burden for patients in terms of returning to normal function indicate a vital need to understand it better.

CONCLUSION

The postdrome prolongs the symptoms experienced by patients following migraine headache attacks and is important to clinically recognize. Unraveling what happens to neural activity during this phase may help us improve our understanding of migraine pathophysiology and may also potentially lead to new therapeutic targets and interventions. Functional neuroimaging studies hold the key to unlocking the neural activity in the postdrome phase and identifying therapeutic targets.

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DISCLOSURE

Continued from page 1023

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Acute Treatment of Migraine

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UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Vargas discusses the unlabeled/investigational use acetaminophen, acetylsalicylic acid, dexketoprofen, diclofenac, dipyrone, droperidol, haloperidol, ibuprofen, ketorolac, lasmiditan, metoclopramide, naproxen, peripheral nerve block, prochlorperazine, and valproate for the acute treatment of migraine.

ABSTRACT

PURPOSE OF REVIEW: This article provides a framework to help providers formulate a plan for the acute treatment of migraine. Topics covered include the cost-effective patient-centered approach known as stratified care and a summary of evidence-based treatment options that are currently available. Strategies for improving treatment response, troubleshooting suboptimal results, and addressing the needs of special populations are also reviewed.

RECENT FINDINGS: Both the American Headache Society and the Canadian Headache Society have released evidence-based assessments and reviews of acute treatments for migraine that can be used to help guide treatment decisions. Although several older medications have been re-released with new formulations or new delivery systems, several new medications have also become available or are in the final phases of study, further increasing the number of options available for patients.

SUMMARY: The acute management of migraine should incorporate a stratified care model in concert with evidence-based treatment options. The response to treatment should be monitored regularly, and measures should be taken to identify suboptimal tolerability or efficacy.

INTRODUCTION

One of the cornerstones of migraine management is establishing an effective acute and rescue treatment plan. Unfortunately, many times the treatment plan does not reflect patient preferences nor does it address patients' unique individual needs based on their migraine characteristics. The fact that up to 40% of patients are dissatisfied with their acute treatment suggests that health care providers should be mindful of the myriad factors that can contribute to treatment success, including medication selection, dosing, route of administration, timing of administration, safety, tolerability, and whether the treatment addresses the patient's definition of effectiveness.[1] Despite a number of advances in diagnosis and treatment, only 22% of patients with migraine use a migraine-specific medication, and a nearly equivalent percentage use barbiturates or opioids for their attacks.[2] This is especially important as inadequate acute treatment exerts a significant socioeconomic burden[3] and has also been associated with transition from an episodic to a chronic pattern of migraine.[4]

Although the American Headache Society (AHS) and the Canadian Headache Society (CHS) have released evidence-based assessments and reviews of various acute treatments for migraine,[5,6] the subsequent release of literature providing guidance on how to properly use these guidelines and how to assess efficacy and patient satisfaction suggests that selecting the best individualized treatment is far more nuanced than simply selecting a medication from a list of evidence-based options.

This article serves to highlight acute treatment options in the context of their level of evidence but also serves to provide guidance on factors to consider while making treatment selections.

MODELS OF ACUTE TREATMENT

A plan for acute and rescue treatment should be provided to every patient with migraine. The plan should be individualized and address the issues and treatment barriers that are specific to each patient and each attack, including the presence of associated nausea or vomiting and the time to peak severity. Treatment approaches frequently follow one of three models of care including step care across attacks, step care within attacks, and stratified care.[7]

In step care across attacks, the patient is usually prescribed an inexpensive, nonspecific analgesic medication and, if unsuccessful, will return to their provider for consideration of a different medication along a stepwise pattern of treatment that eventually incorporates more migraine-specific options. A significant drawback to this model is that when unsuccessful, it may lead to suboptimal and delayed treatment as patients must frequently wait for follow-up visits from their providers for the next step in their care.[7]

In step care within attacks, the patient is counseled to initiate treatment with a low-cost nonspecific analgesic medication and, if unsuccessful, can advance themselves after several hours to more migraine-specific treatment options along a stepwise pattern within each individual attack. One of the drawbacks, however, is that this can lead to suboptimal efficacy of treatment as many migraine-specific treatments, including triptans, are best taken early in the attack rather than several hours after an initial failed treatment.[7]

In stratified care, the patient is entrusted with determining which attacks will respond to various treatments and is given the autonomy to make the appropriate treatment decision based on his or her personal experiences and preferences. Of these three models of care, it is stratified care that best considers individual variance in headache severity and associated features such as nausea or vomiting; this also allows the patient the ability to make his or her own treatment decisions based on their unique needs. Stratified care is equated with higher patient satisfaction and also with decreased health care costs (CASE 4-1).[7]

FIRST-LINE TREATMENT

In 2015, the AHS published a detailed evidence assessment of acute migraine therapies and in 2016 published subsequent guidance on how to interpret and apply the evidence assessment to the clinical setting.[5,8] The CHS published a similar review of acute treatments for migraine in 2013, which addressed the quality of evidence alongside practical recommendations, taking into account factors such as side effect profile and potential for abuse or misuse.[6] These recommendations are summarized in TABLE 4-1. Acute treatments with the highest level of evidence include all triptans as well as nonspecific analgesics

KEY POINTS

- Inadequate acute treatment of migraine exerts a significant socioeconomic burden and has also been associated with transition from an episodic to a chronic pattern of migraine.
- Stratified care considers individual variance in headache severity and associated features such as nausea or vomiting and allows patients the ability to make their own treatment decisions based on their unique needs.
- Stratified care of patients with migraine is equated with higher patient satisfaction but also with decreased health care costs.
- Acute treatments of migraine with the highest level of evidence include all triptans as well as nonspecific analgesics including acetaminophen and certain nonsteroidal anti-inflammatory drugs.

including acetaminophen and certain nonsteroidal anti-inflammatory drugs (NSAIDs). Conflicting opinions exist on the strength of evidence for intranasal dihydroergotamine; however, both groups include it as a first-line option, with the CHS assigning it a weak recommendation. Conflicting opinions on strength of evidence were reported for the opioid medication butorphanol, with the CHS making strong recommendations against its use despite Level A evidence cited by the AHS. The following medication summaries highlight only medications with both the highest level of evidence from AHS and strongest recommendations from CHS.

Triptan Monotherapy

A recent systematic review and meta-analysis demonstrated equivalent or slightly better effectiveness of triptans as a group when compared to NSAIDs, acetaminophen, and acetylsalicylic acid.[9] All triptans and triptan combination medications have strong evidence for effectiveness for acute treatment of migraine at standard doses, with 42% to 76% of patients experiencing pain relief at 2 hours (compared to only 27% of patients treated with placebo), but demonstrated slightly less efficacy than those treated with triptan combination medications such as triptan/acetaminophen and triptan/naproxen (with 2-hour pain relief responses of 80% and 62%, respectively). All standard-dose triptans and triptan combinations also demonstrated superiority with regard to 24-hour headache relief, ranging from 29% to 50% (versus placebo at only 17%), but again triptans in monotherapy performed slightly less well than triptan/acetaminophen and triptan/naproxen, with 24-hour headache relief responses of 50% and 46%, respectively. Triptans also demonstrate superiority to placebo using end points of 2-hour freedom from pain (18% to 50% versus 11%) and 24-hour sustained pain-free periods (18% to 33% versus 10%). Of note, the two orally disintegrating formulations (rizatriptan and zolmitriptan) do not convey

CASE 4-1

A 45-year-old man presented for evaluation of frequently occurring episodic migraine. He reported 6 headache days per month, and on average, two of his attacks were severe, incapacitating, and responsive to a triptan. His headache severity on the other 4 days was typically mild to moderate, and he was usually able to complete his workday with mild impairment in his ability to function. On these mild to moderate days, he felt his triptan was "overkill," and he found nonsteroidal anti-inflammatory drugs to be effective on the rare occasions that he had attempted treatment with them.

COMMENT

This patient was able to make a distinction between attacks that were severe enough to require treatment with a triptan and those that were responsive to over-the-counter nonsteroidal anti-inflammatory drugs. He should be encouraged to treat each of his headaches with a medication commensurate to his attack severity and degree of disability. He should be monitored for overuse, and a prophylactic medication should be considered. This is an example of stratified care.

any significant benefit compared to the standard tablets with regard to their pharmacokinetics but appeared to convey the largest benefit among all oral triptan monotherapies.[9]

Triptan Combination Medications

Several studies have shown the combination of sumatriptan and naproxen (85 mg/500 mg) to be effective for the acute treatment of migraine compared to placebo, with some studies also showing statistical superiority to sumatriptan or naproxen monotherapy. Brandes and colleagues[10] reported the results of two replicate, multicenter, randomized, double-blind, placebo-controlled studies showing that 65% and 57% of subjects reported 2-hour headache relief with the sumatriptan/naproxen combination for both studies compared to placebo (28% and 29%, respectively). In both studies, statistically significant improvement compared to placebo was also demonstrated at 2 hours for resolution of photophobia and phonophobia but not for nausea.

Another study by Mathew and colleagues[11] investigated the sumatriptan/naproxen combination in a population of patients with migraine who had previously discontinued an average of 3.3 triptans because of intolerance or inefficacy. In this population of subjects designated as triptan nonresponders, two randomized, multicenter, double-blind, placebo-controlled studies demonstrated statistical superiority of sumatriptan/naproxen over two attacks for a 2-hour to 24-hour pain-free response in both studies (26% and 31%, respectively) over placebo (8% and 8%, respectively) and a 2-hour pain-free response for both studies of 40% and 44% versus placebo (17% and 14%, respectively).[11]

Of note, taking sumatriptan 50 mg and naproxen 500 mg as two separate tablets for acute treatment also seems to convey some benefit over taking either of the two medications in monotherapy. Effectiveness of this combination was supported with a large, multicenter, randomized, double-blind, double-dummy, placebo-controlled, four-arm study with 46% of subjects taking the active two-tablet combination achieving a statistically superior 24-hour sustained pain-free response versus sumatriptan monotherapy (29%), naproxen monotherapy (25%), or placebo (17%).[12]

Triptan Contraindications and Updates

Triptans are contraindicated in individuals with a history of stroke, heart attack, coronary artery disease, hemiplegic migraine, uncontrolled hypertension, migraine with brainstem aura, and peripheral vascular disease. Rizatriptan, zolmitriptan, and sumatriptan should be avoided within 14 days of using a monoamine oxidase inhibitor.[8]

New developments since the publication of the AHS and CHS guidelines include the addition of a breath-powered device for the delivery of intranasal sumatriptan 22 mg in a powdered versus nasal spray formulation and the voluntary withdrawal of the sumatriptan 6.5 mg iontophoretic patch because of concerns of site irritation, scarring, and burns.[13]

Nonspecific Analgesics

Several nonspecific analgesics have been shown to be efficacious when compared to placebo in the acute treatment of migraine. These include acetylsalicylic acid, acetaminophen, ibuprofen, naproxen, and diclofenac, with both the AHS and CHS ascribing to them the highest level of evidence and with the CHS review

KEY POINTS

- Triptans are contraindicated in individuals with a history of stroke, heart attack, coronary artery disease, hemiplegic migraine, uncontrolled hypertension, migraine with brainstem aura, and peripheral vascular disease.
- A number of nonspecific analgesics have been shown to be efficacious when compared to placebo in the acute treatment of migraine.

TABLE 4-1 **Summary of American and Canadian Headache Societies' Evidence-Based Assessments, Reviews, and Recommendations for Acute Migraine Treatment[a]**

Medication and Dose	American Headache Society Evidence Assessment[b]	Canadian Headache Society Quality of Evidence	Canadian Headache Society Recommendation
		Recommendation for Use in Episodic Migraine	
Analgesics			
Acetaminophen 1000 mg	Level A	High	Strong
Nonsteroidal anti-inflammatory drugs			
Acetylsalicylic acid 500 mg	Level A	High	Strong
Diclofenac 50 mg, 100 mg	Level A	High	Strong
Ibuprofen 200 mg, 400 mg	Level A	High	Strong
Naproxen 500 mg, 550 mg	Level A	High	Strong
Triptans			
Almotriptan 12.5 mg	Level A	High	Strong
Eletriptan 20 mg, 40 mg, 80 mg	Level A	High	Strong
Frovatriptan 2.5 mg	Level A	High	Strong
Naratriptan 1 mg, 2.5 mg	Level A	High	Strong
Rizatriptan 5 mg, 10 mg	Level A	High	Strong
Sumatriptan (oral) 25 mg, 50 mg, 100 mg	Level A	High	Strong
Sumatriptan (intranasal) 10 mg, 20 mg	Level A	High	Strong
Sumatriptan (subcutaneous) 4 mg, 6 mg	Level A	High	Strong
Zolmitriptan (oral) 2.5 mg, 5 mg	Level A	High	Strong
Zolmitriptan (subcutaneous) 2.5 mg, 5 mg	Level A	High	Strong
Ergots			
Dihydroergotamine (intranasal) 2 mg	Level A	Moderate	Weak
Dihydroergotamine (subcutaneous) 1 mg	Level B	Moderate	Weak
Dihydroergotamine (IV, IM) 1 mg	Level B	N/A	N/A
Combinations			
Sumatriptan/naproxen 85 mg/500 mg	Level A	High	Strong
Acetaminophen/acetylsalicylic acid/caffeine 500 mg/500 mg/130 mg	Level A	N/A	N/A

CONTINUED ON PAGE 1037

CONTINUED FROM PAGE 1036

Medication and Dose	American Headache Society Evidence Assessment[b]	Canadian Headache Society Quality of Evidence	Canadian Headache Society Recommendation
		Recommendation for Nonroutine Use in Episodic Migraine	
Oral opioid and tramadol combinations			
Tramadol/acetaminophen 75 mg/650 mg	Level B	Moderate	Weak
Codeine/acetaminophen 25 mg/400 mg	Level B	Low	Weak
Codeine 30 mg	Level C	Low	Weak
Ergots			
Ergotamine 1-2 mg	Level C	Moderate	Weak
		Recommendation Against Use in Episodic Migraine Except Under Unusual Circumstances	
Opioids			
Butorphanol (intranasal) 1 mg	Level A	Low	Strong
Butalbital-containing medications			
Butalbital/acetaminophen/caffeine 50 mg/325 mg/40 mg	Level C	Low	Strong
Butalbital/acetaminophen/caffeine/codeine 50 mg/325 mg/40 mg/30 mg	Level C	Low	Strong

IM = intramuscular; IV = intravenous; N/A = not applicable.
[a] Data from Marmura MJ, et al, Headache,[5] and Worthington I, et al, Can J Neurol Sci.[6]
[b] Level A = medications are established as effective for acute migraine treatment based on available evidence; Level B = medications are probably effective based on available evidence; Level C= medications are possibly effective based on available evidence.

adding a strong recommendation for first-line use.[5,6] In general, most of the medications in this class performed only slightly less effectively than triptans when compared to placebo, are generally well tolerated, and are potentially useful options for treating mild to moderate headache (taking into account the model of stratified care). For some patients, nonspecific analgesics are also useful as the primary acute treatment for more severe pain.

NAPROXEN. In a meta-analysis that included four randomized, double-blind, placebo-controlled studies, naproxen sodium was found to be superior to placebo for the acute treatment of migraine with regard to 2-hour pain relief (pooled relative risk ratio of 1.58), 2-hour pain freedom (pooled relative risk ratio of 2.22), and with 2-hour relief of associated nausea (78%), photophobia (73%), and phonophobia (68%).[14]

ACETYLSALICYLIC ACID. Acetylsalicylic acid at doses of 1000 mg has been shown to have similar efficacy to sumatriptan with a high level of supportive evidence, including a Cochrane Review,[15] that it is more effective than placebo for treating acute migraine attacks. Acetylsalicylic acid has also received a strong recommendation by the CHS as a first-line treatment option.[6] In a study by Lipton and colleagues,[16] 2-hour headache relief (52%) and pain-free responses (20%) were superior to placebo (34% and 6%, respectively). When combined with metoclopramide 10 mg, 2-hour headache relief (57%) and 2-hour pain-free responses (18%) are superior to placebo (26% and 7%, respectively); metoclopramide is an excellent and potentially effective option, especially if nausea is a complicating factor.[15]

Effervescent acetylsalicylic acid 1000 mg is another effective option, with a meta-analysis of three studies showing 2-hour headache relief (52%) and 2-hour pain-free responses (27.1%) better than placebo (34% and 15%, respectively). Effervescent acetylsalicylic acid is the active ingredient in some over-the-counter antacids, typically in dosages of 325 mg per tablet.[17]

ACETAMINOPHEN. In a randomized, double-blind, placebo-controlled study of 351 subjects, Lipton and colleagues[18] demonstrated that oral acetaminophen 1000 mg is more effective than placebo for the acute treatment of migraine, including resolution of migraine-related symptoms of photophobia, phonophobia, and functional disability. Although 2-hour response rates and 2-hour pain-free rates for acetaminophen were statistically superior to placebo (57.8% versus 38.7% and 22.4% versus 11.3%), this study excluded patients with severe attacks that limited daily activity or required bed rest more than 50% of the time and excluded subjects with nausea in more than 20% of their attacks. A subsequent Cochrane Review supported the finding that acetaminophen is effective for the acute treatment of migraine occurring without a severe level of disability.[19]

IBUPROFEN. One large, multicenter, double-blind, placebo-controlled study of 660 subjects demonstrated that ibuprofen 200 mg and 400 mg is effective for treatment of acute migraine not requiring bed rest in more than 50% of attacks or with associated nausea more than 20% of the time.[20] Both the 200 mg and 400 mg doses of ibuprofen resulted in improvement of either mild or no pain at 2 hours (41.7% and 40.8%) compared to placebo (28.1%). For 2-hour reduction of severe pain to mild or no pain, the 400 mg dose proved to be more efficacious

than placebo (36.9% versus 21.6%); however, the 200 mg dose did not demonstrate statistically significant improvement. Of note, 280 (42.4%) of the subjects enrolled eventually withdrew from the study; 272 of which withdrew because of the need for rescue medication. Subsequent meta-analysis and a Cochrane Review yielded similar conclusions that low-dose ibuprofen is safe, well tolerated, and effective at relieving acute attacks of migraine and that the 400 mg dose outperformed the 200 mg dose.[21,22]

DICLOFENAC. Several randomized, double-blind, placebo-controlled studies and a Cochrane Review have shown efficacy of diclofenac for the acute treatment of migraine when compared to placebo.[5,6,23] Diclofenac can be administered orally both in a tablet formulation and also in a buffered, water-soluble, powder formulation that can be dissolved in approximately 2 oz of water. In one crossover study, subjects were significantly more likely to report 2-hour headache freedom with the 50 mg diclofenac powder in oral solution than with 50 mg diclofenac tablets (24.7% versus 18.5%) or placebo (24.7% versus 11.7%). Although somewhat less effective than diclofenac oral solution in this particular study, subjects taking 50 mg tablets were still significantly more likely to report being headache free at 2 hours than subjects taking placebo (18.5% versus 11.7%).[24] Another double-blind, placebo-controlled study investigating diclofenac powder in oral solution for a single moderate to severe migraine attack also showed statistical superiority versus placebo for 2-hour pain-free response (25% versus 10%) as well as an onset of pain relief in 30 minutes, outperforming placebo up to the 24-hour end point.[25]

Nonoral Treatments

In situations where standard evidence-based oral medications are ineffective, poorly tolerated, or contraindicated, it may be necessary to consider any of the several other nonoral treatment options.

PARENTERAL MEDICATIONS. With respect to parenteral options, the AHS has not identified any medications as having Level A evidence or that have a strong recommendation from the CHS for treating acute migraine attacks.[5,26] However, a number of parenteral medications have Level B evidence, including chlorpromazine 12.5 mg, droperidol 2.75 mg, metoclopramide 10 mg, prochlorperazine 10 mg (can also be given IM), dihydroergotamine 1 mg (can also be given IM/subcutaneously), ketorolac 30 mg to 60 mg (can also be given IM), and magnesium sulfate 1 g to 2 g (for migraine with aura). Options with Level C evidence include valproate 400 mg to 1000 mg, tramadol 100 mg, and dexamethasone 4 mg to 16 mg.[5] Parenteral options can be useful considerations for rescue therapy in the emergency department, an outpatient infusion center, or for those who are hospitalized. A separate AHS evidence assessment of parenteral therapies for acute treatment in the emergency department used levels of evidence to stratify various treatments into the following categories:

- **Should offer (Level B)**
  - **Metoclopramide**
  - **Prochlorperazine**
  - **Sumatriptan**

KEY POINT

- **In situations where standard evidence-based oral medications are ineffective, poorly tolerated, or contraindicated, it may be necessary to consider nonoral treatment options for migraine.**

- May offer (Level C)
  - Acetaminophen
  - Acetylsalicylic acid
  - Chlorpromazine
  - Dexketoprofen (not available in the United States)
  - Diclofenac
  - Dipyrone (not available in the United States)
  - Droperidol
  - Haloperidol
  - Ketorolac
  - Valproate

As with other evidence assessments, it was recommended based on Level C evidence that opioids "may be avoided" along with lidocaine, octreotide, and diphenhydramine. There is inadequate evidence (Level U) and no recommendation for acute parenteral treatment with dexamethasone, dihydroergotamine, ergotamine, magnesium (except for migraine with aura), propofol, ketamine, tramadol, promethazine, trimethobenzamide, meperidine, nalbuphine, and lysine clonixinate.[26] It is noted that the AHS evidence for some parenteral treatments in the emergency department differs slightly from the AHS acute treatment assessments.

NERVE BLOCKS

Although expert consensus recommendations from the AHS Special Interest Section for Peripheral Nerve Blocks and Other Interventional Procedures identified a lack of high-level evidence for peripheral nerve blocks in the acute treatment of migraine, a number of retrospective and noncontrolled prospective studies demonstrated efficacy for greater occipital, supratrochlear, and supraorbital nerve blocks.[27] Despite the short duration of local anesthesia, peripheral nerve blocks have been reported to provide long-term improvement lasting weeks as well as resolution of allodynia.[28] Despite a relative lack of evidence, peripheral nerve blocks are easily performed in the outpatient setting, are generally accepted as safe and well tolerated,[28] and continue to be a commonly employed treatment for acute migraine, with 69% of headache practitioners surveyed by the AHS Special Interest Section for Peripheral Nerve Blocks and Other Interventional Procedures consensus incorporating them into their practice.[27] Additional well-designed studies will be necessary to better delineate the efficacy and cost-effectiveness of these treatments in migraine populations.

NEUROSTIMULATION

Devices for external neurostimulation are emerging as effective strategies for the acute treatment of migraine. Specifically, transcutaneous supraorbital nerve stimulation was recently investigated in an open-label trial of 30 subjects using 1 hour of stimulation for an acute migraine attack. After 1 hour of treatment, pain intensity was reduced by 57.1% (−3.22 ± 2.40), and at 2 hours, pain was reduced by 52.8% (−2.98 ± 2.31); however, 36.4% of subjects required rescue medication within 24 hours of stimulation.[29]

One open-label study of 20 patients investigated noninvasive vagal nerve stimulation and demonstrated the effectiveness of both the prevention and acute treatment of episodic and chronic migraine.[30] Two additional open-label studies enrolled a total of 80 patients and specifically investigated noninvasive vagal nerve stimulation for the acute treatment of migraine attacks—one study for episodic migraine and the other for both episodic and chronic migraine. In the episodic study, 2-hour pain freedom for the first attack was reported by 21%, and 2-hour pain improvement was reported by 47% for treatment of moderate to severe pain. Of those treating mild pain, 63% reported 2-hour pain freedom.[31] In the study investigating acute treatment in episodic and chronic migraine, 56.3% of subjects reported improvement of 50% or more in headache severity at 1 hour (35.4% of whom reported pain freedom), and 64.6% reported improvement of 50% or more at 2 hours (39.6% of whom reported that they were pain free). In all studies, noninvasive vagal nerve stimulation was found to be safe and well tolerated. In January 2018, noninvasive vagus nerve stimulation obtained US Food and Drug Administration (FDA) approval for treatment of migraine pain.

In 2014, the FDA approved single-pulse transcranial magnetic stimulation for the acute treatment of migraine with aura. A randomized, double-blind, parallel-group, two-phase, sham-controlled study conducted by Lipton and colleagues[32] demonstrated efficacy of single-pulse transcranial magnetic stimulation versus placebo in subjects treating up to three attacks occurring with aura over 3 months. Pain-free response at 2 hours was 39% for single-pulse transcranial magnetic stimulation versus 22% for sham stimulation for a therapeutic gain of 17% with a sustained pain-free response versus placebo at 24 hours (29% versus 16%) and 48 hours (27% versus 13%).[32]

CALCITONIN GENE-RELATED PEPTIDE ANTAGONISTS

A large body of research supports the significant role of calcitonin gene-related peptide (CGRP) in the pathophysiology of migraine, which has led to the development of a new class of CGRP antagonists. Several CGRP antagonists are under development, including both small molecules and monoclonal antibodies directed at either the CGRP receptor or the peptide itself. A number of CGRP antagonists were shown to be effective acutely and are also being studied for migraine prevention; however, ubrogepant is the only medication in this class that is currently in phase 3 studies for acute treatment.[33] Phase 2b data showed that ubrogepant 100 mg was superior to placebo for the 2-hour pain-free end point (25.5% versus 8.9%) and was safe and well tolerated.[34] CGRP is a vasodilator, and its antagonism does not produce vasoconstriction,[35] suggesting that it might be a viable treatment option in patients with cardiovascular risk factors who are unable to take other migraine-specific medications such as triptans or ergotamines.

5-HT_{1F} AGONISTS

In early studies, agonism of the 5-HT_{1F} (serotonin) receptor has been shown to be effective for acute treatment of migraine, has anti-inflammatory effects, and does not produce vasoconstriction, making it a possible future treatment option in patients with cardiovascular risk factors.[35] One medication in this class, lasmiditan, has now been shown in phase 3 studies to be superior to placebo with regard to 2-hour pain-free response at a dose of 200 mg (32.2% versus 15.3%).[35]

KEY POINTS

- Despite a relative lack of evidence, peripheral nerve blocks are easily performed in the outpatient setting, are generally accepted as safe and well tolerated, and continue to be a commonly employed treatment for acute migraine.
- A large body of research supports the significant role of calcitonin gene-related peptide in the pathophysiology of migraine, which has led to the development of a new class of calcitonin gene-related peptide antagonists.

While the concept behind this class of medications is promising, clearly further research is warranted.

CONSIDERATIONS IN PATIENTS WHO ARE PREGNANT OR BREAST-FEEDING

Acute treatment of migraine in women who are either pregnant or breast-feeding presents a unique challenge; however, several observational studies and registry data have provided some guidance on medications that are considered to be among the safest options.

Among many providers, acetaminophen remains the first-line medication of choice and is the most commonly used medication for treatment of pain in pregnant women.[36] Although acetaminophen is generally considered to be safe, some studies have indicated a possible increased risk of hyperkinetic disorders, attention deficit hyperactivity disorder, and attention deficit hyperactivity disorder–like behavioral problems.[37–39] Acetaminophen is considered by the CHS to be the safest first-line medication for pregnant women.[40]

For many years, opioids had also been considered among the safer options for pregnant and breast-feeding women; however, many studies have demonstrated associations with congenital malformations and developmental defects.[41] A 2017 systematic review of opioid use in pregnancy conducted by Lind and colleauges[41] noted that while several retrospective and observational studies identified significant associations with congenital malformations, a number of important limitations in the quality of these studies influence their interpretation. This review did not provide a definitive recommendation against the use of opioids but rather suggested a judicious approach, taking into account risks and benefits. Additionally, codeine use in the third trimester has been associated with a higher risk of heart malformations, acute cesarean deliveries, and postpartum hemorrhage.[41,42] The additional risks of overuse and dependence in the mother suggest that this class of medications should be avoided if possible.

Caution has been advised regarding the use of triptans in pregnant women especially given the presence of 5-$HT_{1B/1D}$ receptors in the brain and the umbilical cord artery of the fetus.[43] Although numerous studies and registry data seem to indicate no increased risk for congenital malformations, developmental delay, behavioral, or motor problems,[44] some studies suggest that triptan use may result in a small increased risk for preeclampsia and, if used later in pregnancy, preterm delivery.[45] The use of sumatriptan in lactation has been determined to be safe according to the American Academy of Pediatrics, and minimal drug concentrations of eletriptan have been found in infants after breast-feeding. Similar studies on other triptans in humans have not been conducted.[46,47]

Evidence exists suggesting that NSAIDs may result in an increased risk of adverse fetal outcomes if taken in either the first or third trimesters. Specifically, a higher risk of miscarriage in the first weeks of pregnancy, a risk of cleft lip and palate, premature closure of the patent ductus arteriosus, and bleeding risks such as neonatal intraventricular hemorrhage appear to be present if used after the 32nd week of pregnancy.[43,46]

Metoclopramide is frequently used for nausea in pregnancy and also has some evidence for utility in acute treatment of migraine. It is generally considered to be

safe and is considered the preferred antiemetic for pregnant women with migraine according to the CHS.[40] A paucity of similar safety data exist for other antiemetics in pregnancy including domperidone (not available in the United States), ondansetron, and prochlorperazine.[40,43,46]

Ergots remain contraindicated with a high risk of adverse fetal outcomes in pregnancy and can result in decreased milk production and numerous potential adverse effects to the breast-fed infant.

Ultimately, no well-designed or definitive studies demonstrate the safety of any acute migraine medication in pregnant[48] or breast-feeding women. Nonetheless, providers should weigh the risks of using any medication in pregnant women versus the potentially detrimental effects of inadequately addressing headache and associated disability in the mother.[46] Treatment decisions should take into account other risk factors for poor fetal outcomes, headache characteristics (including frequency and degree of disability), and should also include input from the patient's obstetrician and pediatrician.[47] Whenever possible, nonpharmacologic options should be considered. For more information, refer to the article "Headache in Pregnancy" by Matthew S. Robbins, MD, FAAN, FAHS,[49] in this issue of *Continuum*.

TRIPTANS IN COMBINATION WITH SEROTONIN REUPTAKE INHIBITORS

When prescribing the combination of triptans and selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs), it is common for providers to receive alerts or warnings from pharmacies or the electronic medical record. These alerts are based on a 2006 FDA report concerning the risk of serotonin syndrome associated with the combination of triptans and either SSRIs or SNRIs and was based on 29 reported cases of serotonin syndrome in patients using one of these combinations. Evans and colleagues[50] conducted an in-depth review, which was reported as an evidence-based recommendation and AHS position paper. Ultimately, it was found that of the 27 cases prompting the FDA alert, only 10 met criteria for either of two established criteria for serotonin syndrome.[50] Taking into account the high frequency of coadministration of SSRIs/SNRIs and triptans, the overall annual incidence of serotonin syndrome with these combinations was estimated at less than 0.03%, and the incidence of life-threatening events was estimated to be less than 0.002%, both of which are less than the annual incidence of serotonin syndrome in SSRI/SNRI monotherapy.[51] Based solely on Class IV evidence, a Level U recommendation was ultimately rendered regarding this warning, reflecting a determination that the existing data are conflicting or inadequate to support the concern that coadministration of triptans with SSRIs or SNRIs confer any additional risk of serotonin syndrome.[50]

WHAT PATIENTS EXPECT FROM ACUTE TREATMENT

Among the numerous considerations that can influence the selection of an acute treatment, patient preference is important and occasionally overlooked. As only 29% of patients with migraine report being very satisfied with their treatment, it is important to understand the preferred outcomes and treatment shortcomings identified by most patients. Regarding preferred treatment outcomes, 87% of patients want complete pain relief, 86% want no recurrence of pain, 83% want fast relief of pain, 79% want their medication to be well tolerated without side effects, and 76% want relief of migraine-associated symptoms.[52] Compared to

KEY POINTS

- **Existing data are conflicting or inadequate to support the concern that coadministration of triptans with selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors confer any additional risk of serotonin syndrome in patients treated for migraine.**
- **Some common causes of suboptimal treatment include (but are not limited to): inadequate dosing, delay in treatment, not repeating treatment, suboptimal route of administration, and headache with a rapid time to peak severity.**

the previous attributes, the route of administration is less important but is a significant factor for 53% of patients, with 73% preferring tablets or capsules, 15% preferring orally disintegrating tablets, 8.3% preferring nasal sprays, and 2.6% preferring injections.[52]

Five Tips for Successful Acute Treatment of Migraine

The following are five tips for the successful acute treatment of migraine.

ENSURE THE HEADACHE DISORDER IS CORRECTLY DIAGNOSED. Not all primary headache disorders respond to the same medications, and levels of evidence for commonly used headache medications may vary greatly from one headache disorder to the next. Incorrect diagnosis may be one important factor for a lack of response to medications that should be effective based on existing evidence.[53] The initial consultation should always aim to identify and eliminate secondary causes of headache and then make a diagnosis based on the *International Classification of Headache Disorders, Third Edition* (*ICHD-3*) criteria.[54]

USE EVIDENCE-BASED RECOMMENDATIONS AS A GUIDE TO SELECT AN INDIVIDUALIZED TREATMENT. Although the AHS and CHS evidence assessments are useful as a guide, it is important to note that findings in study populations are not always generalizable to individual patients and that other factors can influence medication selection including cost, tolerability, contraindications,[8] and the patient preferences discussed above. Treatment decisions should also always be made after a thorough review of other medications taken and comorbid medical conditions, both of which may limit or eliminate some treatment options.

A stratified approach should be taken, which includes arming the patient with a plan for milder headaches (which may respond adequately to nonspecific analgesics), a plan for moderate to severe attacks or attacks with disabling associated symptoms (which may respond best to migraine-specific medications), and the autonomy to make the appropriate treatment decision based on the specific features of each attack. A plan for rescue treatment or attacks that are refractory to a patient's usual treatment is also recommended and may include a plan for administering parenteral or IM injections, or (in very rare or unique circumstances) medications including opioids, opioid combinations, corticosteroids, or barbiturate combinations, taking into account their lower strengths of evidence and risks if overused or misused.[5,6,8]

OPTIMIZE TREATMENT. Recognize that the efficacies reported in many studies reflect acute treatment in select populations or suboptimal situations including many NSAID studies conducted on mild to moderate minimally disabling pain without nausea, or triptan studies conducted on pain that is already moderate to severe. In many instances, clinical performance can exceed performance in clinical trials by optimizing how specific treatments are administered, when (in the headache phase) they are administered, and which doses are used.

Nausea, vomiting, and gastroparesis frequently complicate migraine treatment and can often be the underlying cause of treatment failure with oral medications (CASE 4-2).[55] In these situations, intranasal or injectable formulations may confer a significant degree of additional benefit. As treatment is typically more effective when taken early in the headache phase, the time to peak severity of attacks is another important detail that can guide treatment selection. It is generally accepted that treating attacks early equates to better

outcomes,[8] suggesting that fast-onset attacks should be treated with medications that have a faster onset of action and shorter time to maximum plasma concentration (T_{max}). TABLE 4-2 provides a useful guide to onset of action, T_{max}, half-life, and maximum daily dosage.

ASSESS RESPONSE TO TREATMENT. At follow-up visits, patients should be asked specific questions about efficacy and tolerability of acute medications. It is never adequate to only ask if their treatment is "working," as this open-ended question does not adequately address specific questions about patient satisfaction with speed of onset, degree of improvement, recurrence of headache, and tolerability. In fact, it is estimated that a significant number of patients are dissatisfied with or respond suboptimally to treatment, including 30% to 40% of triptan users.[52,56] The four-item Migraine Treatment Optimization Questionnaire (mTOQ-4) (TABLE 4-3) is a validated questionnaire that can help assess treatment optimization.[57] Taking a more detailed inventory of the patient's response to acute therapy is important as suboptimal treatment can influence patient compliance, and patients with "poor" or "very poor" treatment efficacy are significantly more likely to progress to chronic migraine within 1 year (CASE 4-3).[4]

TROUBLESHOOT SUBOPTIMAL RESPONSE TO TREATMENT. If a suboptimal response to acute treatment is identified, it is important to review underlying possibilities before changing medications or classes of medications. Some common causes of suboptimal treatment include (but are not limited to): inadequate dosing, delay in treatment, not repeating treatment, suboptimal route of administration, and headache with a rapid time to peak severity. TABLE 4-4 can be used as a troubleshooting guide for addressing any of the above issues and are generalizable to most classes of medications (CASE 4-4).

CONCLUSION

Despite a growing armamentarium of treatment options for migraine, many patients remain unsatisfied with their acute medications. A comprehensive

CASE 4-2

A 22-year-old woman presented for consultation regarding her episodic migraine. She had a 4-year history of episodic migraine without aura with a time to peak severity of under 1 hour and prominent nausea and vomiting with most attacks. She stated that her orally administered acute treatment was effective only if she took it immediately and only if she could avoid vomiting.

COMMENT

This patient faces at least two barriers to effective treatment: the rapid onset of maximal pain severity and difficulty in taking oral medications because of nausea and vomiting. She would likely benefit from a change to an intranasal or injectable medication, which typically has a faster onset of action and bypasses the gastrointestinal system.

TABLE 4-2 **Pharmacology of Commonly Used Acute Migraine Medications**

Treatment	Onset (Minutes)	T_{max} (Hours)[a]	Half-life (Hours)	Maximum Daily Dose
Triptans				
Almotriptan	30–120	1.4–3.8	3.2–3.7	25 mg
Eletriptan	30	1.0–2.0	3.6–5.5	80 mg
Frovatriptan	120–180	2.0–4.0	25	7.5 mg
Naratriptan	60–180	2.0–3.0	5.0–6.3	5 mg
Rizatriptan (tablet)	30–120	1.2	2.0–3.0	30 mg (15 mg if taking propranolol)
Rizatriptan (orally disintegrating tablet)	30–120	1.6–2.5	2.0–3.0	30 mg (15 mg if taking propranolol)
Sumatriptan (tablet)	20–30	2.5	2.0	200 mg
Sumatriptan (nasal spray)	15	1.0–1.5	2.0	40 mg
Sumatriptan (nasal powder)	15	0.75	3.0	44 mg
Sumatriptan (injection)	10–15	0.2	1.7–2.0	12 mg
Sumatriptan/naproxen	20–30	1.0 (sumatriptan)/5.0 (naproxen)	2.0 (sumatriptan)/19 (naproxen)	2 tablets
Zolmitriptan (tablet)	45	2.0	2.5–3.0	10 mg
Zolmitriptan (orally disintegrating tablet)	45	3.3	2.5–3.0	10 mg
Zolmitriptan (nasal spray)	15	3.0	3.0	10 mg
Ergots				
Dihydroergotamine (nasal spray)	30	0.75	10	4 mg (maximum weekly dose 12 mg)
Simple analgesics				
Acetaminophen	30	0.5–1.0	2.0	4000 mg
Acetylsalicylic acid (effervescent)		0.3–0.5	0.25	2600 mg
Acetylsalicylic acid (tablet)	30	1.0–2.0	2.0–4.5 (<250 mg) 15–30 (>4000 mg)	4000 mg
Ibuprofen (tablet)	60	1.0–2.0	2.0	2400 mg
Naproxen sodium	30	2.0	14	1375 mg
Diclofenac potassium (tablet)	60	<1.0	2.0	150 mg
Diclofenac potassium (powder)	15	0.25	2.0	Safety and efficacy of a second dose not established

[a] T_{max} refers to time to maximum plasma concentration.

Migraine Treatment Optimization Questionnaire (mTOQ-4) to Assess Response to Acute Treatment[a]

TABLE 4-3

Domain	Never/ Rarely	Less Than Half the Time	Half the Time or More
After taking your migraine medication, are you pain free within 2 hours of most attacks?	0	1	2
Does one dose of your migraine medication relieve your headache and keep it away for at least 24 hours?	0	1	2
Are you comfortable enough with your migraine medication to be able to plan your daily activities?	0	1	2
After taking your migraine medication, do you feel in control of your migraines enough so that you feel there will be no disruption to your daily activities?	0	1	2
Subtotal			
	Total of all columns[b]		

[a] Data from Lipton RB, et al, Cephalalgia.[57]

[b] Scoring is as follows: 0 = very poor treatment efficacy; 1–5 = poor treatment efficacy; 6–7 = moderate treatment efficacy; 8 = maximum treatment efficacy.

CASE 4-3

A 32-year-old woman with a history of episodic migraine with aura was seen for a 3-month follow-up visit. She had been started on a new medication at her last visit. On the current visit, she stated that her response to treatment had been "good." A more detailed inventory of her response indicated that, although she could fully abort each attack with her new medication when taken early, she frequently delayed treatment or avoided treatment altogether because of the presence of medication side effects including nausea and chest tightness, which impaired her ability to function at work. When she delayed treatment, she often noted that her acute attacks improved but did not fully resolve. She had a total score of 5 on the four-item Migraine Treatment Optimization Questionnaire (mTOQ-4) administered in clinic.

COMMENT

Although this patient initially seemed pleased with her response to treatment, her response to directed questions and her mTOQ-4 score indicated that her acute treatment efficacy was poor. A change to a better-tolerated medication that does not impair her ability to function at work or cause her to delay treatment should be considered.

treatment plan for every patient with migraine should include an individualized, evidence-based approach to acute treatment. A stratified approach allows the patient to make autonomous decisions regarding the appropriate treatment for specific types and severities of attacks under the guidance of providers who should help patients select treatments based on their unique needs.

Triptans, intranasal dihydroergotamine, and nonspecific analgesics remain the mainstays of first-line treatment. Factors that should be considered when selecting an optimal first-line treatment include onset of action, T_{max}, half-life, route of administration, time to peak severity, recurrence of headache, and patient preference. Response to treatment and patient satisfaction with treatment should be assessed regularly.

TABLE 4-4 **Troubleshooting Guide for Suboptimal Response to Acute Migraine Treatment**[a]

Patient Response	Treatment Considerations
No response	Increase dose, ensure treatment is early, consider a need to change route of administration, try a different medication after two adequate trials
Partial response	Increase dose, ensure treatment is early, ensure a second dose is taken
Recurrence	Ensure treatment is early, ensure a second dose is taken, consider a longer-acting medication (TABLE 4-2), consider adding a complementary medication such as a nonsteroidal anti-inflammatory drug or antiemetic
Inconsistent response	Increase dose, consider a need to change route of administration
Overuse	Establish use limits and plan of care with patient, limit number prescribed, add prophylactic treatment

[a] Courtesy of David W. Dodick, MD.

CASE 4-4

A 19-year-old man with a history of migraine without aura presented for evaluation of 3 years of inconsistent response to sumatriptan 25 mg, which had previously provided consistent and complete relief since age 10. No changes had occurred in his health or migraine history, and he continued to tolerate the medication well.

COMMENT

This patient tolerated the medication well and should attempt treatment with a standard adult dose of sumatriptan of 100 mg. His inconsistent response may reflect suboptimal dosing that may have previously been effective prior to adolescence.

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Preventive Therapy of Migraine

By Todd J. Schwedt, MD, FAAN

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RELATIONSHIP DISCLOSURE:
Dr Schwedt serves on the board of directors for the American Headache Society and the International Headache Society; receives personal compensation as associate editor for *Cephalalgia*, *Headache*, and *Pain Medicine*; and receives personal compensation as a consultant for Alder BioPharmaceuticals, Inc; Allergan; Amgen Inc; Autonomic Technologies, Inc; Avanir Pharmaceuticals, Inc; Dr. Reddy's Laboratories Ltd; Eli Lilly and Company; Ipsen Bioscience, Inc; Nocira, LLC; Novartis AG; and Teva Pharmaceutical Industries Ltd. He has stock options in Aural Analytics; Nocira, LLC; and Second Opinion.
Continued on page 1065

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Schwedt discusses the unlabeled/investigational use of numerous medications for the treatment of migraine; none of the therapies discussed are approved by the US Food and Drug Administration except for caloric vestibular stimulation, divalproex sodium, erenumab, propranolol, timolol, topiramate, transcranial magnetic stimulation, and transcutaneous supraorbital nerve stimulation for the treatment of migraine and the use of onabotulinumtoxinA for the treatment of chronic migraine.

ABSTRACT

PURPOSE OF REVIEW: This article reviews the preventive therapy of migraine, including indications, strategies for use, and available treatments.

RECENT FINDINGS: Lifestyle modifications and migraine trigger avoidance are recommended as preventive measures for all individuals with migraine. The decision to recommend additional migraine preventive therapy should consider the frequency of migraine attacks and headaches, extent of migraine-associated disability, frequency of using acute migraine treatments and the responsiveness to such treatments, and patient preferences. Additional therapies include prescription medications, nutraceuticals, neurostimulation, and behavioral therapy. Considering evidence for efficacy and the risk of potential side effects and adverse events, treatments with the most favorable profiles include (in alphabetical order): amitriptyline, beta-blockers (several), biofeedback, candesartan, coenzyme Q10, cognitive-behavioral therapy, magnesium citrate, onabotulinumtoxinA (for chronic migraine only), relaxation therapy, riboflavin, and topiramate. In addition, erenumab, a calcitonin gene-related peptide (CGRP) receptor monoclonal antibody, received approval from the US Food and Drug Administration (FDA) for the prevention of migraine in May 2018.

SUMMARY: Successful migraine preventive therapy reduces the frequency and burden of attacks while causing limited side effects. Individual treatment recommendations are determined based upon evidence for efficacy, side effect and adverse event profiles, medication interactions, patient comorbidity, costs, and patient preferences. Patients must be counseled on reasonable expectations for their preventive therapy and the importance of adhering to the recommended treatment plan for a period of time that is sufficient to determine outcomes.

INTRODUCTION

Migraine prevention is multifaceted and includes lifestyle modifications, migraine attack trigger identification and avoidance, avoidance of risk factors for developing more frequent migraine attacks, and, when indicated, medications, nutraceuticals, neurostimulation, and behavioral therapies. The goal of preventive therapy is to reduce the frequency of migraine attacks, days with migraine and headache, severity of symptoms, frequency of taking acute

migraine therapy, and migraine-related disability. Commonly used measures of efficacy in clinical trials of migraine preventive therapies include reductions in the number of migraine days, reductions in the number of headache days, and responder rate, typically defined as at least a 50% reduction in headache frequency. However, in the clinical setting, measures of success and failure are often more subjective and individualized according to the specific patient. For example, the patient who has substantial reductions in migraine symptom severity and migraine-related disability with minimal side effects might find a preventive therapy successful even if headache frequency is only modestly reduced. On the other hand, a preventive therapy that is very effective in reducing migraine frequency would be considered a failure if it causes intolerable side effects.

When formulating recommendations for specific preventive therapies, clinicians must consider the likelihood for effectiveness and side effects as well as other factors such as potential interactions with other therapies that the patient uses, the patient's comorbidities, the cost of the therapy, and the patient's ability to adhere to the recommended treatment schedule. The clinician-patient conversation about preventive therapies must set realistic expectations regarding the likely magnitude of benefit, realizing that reductions but not elimination of migraine burden is expected. It is also essential to discuss the timing by which a patient is expected to note the benefits from a preventive therapy. For example, with the most commonly prescribed oral migraine preventive medications, the patient may need to take the medication at the target dose for 2 to 3 months before realizing substantial benefits.

In this article, the following migraine preventive therapy topics are discussed: (1) lifestyle modifications and avoidance of migraine attack triggers; (2) avoiding factors associated with development of more frequent headaches; (3) indications for medications, nutraceuticals, neurostimulation, and behavioral therapies; (4) currently available therapies and those in the pipeline; and (5) adherence and persistence with therapy.

LIFESTYLE MODIFICATION AND TRIGGER AVOIDANCE

Lifestyle modifications and migraine attack trigger identification and avoidance should be discussed with all patients with migraine. Although limited published data support the notion that lifestyle modifications and avoidance of triggers are effective in reducing migraine burden, they are commonly recommended and are associated with little risk to the patient.[1]

It is generally believed that fluctuations/changes in a person's usual daily routine can trigger migraine attacks. Thus, individuals with migraine are likely to do better if they maintain a stable daily schedule that includes going to sleep the same time each night, waking at the same time each day, eating regular meals, exercising, and maintaining a consistently low-stress lifestyle. Although such a lifestyle is not easy to maintain, or is not possible in some situations, patients are counseled to adhere to such a lifestyle as closely as possible.

Although the evidence strength is low, several studies and systematic reviews of the literature have concluded that aerobic exercise can provide benefits to headache patterns.[2,3] Aerobic exercise as monotherapy and multicomponent behavioral headache interventions that include aerobic exercise are associated with reductions in headache frequency and severity as well as with improvements in health-related quality of life.[2–7] Although the exercise protocols used in these studies are varied, based on these studies and recommendations from the Office

KEY POINTS

- Migraine prevention is multifaceted and includes lifestyle modifications, migraine attack trigger identification and avoidance, avoidance of risk factors for developing more frequent migraine attacks, and, when indicated, medications, nutraceuticals, neurostimulation, and behavioral therapies.
- The goal of preventive therapy is to reduce the frequency of migraine attacks, days with migraine and headache, severity of symptoms, frequency of taking acute migraine therapy, and migraine-related disability.
- When formulating recommendations for specific preventive therapies, clinicians must consider the likelihood for effectiveness and side effects as well as other factors such as potential interactions with other therapies that the patient uses, the patient's comorbidities, the cost of the therapy, and the patient's ability to adhere to the recommended treatment schedule.
- Lifestyle modifications and migraine attack trigger identification and avoidance should be discussed with all patients with migraine.
- Moderate-intensity aerobic exercise (150 minutes per week, generally divided among three to five sessions) should be considered for migraine prevention in adults.

of Disease Prevention and Health Promotion (*health.gov*), 150 minutes per week of moderate-intensity aerobic exercise (generally divided among three to five sessions) should be considered for migraine prevention in adults.[8]

Maintenance of a daily headache diary is recommended to obtain an accounting of migraine frequency, treatment patterns, and potential migraine attack triggers. Identification of triggers can be a complicated process since several triggers might need to be present simultaneously for them to actually trigger a migraine attack and because a causal relationship between trigger exposure and an individual migraine attack is very difficult to prove. Despite

CASE 5-1

A 35-year-old woman presented for evaluation and management of frequent headaches. She reported having onset of headaches approximately 20 years ago. Initially, she had two to three episodes per month, during which she experienced moderate or severe, unilateral, throbbing headaches associated with sensitivity to light, sound, and nausea. Typically, to avoid exacerbation of her symptoms, she would lie in bed for several hours with each attack. Less severe attacks were treated with an over-the-counter nonsteroidal anti-inflammatory drug (NSAID)/acetaminophen/caffeine combination pill, while more severe attacks were treated with a triptan.

Over the years, she had a slow increase in the frequency of her attacks. Since she was treating all episodes with medication, the frequency of medication use also increased. Over the past few years, she noted that between her full-blown attacks, she had a constant mild to moderate headache that would partially respond to the NSAID/acetaminophen/caffeine combination pill. At the time of presentation, she reported taking the NSAID/acetaminophen/caffeine combination pill several times each day and a triptan for full-blown attacks approximately 10 days per month.

COMMENT

This patient was diagnosed with chronic migraine with medication overuse. Chronic migraine was diagnosed since she experienced 15 or more days with headache each month, including at least 8 days on which she had full-blown migraine attacks. The patient also met criteria for overuse of triptans and for overuse of combination analgesics, each being used on 10 or more days per month. It is likely that the frequent use of migraine acute medications led to medication-overuse headache.

The treatment of chronic migraine with medication overuse includes the use of migraine preventive therapy and reductions in the frequency of using acute treatments. Since many patients are not familiar with medication-overuse headache, education about this secondary headache disorder and the risks of taking frequent acute medications must be discussed. Typically, the patient with medication overuse is switched from the overused medication(s) to an acute therapy that is from a different medication class and is instructed to limit use of the new medication to 2 to 3 days per week.

these limitations, commonly cited triggers include: high stress, stress let down (moving from high-stress to low-stress environments, such as might occur during a vacation), weather changes, sex hormone fluctuations in women, not eating, alcohol, sleep disturbance, odors, light, smoke, heat, and certain foods.

Foods that are commonly cited as triggers include those with monosodium glutamate, those with nitrates/nitrites (eg, processed meats), aged cheeses, and artificial sweeteners. Caffeine overuse and caffeine withdrawal are both associated with headaches and migraine.

Avoiding Factors That Increase Risk of Developing More Frequent Migraine

Several factors are associated with increased risk for developing more frequent headaches (eg, transitioning from episodic migraine to chronic migraine), including obesity, sleep disorders, excessive caffeine intake, psychiatric disease, higher baseline headache frequency, the frequent use of abortive migraine medications, female sex, lower socioeconomic status, comorbid pain disorders, major life events, history of head or neck injury, ineffective acute treatment of migraine attacks, and presence of cutaneous allodynia.[9–11] It is presumed that avoiding these risk factors, when possible, reduces the risk of developing more frequent headaches. Among these risk factors, caffeine, obesity, certain sleep disorders, and medication overuse are avoidable or modifiable.

CAFFEINE. A complex relationship exists between caffeine and migraine: caffeine can be an effective treatment for migraine attacks, likely via its action as an adenosine receptor antagonist; withdrawal from caffeine can cause headaches, perhaps due to upregulation of the adenosine receptors; and regular caffeine use is a risk factor for developing more frequent headaches.[12,13] Caffeine cessation among frequent users will improve migraine burden for some individuals.[14] Thus, a period of caffeine cessation lasting at least 2 to 3 months is recommended for individuals with frequent migraines to determine if caffeine avoidance results in reduced frequency of migraine attacks/headaches. Individuals with a regular intake of large amounts of caffeine should slowly taper their caffeine intake to avoid an initial headache exacerbation due to caffeine withdrawal.

OVERUSE OF ACUTE HEADACHE MEDICATIONS. The term *medication overuse* refers to taking migraine-abortive medications too frequently. Medication overuse is a risk factor for developing more frequent headaches and can lead to medication-overuse headache (**CASE 5-1**). The definition of medication overuse differs according to the medication(s) being used. Simple analgesics are overused if taken on 15 or more days per month (regardless of the reason for taking the medication), whereas triptans, dihydroergotamine, combination analgesics, opiates, and combinations of medications from different medication classes are overused when taken on 10 or more days per month.[15] Despite these definitions, it is likely that intake of butalbital-containing medications or opiates on fewer than 10 days per month still increases the risk of developing more frequent headaches, and thus their use should be severely limited or avoided altogether.

SLEEP. Sleep is an effective treatment for migraine attacks. Sleep disturbances are common among individuals with migraine, and poor sleep is positively associated with the occurrence and frequency of migraine attacks. Common sleep disturbances among individuals with migraine include: insomnia, poor quality sleep, short sleep duration, snoring, sleep-related breathing disorders, and restless

KEY POINTS

- Maintenance of a daily headache diary is recommended to obtain an accounting of migraine frequency, treatment patterns, and potential migraine attack triggers.
- Commonly cited migraine triggers include: high stress, stress let down (moving from high-stress to low-stress environments, such as might occur during a vacation), weather changes, sex hormone fluctuations in women, not eating, alcohol, sleep disturbance, odors, light, smoke, heat, and certain foods.
- Caffeine overuse and caffeine withdrawal are both associated with headaches and migraine.
- Several factors are associated with increased risk for developing more frequent headaches (eg, transitioning from episodic migraine to chronic migraine), including obesity, sleep disorders, excessive caffeine intake, psychiatric disease, higher baseline headache frequency, the frequent use of abortive migraine medications, female sex, lower socioeconomic status, comorbid pain disorders, major life events, history of head or neck injury, ineffective acute treatment of migraine attacks, and presence of cutaneous allodynia.
- A period of caffeine cessation lasting at least 2 to 3 months is recommended for individuals with frequent migraine.

legs syndrome.[16–19] In addition to being comorbid with migraine, sleep disturbances can be associated with greater migraine burden, such as higher headache frequency.[20] Effective treatment of sleep disturbances may lead to improved migraine patterns. For example, behavioral treatment of insomnia and continuous positive airway pressure (CPAP) therapy for sleep apnea have been associated with reductions in migraine burden such as reduced headache frequency.[21,22] Identification and treatment of sleep disturbances is recommended as part of a comprehensive preventive treatment plan for patients with migraine.

OBESITY. Obesity is associated with a moderately higher risk of migraine and with an increasing number of headache days among those with migraine.[23,24]

CASE 5-2

A 40-year-old woman presented for evaluation and management of migraine. She had a 20-year history of migraine without aura. For many years, she had migraine attacks 1 to 2 times per month, each lasting no longer than 1 day, which were often triggered by menstruation and typically relieved by an oral triptan. However, over the last 8 to 10 years, she had a slow increase in the frequency of her headaches, which progressed to her current pattern of full-blown migraine attacks 4 times per month, each lasting 1 to 2 days, and milder headaches on an additional 2 days per week. Overall, she estimated having a headache of some severity on about 14 days per month, with complete headache freedom on the remaining days. She reported that her migraine attacks felt the same as they had for many years, but they were more frequent, of a longer duration, and were less responsive to her usual triptan. She had severe migraine-related disability requiring bedrest 3 days per month.

Her past medical history was notable for kidney stones (calcium phosphate), obesity, and borderline hypertension. Her medications included a daily multivitamin, sumatriptan 100 mg tablet that she took for each migraine attack, and ibuprofen that she took for her milder headaches. She had never tried other treatments for her migraine. Her mother, sister, and daughter all had migraine.

On examination, her body mass index was 32 kg/m^2, her blood pressure was 145/88 mm Hg, and her heart rate was 85 beats/min. General physical, neurologic, and funduscopic examinations were normal.

COMMENT

This patient was clearly a candidate for migraine preventive therapy given the frequency and duration of her migraine attacks and headaches, their relative lack of response to acute medication, and her migraine-related disability. Since she had not previously been treated with migraine preventive therapy, a first-line agent such as a beta-blocker, topiramate, or amitriptyline should be considered. Her history of calcium phosphate kidney stones is a contraindication to the use of topiramate, and her obesity is a relative contraindication to amitriptyline. Given these contraindications and the presence of borderline hypertension, propranolol would be a good choice.

Although further studies are needed to confirm findings, weight loss may be associated with reductions in headache frequency and severity.[25] Monitoring of a patient's weight, including the effects of migraine preventive treatment on a patient's weight, and treatment of obesity should be considered part of a comprehensive migraine preventive therapy plan.

INDICATIONS FOR ADDITIONAL MIGRAINE PREVENTION

The decision to recommend further migraine preventive therapy to a patient is based upon headache frequency, migraine attack frequency and duration, the severity of symptoms, the frequency of taking migraine acute therapies, the patient's responsiveness to migraine acute therapies, extent of migraine-related disability, and patient preference.

For example, a patient who has four migraine attacks per month, each of which responds completely to a single dose of abortive therapy, lasts only for 2 hours, and causes limited disability, might not warrant preventive therapy. However, the patient who has four migraine attacks per month, most of which do not respond to abortive therapy, continue for 2 days, and cause substantial disability, is likely to desire preventive therapy.

Guidelines regarding when to offer migraine preventive therapy are available from the American Academy of Neurology (AAN), the American Headache Society, the Canadian Headache Society, and an expert panel of the American Migraine Prevalence and Prevention Study.[26–28] Although the guidelines have slightly differing recommendations, taken together they suggest that migraine preventive therapy should be considered when one or more of the following are present:

- Three or more moderate or severe headache days per month causing functional impairment and that are not consistently responsive to acute treatments
- At least 6 to 8 headache days per month even if acute medications are effective
- Contraindications to acute migraine treatments
- Particularly bothersome symptoms even if infrequent attacks (eg, migraine with brainstem aura, hemiplegic migraine)
- Migraine has a significant impact on patient's life despite lifestyle modifications, trigger avoidance, and use of acute treatment
- Patient is at risk of developing medication-overuse headache

Migraine Preventive Treatments

Currently, our knowledge is insufficient to accurately predict which individual patient is most likely to benefit from a particular preventive therapy. Thus, the decision of which preventive therapy or therapies to recommend is based on the level of evidence that a specific therapy is effective, the likelihood of a patient tolerating the therapy, its safety profile and cost, patient comorbidities, potential interactions with other therapies that the patient uses, the patient's prior experiences with similar or related therapies (eg, choose a medication that works differently than medications that were previously ineffective or not tolerated), and patient preferences (CASE 5-2).

For most patients, a treatment's effectiveness and side effects are the most important qualities in determining their satisfaction with the treatment. Although

KEY POINTS

- Medication overuse is a risk factor for developing more frequent headaches and can lead to medication-overuse headache.
- Sleep is an effective treatment for migraine attacks. Sleep disturbances are common among individuals with migraine, and poor sleep is positively associated with the occurrence and frequency of migraine attacks.
- Identification and treatment of sleep disturbances is recommended as part of a comprehensive preventive treatment plan for patients with migraine.
- Obesity is associated with a moderately higher risk of migraine and with an increasing number of headache days among those with migraine.
- Weight loss may be associated with reductions in headache frequency and severity.
- The decision to recommend migraine preventive therapy to a patient is based upon headache frequency, migraine attack frequency and duration, the severity of symptoms, the frequency of taking migraine acute therapies, a patient's responsiveness to migraine acute therapies, extent of migraine-related disability, and patient preference.

the majority of preventive therapies have been studied in episodic migraine populations, medications used for episodic migraine are also used for prevention of chronic migraine (ie, headaches on at least 15 days per month including at least 8 days on which symptoms meet diagnostic criteria for migraine or are treated with a migraine-specific acute medication). OnabotulinumtoxinA is effective for prevention of chronic migraine but not episodic migraine. The discussion of individual therapies herein includes only those medications, nutraceuticals, neurostimulation devices, and behavioral therapies that are commonly available at the time of writing this article. This section ends, however, with a brief description of migraine preventive therapies that are in late stages of clinical development.

Medications and Nutraceuticals

Most prescription medications currently used for the prevention of migraine were developed for other purposes such as epilepsy, hypertension, and depression. To reduce the risk of a patient feeling uncertain about the prescriber's recommendation for one of these medications and, as a result, never filling the initial prescription, the clinician should acknowledge this fact when discussing treatment plans with the patient.

Guidelines from the American Headache Society, AAN, and Canadian Headache Society help to define which medications and nutraceuticals should be considered for migraine prevention.[27,29–31] Medications and nutraceuticals recommended for use from at least one of these guidelines include: topiramate, propranolol, nadolol, metoprolol, timolol, amitriptyline, gabapentin, candesartan, divalproex sodium, sodium valproate, flunarizine, pizotifen, venlafaxine, verapamil, lisinopril, coenzyme Q10, magnesium citrate, riboflavin, and feverfew (flunarizine and pizotifen are not approved by the US Food and Drug Administration [FDA] for use in the United States). OnabotulinumtoxinA is recommended for prevention of chronic migraine. In addition, erenumab, a calcitonin gene-related peptide (CGRP) receptor monoclonal antibody, received FDA approval for the prevention of migraine in May 2018. [32–34]

TABLE 5-1 includes recommended daily doses of medications, the AAN's and American Headache Society's evidence levels for efficacy of medications, and the Canadian Headache Society's overall recommendation and evidence levels for efficacy of medications.[27,29–37] It must be noted that the rating of evidence level for efficacy does not take into account other factors such as tolerability, side effects, toxicities, ease of administration, cost, or patient preferences. However, these factors must be considered when making treatment recommendations, and these factors have been considered in the Canadian Headache Society's "recommendation" level. For example, although divalproex sodium/sodium valproate received a level A rating for level of evidence from the AAN and a "high" rating for evidence of efficacy from the Canadian Headache Society, it was given a "weak" recommendation from the Canadian Headache Society, presumably because of its potential for being associated with serious adverse events such as fetal malformations and liver toxicity. Furthermore, the 2000 AAN guideline[28] has since been replaced by the 2012 AAN guideline,[30] and the 2012 AAN guideline "NSAIDs and Other Complementary Treatments for Episodic Migraine Prevention in Adults"[29] has been retired because of concerns about the safety of butterbur related to changes in its manufacturing that occurred after these guidelines were developed. TABLE 5-2 lists contraindications, precautions, and the most common adverse effects associated with each medication and nutraceutical.

Neurostimulation

Several modalities of invasive and noninvasive neurostimulation have been studied or are currently being studied for the prevention of migraine, including transcranial magnetic stimulation, transcutaneous supraorbital nerve stimulation, sphenopalatine ganglion stimulation, occipital and supraorbital nerve stimulation via implanted stimulators, transcutaneous vagal nerve stimulation, percutaneous mastoid electric stimulation, and caloric vestibular stimulation.[38–40] Transcutaneous supraorbital nerve stimulation, transcranial magnetic stimulation, and caloric vestibular stimulation (not yet commercially available) have received clearance from the FDA for migraine prevention. These devices are used on a daily basis for the prevention of migraine. Additional studies are needed to determine if other forms of noninvasive neurostimulation are effective for the primary or adjunctive prevention of migraine. Invasive neurostimulation might play a limited role for migraine prevention in those patients with very severe migraine who are refractory to other treatments; studies are needed to determine which subsets of these patients are most likely to benefit from and tolerate invasive neurostimulation.

Behavioral Therapy

Behavioral therapies for migraine are used with the intent of reducing the frequency of migraine attacks and the impact of such attacks on the individual, such as headache-related disability, quality of life, and psychological comorbidity.[41] Although behavioral therapies should be considered for all patients significantly impacted by migraine, special consideration should be given when a patient prefers nonpharmacologic therapy; does not tolerate, respond well, or has contraindications to pharmacologic therapy; and when patient behaviors and stress are triggers for migraine attacks or add significantly to migraine-related disability.[42] The 2000 AAN practice parameter gave Grade A recommendations for using relaxation training, thermal biofeedback combined with relaxation training, electromyographic biofeedback, and cognitive-behavioral therapy for the treatment of migraine.[28] Each of these therapies has been shown in randomized clinical trials to result in substantial improvements in migraine.[41] Furthermore, combining pharmacologic treatment with behavioral therapies is likely to provide greater benefits than either therapy alone, as has been shown in a study of combined therapy with propranolol and cognitive-behavioral therapy.[43]

Combination Therapy

A combination of treatments can be used for migraine prevention when a patient has inadequate response to a single therapy. Although limited data support the idea that therapy with a combination of medications can be superior to monotherapy, it is a common practice in the clinical setting. When done, it is recommended that the medications work via complementary but different mechanisms of action. Of note, however, one study demonstrated that a combination of topiramate and propranolol is no more effective than topiramate alone for chronic migraine treatment.[44] Clinicians must ensure that combination medication therapy is being used with the intent of obtaining greater effectiveness, as opposed to prescribing one medication to treat the side effects of another migraine medication, a practice that is discouraged. In addition to therapy with combinations of prescription medications, combination therapy that includes combining a medication with a nutraceutical or neurobehavioral therapy or

KEY POINTS

- **Transcutaneous supraorbital nerve stimulation, transcranial magnetic stimulation, and caloric vestibular stimulation have received clearance from the US Food and Drug Administration for migraine prevention.**
- **Behavioral therapies for migraine are used with the intent of reducing the frequency of migraine attacks and the impact of such attacks on the individual, such as headache-related disability, quality of life, and psychological comorbidity.**
- **Although behavioral therapies should be considered for all patients significantly impacted by migraine, special consideration should be given when a patient prefers nonpharmacologic therapy; does not tolerate, respond well, or has contraindications to pharmacologic therapy; and when patient behaviors and stress are triggers for migraine attacks or add significantly to migraine-related disability.**
- **A combination of treatments can be used for migraine prevention when a patient has inadequate response to a single therapy.**
- **In addition to therapy with combinations of prescription medications, combination therapy that includes combining a medication with a nutraceutical or neurobehavioral therapy or noninvasive neurostimulation can be considered and may be necessary for the effective treatment of patients who are refractory to single treatments.**

noninvasive neurostimulation can be considered and may be necessary for the effective treatment of patients who are refractory to single treatments.

Therapies in the Pipeline

In addition to several modes of noninvasive neurostimulation briefly discussed above, several other migraine preventive therapies are in the pipeline including CGRP monoclonal antibodies that target the CGRP ligand. Results from Phase 2 and Phase 3 clinical trials of CGRP monoclonal antibodies demonstrate their efficacy, tolerability, and safety for prevention of episodic migraine and chronic migraine.[32–34,45–50] The CGRP monoclonal antibodies are the only class of medication specifically designed for the prevention of migraine. Erenumab has recently received FDA approval for the prevention of migraine.[32–34] Beyond

TABLE 5-1 **Medications and Nutraceuticals With Evidence for Efficacy in Preventing Migraine**

	Daily Dose[a]	American Academy of Neurology Evidence Level for Efficacy[29–31,b,c]	Canadian Headache Society Recommendation[27,d]	Canadian Headache Society Evidence Level for Efficacy[27,d]
Medication				
Metoprolol	100–200 mg	A	Strong	High
Propranolol	80–240 mg	A	Strong	High
Topiramate	50–200 mg	A	Strong	High
Amitriptyline	10–200 mg	B	Strong	High
Timolol	20–60 mg	A	N/A	N/A
Nadolol	20–160 mg	B	Strong	Moderate
Divalproex sodium/ sodium valproate	500–2000 mg	A	Weak	High
Venlafaxine	75–225 mg	B	Weak	Low
Atenolol	50–200 mg	B	N/A	N/A
Gabapentin[e]	600–3600 mg	U	Strong	Moderate
Candesartan[f]	16–32 mg	C	Strong	Moderate
Lisinopril	10–40 mg	C	Weak	Low
Flunarizine[g]	5–10 mg	N/A	Weak	High
Pizotifen[g]	1.5–4 mg	N/A	Weak	High
Verapamil	120–480 mg	U	Weak	Low
OnabotulinumtoxinA (chronic migraine only)	155 units every 12 weeks	A	N/A	N/A
Erenumab[h]	70 mg or 140 mg each month	N/A	N/A	N/A

CONTINUED ON PAGE 1061

CGRP monoclonal antibodies, other migraine preventive therapies that are under investigation include small-molecule CGRP antagonists and therapies that target pituitary adenylate cyclase-activating polypeptide, kappa opioid receptors, nitric oxide synthase, orexins, and glutamate.[51,52]

Adherence and Persistence With Preventive Therapy

Rates of adherence and persistence with migraine preventive therapies are low. Even among individuals with chronic migraine (ie, those with the most severe disease), adherence to oral migraine preventive medications ranges from only 26% to 29% at 6 months and 17% to 20% at 12 months.[53] Although the reasons for low adherence vary, side effects and lack of efficacy are commonly cited. Thus, it is important to educate patients that persistence with a medication will, in

CONTINUED FROM PAGE 1060

	Daily Dose[a]	American Academy of Neurology Evidence Level for Efficacy[29–31,b,c]	Canadian Headache Society Recommendation[27,d]	Canadian Headache Society Evidence Level for Efficacy[27,d]
Nutraceuticals				
Coenzyme Q10	300 mg	C	Strong	Low
Magnesium citrate	400–600 mg	B	Strong	Low
Riboflavin	400 mg	B	Strong	Low
Feverfew	50–300 mg	B	Strong against	Moderate

N/A = not applicable.

[a] Daily dose refers to the recommended total daily dose for migraine prevention.

[b] The American Academy of Neurology's ratings for level of evidence that each medication is effective for migraine prevention include the following: A = medication with established efficacy (at least two Class 1 trials); B = medication probably effective (one Class 1 or two Class 2 studies); C = medication possibly effective (one Class 2 study); U = inadequate or conflicting data to support or refute medication efficacy.

[c] The 2012 American Academy of Neurology guideline has been retired because of concerns about the safety of butterbur related to changes in its manufacturing.[29]

[d] The Canadian Headache Society's guidelines provide a level of evidence and recommendation based upon the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group system (high = confident that the true effect lies close to the estimate; moderate = moderately confident in the effect estimate; low = confidence in the effect estimate is limited; very low = little confidence in the effect estimate), and a recommendation that considers the balance between desirable and undesirable consequences of therapy, and the quality of the evidence on which judgments of the magnitude of benefit and harm are based (strong = benefits clearly outweigh risks and burdens for most patients; weak = benefits are more closely balanced with risks and burdens for many patients).

[e] Although the Canadian Headache Society gives gabapentin a strong recommendation and moderate evidence rating, publication bias and selective reporting of clinical trial results suggest that lower ratings might be appropriate.[35,36]

[f] Since the publication of the American Academy of Neurology and Canadian Headache Society treatment guidelines, there has been an additional positive randomized, placebo-controlled trial with candesartan, a study that might strengthen its rating for an efficacy evidence level.[37]

[g] Flunarizine and pizotifen are not approved by the US Food and Drug Administration for use in the United States.

[h] Erenumab trials were completed after publication of the American Academy of Neurology's and Canadian Headache Society's guidelines.[32–34]

TABLE 5-2 **Contraindications and Precautions to Migraine Preventive Therapies[a]**

	Contraindications/Precautions	Most Common Adverse Effects
Medications		
Beta-blockers (metoprolol, propranolol, timolol, nadolol, atenolol)	Bradycardia, hypotension, asthma, heart failure, may mask signs and symptoms of hypoglycemia	Orthostatic intolerance, exercise intolerance, fatigue, dizziness
Topiramate	Nephrolithiasis, renal impairment, metabolic acidosis	Paresthesia, weight loss, memory impairment, word-finding difficulties
Amitriptyline	Suicidal thinking/behavior, cardiac conduction abnormalities/arrhythmia	Weight gain, dry mouth, fatigue, blurred vision, constipation
Divalproex sodium/sodium valproate	Liver impairment, pancreatitis, certain hematologic disorders, childbearing potential	Weight gain, tremor, nausea, alopecia, fatigue
Venlafaxine	Suicidal thinking/behavior, renal impairment, hepatic impairment	Nausea, dizziness, insomnia, diaphoresis, sexual dysfunction
Gabapentin	Renal impairment	Dizziness, fatigue, peripheral edema
Candesartan	Hyperkalemia	Hypotension, dizziness
Lisinopril	Hyperkalemia, renal impairment	Hypotension, dizziness, cough
Flunarizine[b]	Hepatic impairment, extrapyramidal symptoms	Weight gain, fatigue, blurred vision
Pizotifen[b]	Hepatic impairment, renal impairment, visual disturbances	Weight gain, fatigue, dizziness
Verapamil	Cardiac conduction disorders, renal impairment, hepatic impairment, heart failure	Gingival hyperplasia, constipation, dizziness, hypotension, bradycardia
OnabotulinumtoxinA (chronic migraine only)	Neuromuscular/neuromuscular junction disease	Injection site pain, muscle pain, muscle weakness
Erenumab	None (according to US Food and Drug Administration label)	Injection site reactions, constipation
Nutraceuticals		
Coenzyme Q10	Biliary obstruction, hepatic insufficiency	Nausea, diarrhea
Magnesium citrate	Neuromuscular/neuromuscular junction disease, renal impairment	Diarrhea
Riboflavin	N/A	Urine discoloration, polyuria
Feverfew	Anticoagulant use	Nausea, diarrhea, mouth ulcers

N/A = not applicable.

[a] This table includes a partial listing of contraindications, precautions, and more common side effects associated with each therapy. Clinicians should refer to appropriate sources for comprehensive information. Pregnancy and breast-feeding are relative or absolute contraindications for many migraine preventive medications and nutraceuticals, but are not included within the contraindications/precautions column in this table. To determine the estimated risk of using these medications and nutraceuticals during pregnancy and breast-feeding, please refer to appropriate sources.

[b] Flunarizine and pizotifen are not approved by the US Food and Drug Administration for use in the United States.

some cases, result in waning side effects and improved effectiveness. Furthermore, when assessing response to migraine preventive therapy, it is essential to determine the patient's level of adherence with the treatment before determining that the therapy was ineffective.

Few data exist to help determine the optimal timing for stopping preventive therapy. When oral preventive therapy administered at a target therapeutic dose is ineffective after 2 to 3 months, it should be discontinued or the dose should be increased, if appropriate. At least two to three treatments with onabotulinumtoxinA are suggested prior to determining its efficacy for treatment of chronic migraine. Effective preventive therapy should be continued for at least 3 to 6 months before tapering the dose or discontinuing the treatment. The decision to lower doses or discontinue therapy should be individualized according to a patient's migraine pattern and personal preferences. For example, a patient with episodic migraine who has a reduction in migraine attack frequency down to one attack per month on their first migraine preventive therapy trial should be considered for dose reduction with the aim of discontinuation at the 3- to 6-month follow-up. However, the patient with many decades of chronic migraine who has had numerous treatment failures is not likely to desire preventive medication discontinuation if they finally find an effective migraine preventive approach. For such patients, it can be reasonable to maintain the preventive therapy for periods much longer than 3 to 6 months, all the while assessing for continued need, side effects, and tolerability and utilizing the lowest necessary dose.

KEY POINTS

- **Rates of adherence and persistence with migraine preventive therapies are low.**
- **When assessing response to migraine preventive therapy, it is essential to determine the patient's level of adherence with the treatment before determining that the therapy was ineffective.**

CONCLUSION

Migraine prevention requires a comprehensive approach that should include trigger identification and avoidance and lifestyle modifications that reduce the risk of migraine attacks. Further migraine preventive interventions are required when migraine attacks are frequent, unresponsive to acute therapy, associated with substantial disability, accompanied by particularly bothersome symptoms (eg, brainstem aura, intractable vomiting), or when a patient is at risk of developing overuse of acute migraine medications. Further interventions can include one or a combination of medications, nutraceuticals, behavioral therapies, and neurostimulation. When making migraine preventive recommendations, it is essential that the patient be educated on the expected outcomes and the duration of time that might be required to realize the benefits. Finally, since rates of adherence and persistence with migraine preventive medications are low, patient compliance with the recommended treatment plan must be considered when assessing outcomes.

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DISCLOSURE

Continued from page 1052

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Headaches Due to Low and High Intracranial Pressure

By Deborah I. Friedman, MD, MPH, FAAN

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Dr Friedman has received personal compensation for serving on the advisory boards of Alder BioPharmaceuticals, Inc; Amgen Inc; Avanir Pharmaceuticals, Inc; Biohaven Pharmaceutical; ElectroCore, LLC; Supernus Pharmaceuticals, Inc; Teva Pharmaceutical Industries Ltd; and Zosano Pharma Corporation.
Continued on page 1091

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Friedman discusses the unlabeled/investigational use of acetazolamide for the treatment of pseudotumor cerebri syndrome, the use of gadolinium for MRI myelography for the diagnosis of spontaneous intracranial hypotension, and the use of zonisamide for the treatment of associated headache.

ABSTRACT

PURPOSE OF REVIEW: Headache disorders attributed to low and high intracranial pressure are commonly encountered in specialty headache practices and may occur more frequently than realized. While the headaches resulting from intracranial pressure disorders have what are conventionally thought of as defining characteristics, a substantial minority of patients do not manifest the "typical" features. Moreover, patients with intracranial pressure disorders may also have a preexisting primary headache disorder. Heightening the complexity of the presentation, the headaches of intracranial pressure disorders can resemble the phenotype of a primary disorder. Lastly, patients with so-called intracranial "hypotension" often have normal CSF pressure and neuroimaging studies. Thus, a high index of suspicion is needed. The published literature has inherent bias as many types of specialists evaluate and treat these conditions. This article reviews the key points to emphasize the history, examination, and laboratory evaluation of patients with intracranial pressure disorders from a neurologist's perspective.

RECENT FINDINGS: Lumbar puncture opening pressure in patients with spontaneous intracranial hypotension was low enough to meet diagnostic criteria (≤60 mm CSF) in only 34% of patients in one study. Most patients had an opening pressure in the low normal to normal range, and 5% had an opening pressure of 200 mm CSF or more. Diskogenic microspurs are a common cause of this syndrome. The Idiopathic Intracranial Hypertension Treatment Trial found that most participants had a headache phenotype resembling migraine or tension-type headache. No "typical" or characteristic headache phenotype was found, and headache-related disability was severe at baseline. Headache disability did not correlate with the lumbar puncture opening pressure at baseline or at the 6-month primary outcome period. Although participants who were randomly assigned to acetazolamide had a lower mean CSF opening pressure at 6 months, headache disability in that group was similar to the group who received placebo.

SUMMARY: Significant overlap is seen in the symptoms of high and low CSF pressure disorders and in those of primary headache disorders. Neurologists are frequently challenged by patients with headaches who lack the typical clinical signs or imaging features of the pseudotumor

cerebri syndrome or spontaneous intracranial hypotension. Even when characteristic symptoms and signs are initially present, the typical features of both syndromes tend to lessen or resolve over time; consider these diagnoses in patients with long-standing "chronic migraine" who do not improve with conventional headache treatment. While the diagnostic criteria for pseudotumor cerebri syndrome accurately identify most patients with the disorder, at least 25% of patients with spontaneous intracranial hypotension have normal imaging and over half have a normal lumbar puncture opening pressure. Detailed history taking will often give clues that suggest a CSF pressure disorder. That said, misdiagnosis can lead to significant patient morbidity and inappropriate therapy.

INTRODUCTION

Although they represent opposite extremes on the intracranial pressure spectrum, many similarities occur between the clinical features of high- and low-pressure disorders. Additionally, both conditions share properties seen with primary headache disorders (TABLE 6-1 and TABLE 6-2). Both syndromes can produce new daily persistent headaches, although the headaches are not always daily in either disorder. No typical headache phenotype exists for either condition; nocturnal awakening and worsening with bending over or Valsalva maneuvers are helpful clues for both conditions but are not specific. The longer the duration of symptoms, the more difficult it is to confirm either diagnosis by brain imaging techniques, and even the lumbar puncture opening pressure can be misleading. Although neurologists usually evaluate patients with these conditions because of headaches and other neurologic symptoms, either disorder can be asymptomatic or acephalgic. Finally, there is a fine line between being hypervigilant when considering the two diagnoses in clinical practice and overdiagnosing these conditions, which can lead to inappropriate investigations and treatments, potentially causing harm.[2]

SPONTANEOUS INTRACRANIAL HYPOTENSION

The term *spontaneous intracranial hypotension* is a misnomer. The syndrome is not always spontaneous; a precipitating event is often identified. Additionally, the majority of patients with spinal CSF leaks do not have low CSF pressure, defined as a lumbar puncture opening pressure below 60 mm CSF.[3] It is more accurately conceptualized as low CSF volume, low CSF pressure, and possibly low compliance of the caudal spinal dura. "Intracranial" implies that the problem is within the skull. While most of the clinical manifestations are intracranial, the underlying defect is spinal.[4]

TABLE 6-3 lists the diagnostic criteria for spontaneous intracranial hypotension.[5] The estimated prevalence of spontaneous intracranial hypotension is 1 per 50,000, with an annual incidence of 5 per 100,000.[6] This is likely an underestimation, as patients without typical brain imaging findings are less likely to be diagnosed and are therefore excluded from population-based studies. Additionally, such studies rely on a specific diagnosis code, which does not currently exist for this disorder. Spontaneous intracranial hypotension is more common in women than men and typically presents in the fourth or fifth decades, although it may occur at any age, and patients may have symptoms for years or even decades before being

TABLE 6-1 **Overlap of Clinical Features of High and Low Cerebrospinal Fluid Pressure Disorders and Primary Headache Disorders**

Feature	Pseudotumor Cerebri Syndrome	Intracranial Hypotension	Primary Headache Disorder
Location of pain	Often frontal or retro-orbital but varies	Often posterior but varies	Varies
Timing	Worse in the morning or no fluctuation	Worse as the day progresses	Patterns vary by headache type; migraine is often present upon awakening
Nocturnal awakening	Yes	Yes	Yes; frequent in cluster headache, infrequent in migraine, defining of hypnic headache
Worse with Valsalva maneuver, exercise, bending over	Yes	Yes	Yes; migraine, primary exertional headaches, secondary causes (eg, reversible cerebral vasoconstriction syndrome, aneurysm, Chiari malformation)
Effect of caffeine	None or worsens	Improvement	Either; caffeine may provoke migraine or relieve it
Orthostatic/positional component	Sometimes worse lying flat	Usually better lying flat	Varies; patients with migraine often prefer to lie down, which may be related to avoiding movement
Effect of high altitude	Usually worsens	Usually improves	Either; migraine is a risk factor for headache at high altitude[1]
Effect of Trendelenburg position	None (may theoretically worsen)	Often improves	None
Pulsatile tinnitus	Common	Rare (but may have nonpulsatile tinnitus)	Not associated
Transient obscurations of vision	Common	No	No; transient visual loss in migraine lasts longer than 1 to 2 minutes and is not postural
Joint hypermobility	Not associated	Common	Not associated
Neck or back pain	Common	Common	Common
Radicular pain	Common	Rare	No
Papilledema	Usually present	No	No
Spontaneous venous pulsations	Absent	Usually present	Usually present
Associated with cerebral venous sinus thrombosis	Yes	Yes	No
Sex	Marked female preponderance after puberty	More common in females	Male or female; depends on primary headache diagnosis
Body habitus	Usually obese	Often slim or normal	No association

Comparison of Diagnostic Tests Between High and Low Cerebrospinal Fluid Pressure Disorders and Primary Headaches

TABLE 6-2

Feature	Pseudotumor Cerebri Syndrome	Intracranial Hypotension	Primary Headache Disorder
Sella/pituitary[a]	Usually empty sella	Usually enlarged and hyperemic pituitary	No pattern
Ventricular size	Normal	Normal	Normal
Tonsillar descent	Possible	Common, may resemble Chiari malformation	No relationship
Flattening of anterior pons	No	Common	No
Optic nerve sheath complex	Distended and/or tortuous	Narrowed, straight	No
Lumbar puncture opening pressure[b]	High	Low or normal, occasionally high	Usually normal
Post–lumbar puncture headache possible	Yes	Yes	Yes
Headache improves after lumbar puncture	Often	No, symptoms may worsen	Possibly

[a] Pituitary gland may enlarge during pregnancy.
[b] May be elevated with Valsalva maneuver, extreme pain.

Diagnostic Criteria for Spontaneous Cerebrospinal Fluid Leak and Intracranial Hypotension[a]

TABLE 6-3

A Demonstration of a spinal CSF leak (ie, presence of extrathecal CSF)
Or, if criterion A not met,

B Cranial MRI changes of intracranial hypotension (ie, presence of subdural fluid collections, enhancement of the pachymeninges, or sagging of the brain) and the presence of at least one of the following:

1 Low opening pressure (≤60 mm H_2O)

2 Spinal meningeal diverticulum

3 Improvement of symptoms after epidural blood patching
Or, if criteria A and B not met:

C The presence of all of the following or at least two of the following if typical orthostatic headaches are present:

1 Low opening pressure (≤60 mm H_2O)

2 Spinal meningeal symptoms

3 Improvement of symptoms after epidural blood patching

Note: Patients with onset of symptoms after dural puncture or other penetrating spinal trauma are excluded.

CSF = cerebrospinal fluid; MRI = magnetic resonance imaging.
[a] Reprinted with permission from Schievink WI, et al, AJNR Am J Neuroradiol.[5]

KEY POINTS

- Although they represent opposite ends of a spectrum, spontaneous intracranial hypotension and pseudotumor cerebri syndrome share many clinical similarities.
- Neurologists are often faced with the dilemma of evaluating patients who may have either spontaneous intracranial hypotension or pseudotumor cerebri syndrome, but are "atypical."
- When evaluating a patient with possible spontaneous intracranial hypotension or pseudotumor cerebri syndrome, there is a fine line between being hypervigilant when considering the two diagnoses in clinical practice and overdiagnosing the conditions, which can lead to inappropriate investigations and treatments, potentially causing harm.
- Spontaneous intracranial hypotension is not necessarily spontaneous, is not of intracranial origin, and may not arise solely from low CSF pressure. CSF volume and compliance of the caudal dura may also be contributing factors.
- Typical orthostatic and "end of the day" headaches may be less prominent in spontaneous intracranial hypotension over time.
- A marked variability occurs in the location and character of spontaneous intracranial hypotension–related headaches.

correctly diagnosed. Predisposing factors include hypermobility disorders, including Ehlers-Danlos and Marfan syndromes, and degenerative disk disease. It is postulated that individuals with connective tissue disorders and hypermobility have dural weakness leading to tears and diverticula that allow CSF to egress into the epidural space.[6] TABLE 6-4 lists other causes of the syndrome, such as trauma, intentional or accidental dural puncture, and various physical activities.[8] The physical trauma may be trivial or related to usual activities, such as exercise.

The most common symptom of spontaneous intracranial hypotension is headache. Spontaneous intracranial hypotension is a secondary cause of new daily persistent headache, and the headache may start abruptly. The classic headache is orthostatic, worsening in the upright posture and improving with recumbence. This feature suggests that downward traction on pain-sensitive upper cervical and cranial structures (nerve roots, meninges, ligaments, veins) is responsible for the headache. However, nocturnal awakening is not uncommon, and paradoxical headaches (worse in recumbence and improved in the upright posture) may rarely occur.[9] Patients will often relate that their headache is absent or least intense when they first awaken. It may worsen almost immediately after sitting or arising or progressively worsen throughout the day. Others will experience headache that begins later in the day, sometimes starting at a very specific time. The location and quality of the headache are extremely variable, with the latter ranging from annoying to completely incapacitating. Bilateral posterior head pain is commonly present, but the pain may be unilateral and in any cranial location. Associated neck pain commonly occurs, and trigeminal neuralgic pain has been reported.[10] The orthostatic component may dissipate over time.

Exacerbating factors, which may also occur with intracranial hypertension and other headache disorders, include coughing, sneezing, laughing, lifting, bending, straining (Valsalva maneuver), sexual activity, and exercise. (Worsening with Valsalva maneuvers seems paradoxical, but such maneuvers may exacerbate the CSF leakage through spinal dural defects.) The headache may improve at high altitude, with caffeine, with greater occipital nerve blockade, and possibly with onabotulinumtoxinA injections.[11,12]

Other manifestations of spontaneous intracranial hypotension include chest or back pain ("coat hanger" headache), photophobia, diplopia, blurred vision, facial pain, imbalance, hearing abnormalities, tinnitus, cognitive and mental status changes, hyperkinetic and hypokinetic movement disorders, galactorrhea, subdural fluid collections, and intracranial hemorrhage (TABLE 6-2).

Diagnosis

The key to diagnosis is a high level of clinical suspicion and a careful history. As the manifestations vary and neuroimaging may be normal, the diagnosis may be delayed for many years. The neurologic examination is usually normal or may reveal abnormalities referable to the nonheadache symptoms. Spontaneous venous pulsations on fundoscopy are supportive although not universally present. Patients may be slim with an elongated, slender neck. Improvement of symptoms in the Trendelenburg position (10- to 20-degree head-down tilt for 5 to 10 minutes) is highly suggestive of spontaneous intracranial hypotension.[13] Patients should be queried and examined for joint hypermobility; the Beighton scale is a helpful assessment tool.[13,14] These points are demonstrated in CASE 6-1.

Laboratory Studies

Lumbar puncture is only helpful for diagnosing spontaneous intracranial hypotension if the CSF pressure is low (≤60 mm CSF). In a study of 106 patients meeting the diagnostic criteria of headache due to spontaneous intracranial hypotension developed by Schievink and colleagues,[15] 34% of patients had a CSF pressure of 60 mm CSF or less, 45% had opening pressures between 60 mm CSF and 120 mm CSF, 16% had opening pressure between 120 mm CSF and 200 mm CSF, and 5% had pressures greater than 200 mm CSF.[3,15] Thus, most patients with spontaneous intracranial hypotension have normal CSF pressure. A 24-gauge needle is recommended to avoid a post–dural puncture leak that may

Causes and Predisposing Factors for Spontaneous Intracranial Hypotension Syndrome[a] TABLE 6-4

Connective Tissue Matrix Disorders

- Marfan syndrome
- Ehlers-Danlos syndrome type II
- Autosomal dominant polycystic kidney disease
- Joint hypermobility: hyperflexibility, "party tricks," naturally good at gymnastics, dance, or yoga (inquire about flexibility in childhood)
- Retinal detachment at a young age
- Personal or family history of arterial dissection, aneurysms, nonrheumatic valvular heart disease
- Secondary to unrecognized intracranial hypertension

Trauma

- Previous spine surgery
- History of lumbar puncture
- Nerve root sleeve tears or avulsions
- Previous spinal or epidural anesthesia
- Trivial trauma
  - Valsalva related: heavy lifting, coughing, straining
  - Repetitive truncal torsion: tennis, golf, yoga, kayaking, canoeing
- Impact: motor vehicle accident, whiplash, sports injury

Spine Disorders

- Calcified herniated disks
- Osteophytes and spondylotic spurs
- CSF venous fistula

Bariatric Surgery[7]

Unknown

CSF = cerebrospinal fluid.

[a] Modified with permission from Mokri B, Continuum (Minneap Minn).[8]

worsen the condition. Rarely, spontaneous intracranial hypotension mimics aseptic meningitis with a lymphocytic pleocytosis or elevated CSF protein.[16]

Contrast-enhanced MRI of the brain is generally the first imaging study obtained and is abnormal about 75% of the time. The typical findings are brain sag with cerebellar tonsillar descent, pituitary enlargement and hyperemia, flattening of the anterior pons, straightening of the optic chiasm, distention of the cerebral venous sinuses, ventricular collapse, venous sinus dilatation, and descent and distortion of the midbrain (FIGURE 6-2). Most findings are best viewed on the midline sagittal T1-weighted images. Coronal images reveal thickening and enhancement of the pachymeninges resulting from venous distention (FIGURE 6-3).[17] Subdural fluid collections, subdural hematoma, cerebral venous sinus thrombosis, evidence of reversible cerebral vasoconstriction syndrome, or subarachnoid hemorrhage may be seen. Spontaneous intracranial hypotension occurring in children and young adults may alter the skull morphology with calvarial thickening, expansion of the

CASE 6-1

A 31-year-old woman developed diplopia and intermittent headaches that had become constant within 2 weeks of onset. One month prior to the onset of symptoms, she had begun taking vigorous aerobic exercise classes, and she rode a roller coaster a few days prior to symptom onset. An optometrist had found a right abducens palsy, and a CT scan of the orbits was normal. Two weeks later, the diplopia persisted, and the headache became constant.

At her neurologic evaluation 2 months later, the headache had evolved into a right temple pain with intermittent burning of the right cheek and right ear and sharp retro-orbital pain. The initial dull pain spread to the right neck and occipital regions with intermittent sharp pain just to the right of the vertex. She had severe phonophobia, mild photophobia, nausea, confusion, tinnitus, and dry heaves. The headache was rated 4 out of 10 intensity upon awakening and worsened over hours to 8 out of 10 by the end of the day. It awakened her from sleep at times. Coughing, sneezing, and bearing down increased the pressure sensation in her neck. Lying completely flat improved the headache, and standing worsened it. Caffeine helped the headache. She reported being "double jointed" with a strong family history of joint hypermobility and heart murmurs.

MRI of the brain with contrast was normal (FIGURE 6-1). Neurologic examination showed 50% of normal right eye abduction and normal fundi with spontaneous venous pulsations. Joint hypermobility was present in the fingers, wrists, and hips. Cardiac auscultation was normal. Headache severity prior to the Trendelenburg test was rated 3 out of 10; the patient's headache resolved, and the right abducens palsy improved after being in the Trendelenburg position for 10 minutes.

She underwent two sequential high-volume lumbar epidural blood patches with brief rebound intracranial hypertension that was treated with acetazolamide. Genetic testing for Ehlers-Danlos syndrome was negative. Her symptoms ultimately resolved.

paranasal sinuses, aeration of bones at the skull base, and reduction in the size of the sella turcica.[18]

In one series, patients without dural enhancement had a longer duration of symptoms than those with enhancement; brain sag and venous distention did not correlate with symptom duration.[19] Misinterpretation of the findings may have devastating consequences for the patient. Brain sag may be erroneously diagnosed as a Chiari malformation type I, leading to unnecessary surgery that may make the patient worse. Draining resultant subdural hematomas without addressing the intracranial hypotension may cause rebleeding that can be fatal.

Spinal imaging modalities are incorporated to identify the site, nature, and cause of a leak in order to plan therapy. Collaboration with a neuroradiologist having expertise in the techniques used to diagnose spinal CSF leaks is critical for optimal patient management. Areas of dural thinning and dehiscence allow the herniation of the arachnoid layer through the dural defect, leading to meningeal diverticula that are prone to tear.[19] These diverticula tend to be located along the

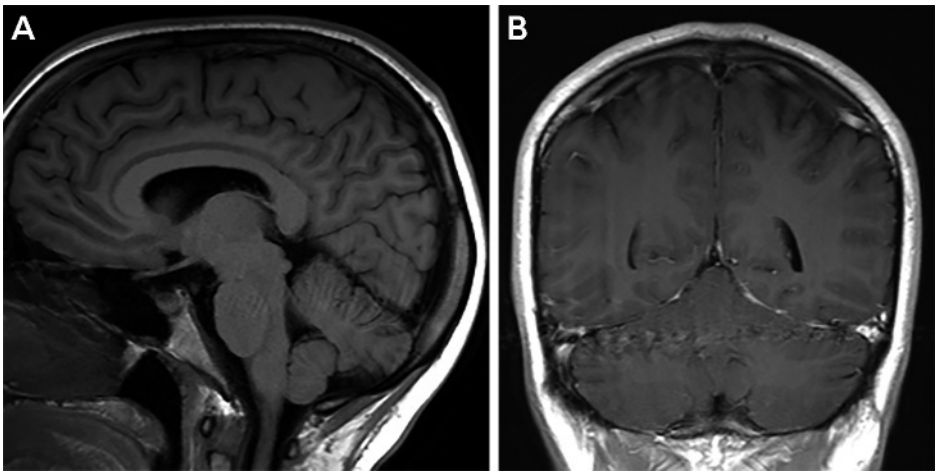

FIGURE 6-1

Imaging of the patient in CASE 6-1. *A*, Sagittal noncontrast T1-weighted MRI shows no evidence of brain sag, pituitary enlargement, or chiasmal flattening. *B*, Coronal postcontrast T1-weighted image reveals normal meningeal contrast enhancement.

COMMENT

Despite normal brain imaging, the patient's symptoms were highly suggestive of spontaneous intracranial hypotension. She had orthostatic head, face, and neck pain that worsened during the day and was associated with tinnitus. Predisposing factors included joint hypermobility, vigorous exercise, and riding a rollercoaster. The headache and sixth nerve palsy improved in the Trendelenburg position. Intracranial hypertension may occur after epidural blood patches, which can usually be managed medically.

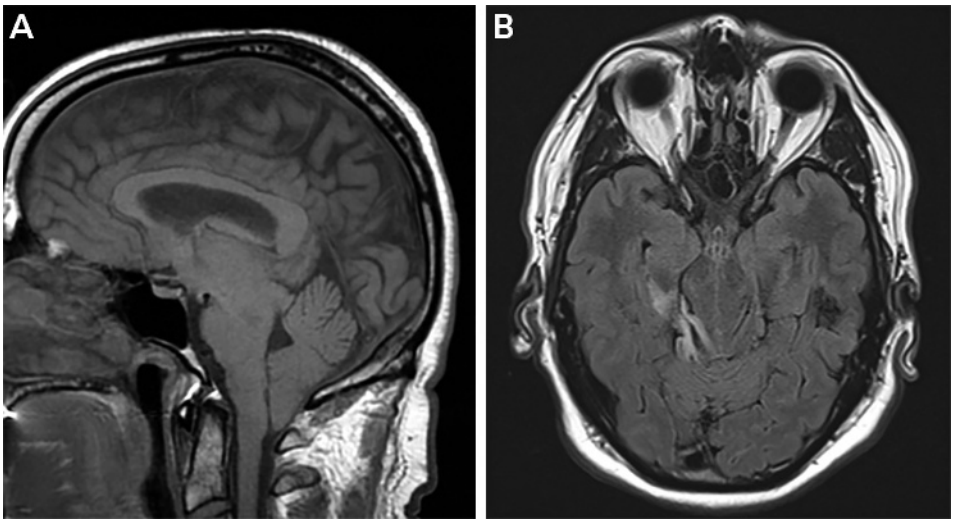

FIGURE 6-2
Imaging findings of spontaneous intracranial hypotension. A 61-year-old man, who worked as a high-level financial executive, underwent neuroimaging for a 3-year history of cognitive decline, which had progressed to the point that he missed paying his bills and could not recall the day of the week. *A*, T1-weighted sagittal MRI showed pronounced brain sag with tonsillar descent, flattening of the anterior pons, midbrain collapse, downward displacement of the posterior corpus callosum, obliteration of the third ventricle, and straightening of the optic chiasm. *B*, Axial fluid-attenuated inversion recovery (FLAIR) image showed marked distention of the midbrain with abnormal high signal in the right hippocampal formation indicating partial herniation. No abnormal pachymeningeal enhancement was seen on the postcontrast images (not shown). The patient had minimal improvement with blood patches and ultimately required surgical repair of his spinal CSF leak, resulting in significant improvement in his cognition. This case illustrates that symptoms other than headache may be predominant in spontaneous intracranial hypotension.

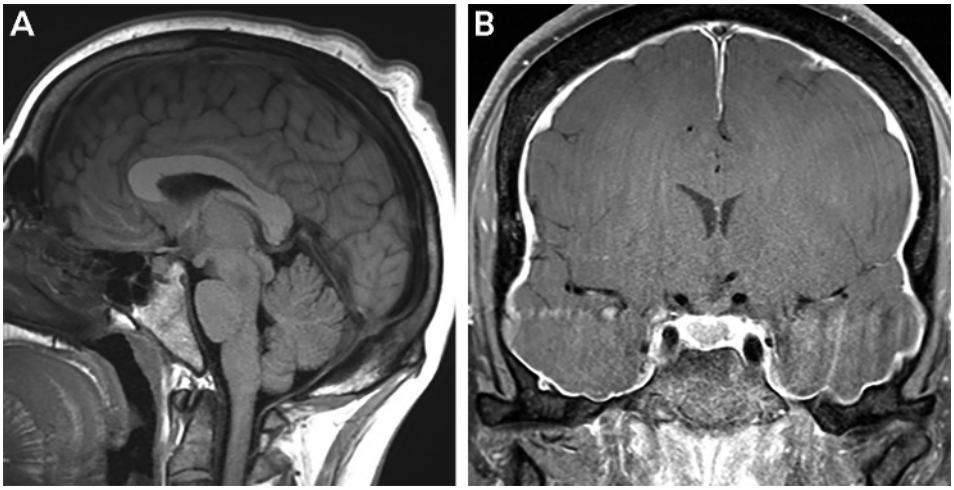

FIGURE 6-3
Spontaneous intracranial hypotension. A 30-year-old man developed a severe orthostatic headache, intense vomiting, vertigo, blurred vision, and neck pain. Imaging 2 weeks later revealed mild flattening of the anterior pons and pituitary enlargement on T1-weighted sagittal MRI (*A*). Despite the relatively normal precontrast images, meningeal thickening and enhancement is seen on the postcontrast T1-weighted coronal MRI (*B*).

nerve root sleeves and are often large and irregular in contour. Degenerative changes, such as osteophytes and calcified disk protrusions, can directly tear the dura and are most commonly located ventrally in the lower cervical or thoracic spine.[20] CSF venous fistulas are identified in a small percentage of patients. The anatomy of a leak may be complex, and localizing the exact leak site or sites may be elusive. In 46% to 55% of cases, including those with slow or intermittent leaks and those caused by CSF venous fistulas, the leak site cannot be found.[21,22]

In fast (high-flow) leaks, a pool of contrast material extravasates into the epidural space surrounding the thecal sac. It may be extensive in some cases, arising at multiple levels and tracking into the paraspinal soft tissues.[3] An extensive leak may impede exact localization of the leak site, which requires high resolution and rapid imaging after the administration of contrast. A large pool of epidural contrast is usually absent with slow (low-flow) leaks. Slow leaks generally occur around nerve root sleeves and are easier to treat than fast ventral leaks. However, if the leak is quite slow or intermittent, identification of the leak site is difficult. Delayed imaging may be helpful. One strategy is to inject the contrast material for the CT and MRI simultaneously after injecting a bolus (approximately 15 mL) of intrathecal saline or artificial CSF to increase the CSF volume. The patient is immediately imaged with CT, followed by delayed imaging using MRI. Both techniques are invasive, and the use of gadolinium for intrathecal injection is off-label. Radiation dose must always be considered with CT.

Digital subtraction myelography is performed under fluoroscopy and allows the real-time visualization of the contrast agent traversing along the spine to identify the site of the leak.[3] The leak appears as a split in the column of contrast material creating a parallel track in the epidural space. The resolution is excellent, but there is a limit to the area of coverage possible, so the lower cervical and thoracic spine are generally scanned unless a leak is suspected elsewhere. The patient must be absolutely immobile, which may require general anesthesia. This technique is performed in the angiography suite and is not widely available.

Spinal MRI with heavily T2-weighted images and fat suppression is a noninvasive technique that best identifies the presence (but not necessarily the location) of high-flow leaks. A retrospinal fluid collection at C1-C2 seen with this technique does not indicate the site of the leak and is a false localizing sign.[23] Disadvantages of this technique are the lower spatial resolution, higher rate of artifacts, decreased likelihood of localizing the leak, and the need for very homogeneous fat suppression.[19] This imaging technique is not generally included in standard MRI software and may require additional programming.

Radionuclide cisternography incorporates an iodinated tracer (indium 111 diethylenetriamine pentaacetic acid [^{111}InDTPA]), which is injected intrathecally with image acquisition immediately and at 1, 2, 4, 24, and sometimes 48 hours after injection. It may show direct or indirect evidence of a leak. Unilateral or bilateral focal areas of increased activity within paraspinal tissues indicate direct evidence.[13] Indirect signs include early uptake in the kidneys and bladder within 4 hours, absence of activity along cerebral convexities at 24 hours (similar to normal pressure hydrocephalus), and rapid loss of spinal activity. Cisternography has only modest sensitivity and specificity, and the cost of the tracer is sometimes prohibitive. False-positive and false-negative results may occur.

KEY POINTS

- Patients with spontaneous intracranial hypotension may be asymptomatic or experience visual, vestibulocochlear, and cognitive problems, as well as an altered level of consciousness, movement disorders, and intracranial hemorrhage.
- Patients who have a typical headache pattern or abnormal brain imaging are generally identified early. The lack or subtle nature of orthostatic symptoms coupled with normal brain imaging leads to considerable delay in diagnosis, sometimes for decades. Spontaneous intracranial hypotension should be considered in patients with headaches of any phenotype that are refractory to conventional headache therapies.
- Brain sag may be erroneously diagnosed as a Chiari malformation type I, leading to unnecessary surgery that may make the patient worse.
- In cases of spontaneous intracranial hypotension, the leak site cannot be identified in about half of cases, and intermittent leaking may occur, which can make identification of the leak site challenging.
- Nerve sheath diverticula and osseous changes are indirect signs of a potential leak site.
- In cases of spontaneous intracranial hypotension, a large pool of epidural contrast suggests a high-flow leak.

Treatment

Conservative treatments may be attempted but are generally unsuccessful (TABLE 6-5); the refractory nature of spontaneous intracranial hypotension headaches to typical headache medications is a clue that the patient may have a secondary disorder. Occasionally, leaks will resolve spontaneously.

A nontargeted, autologous, high-volume epidural blood patch is often the first step in management, and each attempt is successful approximately 30% of the time.[21] A disagreement exists regarding whether this procedure should be tried empirically or whether patients should be evaluated to determine the leak site first. Even transient relief of symptoms supports the diagnosis of spontaneous intracranial hypotension, so the procedure also has diagnostic value in suspected cases with normal brain imaging. Symptoms may subsequently recur, requiring additional blood patches, and at least 5 days are recommended between procedures.[26]

"Nontargeted" midline epidural blood patches are generally performed at one or more spinal levels from T12-L1 through L4-L5, and multilevel patches may be done in one session. The success rate is potentially enhanced by pretreating the patient with acetazolamide (250 mg orally given at 18 and 6 hours prior to the procedure) to decrease CSF volume and allow a higher volume of blood to be injected in the epidural space and placing the patient in the Trendelenburg position during and immediately after the procedure.[27] A volume of 10 mL to 20 mL of autologous blood is initially injected, which may be increased as tolerated in subsequent attempts. The amount of blood injected is generally determined by the patient's level of procedure-related pain or anatomic constraints limiting the volume of injection.

Another technique employs a single puncture in the lower thoracic or lumbar space, passing a guidewire into the epidural space, and advancing in a 4-French vertebral catheter superiorly into the dorsal epidural space. After confirming epidural placement with contrast administration, the guidewire is removed, and autologous blood is injected into the epidural space while slowly withdrawing the catheter to the access site.[28]

The mechanism of epidural blood patches leading to improvement is uncertain and may be related to tamponade and sealing of the leak, restriction of

TABLE 6-5 **Strategies for Conservative Management of Spontaneous Intracranial Hypotension**

- Bedrest (patients can be bedbound because of their symptoms)
- Elevate the foot of the bed (home Trendelenburg position)
- Caffeine, theophylline (often helpful but may produce anxiety and insomnia)
- Abdominal binder
- Analgesics
- Corticosteroids (2- to 4-week gradual prednisone taper starting with 50 mg/d)[24]
- Bilateral greater occipital nerve blocks[25]
- Overhydration
- Time

CSF egress into the epidural space, mild compression of the thecal sac by the epidural blood and secondary increased CSF pressure rostral to the injection, or decreasing the elasticity of the thecal sac. Aspirin, anticoagulant therapy, and nonsteroidal anti-inflammatory drugs all interfere with blood clotting and should be temporarily limited in the periprocedural period, if possible. Detailed postprocedure instructions (TABLE 6-6) are recommended to prolong the duration of relief, although they have not undergone rigorous study.

If leak site(s) or potential leak site(s) are identified, targeted epidural blood patches with percutaneous placement of fibrin sealant ("glue") have the best chance of alleviating the patient's symptoms.[26] This procedure is generally performed with CT guidance and conscious sedation.

Surgery may be needed in cases of a calcified disk or osteophyte causing a dural defect. Leaking meningeal diverticula can be ligated or clipped. Larger dural defects are closed with a muscle or fat pledget, with gelatin sponge and fibrin sealant, or sutured.[26] Suturing may be less successful in patients with thin and friable dural composition. Lumbar dural reduction surgery is occasionally employed in otherwise refractory cases.[29] Transient rebound intracranial hypertension is possible after successful closure of a spinal leak and can generally be managed medically. Intrathecal saline or artificial CSF infusion is a temporizing measure that is incorporated in patients with coma or a decreased level of consciousness, indicative of brain herniation.[30]

Prognosis

Once a leak has been successfully treated, the prognosis is generally good. However, leaks can recur, and new leaks may develop, particularly in patients with underlying connective tissue disorders.

Postprocedure Instructions Following Epidural Blood Patches TABLE 6-6

Bedrest and light activity only for 24–48 hours after the procedure

Unless medically necessary, avoid nonsteroidal anti-inflammatory drugs for at least 48 hours

Patients requiring anticoagulation who were transitioned to enoxaparin sodium may resume enoxaparin sodium 12 hours after the procedure

For the first 4 weeks:

- No lifting more than 4.5 kg (10 lb)
- Avoid straining to have a bowel movement; patients who are prone to constipation should take a stool softener (sennosides, docusate sodium, fiber supplementation)
- Do not bend over to lift objects, tie your shoes, or pick something up; either ask someone else to help you or, if you must bend over, do so from the knees rather than the waist
- Avoid activities that cause twisting of the trunk, such as golf, tennis, canoeing, kayaking, yoga, martial arts, mopping, vacuuming, or contact sports
- If you engage in sexual activity, you should be on the bottom

After 4 weeks, you may gradually increase your activity level as tolerated; however, activities that require heavy lifting, straining, or trunk rotation (see above) may increase your risk of developing another leak and should be kept to a minimum if possible

Chiropractic manipulation or adjustment and similar procedures should be avoided indefinitely as they can tear the dura; massage is acceptable after the first week

KEY POINTS

- CT myelography performed immediately after the instillation of intrathecal contrast is the preferred technique for detecting fast leaks in cases of spontaneous intracranial hypotension; delayed MRI myelography is more sensitive for detecting slow leaks.
- Close collaboration with a neuroradiologist who is experienced in the diagnostic imaging modalities, interpretation of findings, and interventional treatments of spontaneous intracranial hypotension is imperative.
- A retrospinal fluid collection at C1-C2 is a false localizing sign of a spinal CSF leak.
- A nontargeted lower thoracic or lumbar high-volume epidural blood patch is successful in alleviating symptoms in about 30% of patients with spontaneous intracranial hypotension. However, the symptoms may recur over time.
- Of the neurointerventional procedures for spontaneous intracranial hypotension, targeted epidural blood patches with fibrin sealant have the best chance of alleviating the patient's symptoms.
- Headache is the most common symptom of pseudotumor cerebri syndrome and may persist after other symptoms resolve and the CSF pressure normalizes.

PSEUDOTUMOR CEREBRI SYNDROME

The pseudotumor cerebri syndrome primarily affects children and adults younger than age 50. Boys and girls are equally affected until puberty, when the female preponderance manifests.[31] For the most part, the clinical presentation in teenage girls with pseudotumor cerebri syndrome is similar to adult women with the disorder. The etiology is unknown.[32] Many secondary causes have been associated with pseudotumor cerebri syndrome such as exogenous agents, obstruction to cerebral venous outflow, endocrine disorders, obstructive sleep apnea, and head trauma (TABLE 6-7).[34] When no secondary cause is identified, the syndrome is termed idiopathic intracranial hypertension (IIH), which most commonly affects women of childbearing age who are obese. As pseudotumor cerebri syndrome potentially causes blindness, early recognition and treatment are essential. Headache is the most common presenting symptom of pseudotumor cerebri syndrome and often persists for years after the other symptoms resolve and the CSF pressure normalizes.[35–37]

Clinical Features

The diagnostic criteria of pseudotumor cerebri syndrome are listed in TABLE 6-8. A definite diagnosis requires the presence of papilledema, normal level of consciousness, normal MRI (including ventricular size) except for signs referable to intracranial hypertension, and a lumbar puncture with an opening pressure measurement and normal CSF composition confirming the diagnosis. In the absence of papilledema or an abducens palsy, the diagnosis can only be suggested if neuroimaging criteria are met.

Headache is the most common symptom, present in approximately 80% to 90% of patients at diagnosis, and is frequently the initial symptom. No distinguishing characteristics of the headache occur, although it often represents a new or different headache and may be quite severe. In the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) that prospectively studied 165 patients newly diagnosed with papilledema and mild visual field loss from IIH (perimetric mean deviation from –2 dB to –7 dB on Humphrey automated perimetry), headache was present in 84% at the baseline visit.[38] Headache phenotypes, characterized using the *International Classification of Headache Disorders, Third Edition* (*ICHD-3*) criteria,[39] were migraine (52%), probable migraine (16%), tension-type headache (22%), probable tension-type headache (4%), and unclassifiable (7%). Of the participants, 68% described frontal pain that was either pressurelike or throbbing, but many also experienced posterior (39%), ocular (47%), and neck pain (47%); 36% reported global pain, and 30% had unilateral pain. Migraine-associated symptoms were common and included photophobia (70%), phonophobia (52%), nausea (47%), vomiting (15%), and worsening with routine physical activity (50%). Participants indicated substantial to severe headache disability as measured by the six-item Headache Impact Test (HIT-6) questionnaire, and concurrent photophobia significantly worsened the HIT-6 score. The mean headache frequency was 12 days in the month prior to study entry, with 23% having constant, daily head pain.[40]

Most enrollees in the IIHTT with headache also had other symptoms suggesting a secondary cause, such as constant visual loss (34%), transient visual obscurations (68%), diplopia (22%), and dizziness (53%). However, 14% of those with headache had none of those symptoms despite having papilledema. Of all enrollees, intermittent or daily pulse-synchronous tinnitus occurred in

Causes of Pseudotumor Cerebri Syndrome and Commonly Associated Conditions[a]

TABLE 6-7

Primary Pseudotumor Cerebri Syndrome

- **Idiopathic intracranial hypertension**

Secondary Pseudotumor Cerebri Syndrome

- **Cerebral venous abnormalities**
  - Cerebral venous sinus thrombosis
  - Jugular vein obstruction
- **Decreased CSF absorption from previous intracranial infection or subarachnoid hemorrhage**
  - Increased right heart pressure
  - Superior vena cava syndrome
- **Associated with systemic venous hypertension**
- **Medications and exposures**
  - Antibiotics (tetracycline family, fluoroquinolones, nalidixic acid)[33]
  - Vitamin A and retinoids (including isotretinoin, all-transretinoic acid, hypervitaminosis A)
  - Hormones
    - Human growth hormone
    - Thyroxine (in children)
    - Leuprorelin acetate
  - Anabolic steroids
  - Withdrawal from chronic corticosteroids
  - Lithium
  - Chlordecone
- **Medical conditions**
  - Endocrine disorders (Addison disease, hypoparathyroidism)
  - Hypercapnia (sleep apnea, pickwickian syndrome)
  - Anemia
  - Renal failure
  - Turner syndrome
  - Down syndrome

CSF = cerebrospinal fluid.

[a] Modified with permission from Friedman DI, et al, Neurology.[34] © 2013 American Academy of Neurology.

52% of patients and was most frequently bilateral (66%).[37] Daily nonpulsatile tinnitus occurred in 23% of patients. Back pain, including radicular pain, was experienced by 53% of the study cohort. Occasionally, IIH is diagnosed in asymptomatic patients (often children) when papilledema is discovered during a routine ophthalmic examination.[41]

Headaches arising from pseudotumor cerebri syndrome may cause nocturnal awakening and may worsen in high altitude or in recumbence. Young children with pseudotumor cerebri syndrome may not be able to articulate their symptoms, which must be inferred by manifestations such as behavior change, decline in school performance, malaise, withdrawal, light avoidance, apparent inability to see well, decreased appetite, or vomiting.

Papilledema from pseudotumor cerebri syndrome may be asymmetric and is sometimes difficult to discern with direct ophthalmoscopy, so ophthalmologic consultation is recommended. However, misdiagnosis is possible even using more sophisticated techniques of evaluating the optic nerve.[2] The diagnosis of pseudotumor cerebri syndrome in patients without papilledema is challenging

TABLE 6-8 **Diagnostic Criteria for the Pseudotumor Cerebri Syndrome**[a]

1 Required for Diagnosis of Pseudotumor Cerebri Syndrome[b]

- **A** Papilledema
- **B** Normal neurologic examination except for cranial nerve abnormalities
- **C** Neuroimaging: normal brain parenchyma without evidence of hydrocephalus, mass, or structural lesion and no abnormal meningeal enhancement on MRI, with and without gadolinium, for typical patients (female and obese), and MRI, with and without gadolinium, and magnetic resonance venography for others; if MRI is unavailable or contraindicated, contrast-enhanced CT may be used
- **D** Normal CSF composition
- **E** Elevated lumbar puncture opening pressure (≥250 mm CSF in adults and ≥280 mm CSF in children [≥250 mm CSF if the child is not sedated and not obese]) in a properly performed lumbar puncture

2 Diagnosis of Pseudotumor Cerebri Syndrome Without Papilledema

- **A** In the absence of papilledema, a diagnosis of pseudotumor cerebri syndrome can be made if B–E from above are satisfied and, in addition, the patient has a unilateral or bilateral abducens nerve palsy
- **B** In the absence of papilledema or sixth nerve palsy, a diagnosis of pseudotumor cerebri syndrome can be suggested but not made if B–E from above are satisfied and, in addition, at least three of the following neuroimaging criteria are satisfied:
  - **i** Empty sella
  - **ii** Flattening of the posterior aspect of the globe
  - **iii** Distention of the perioptic subarachnoid space with or without a tortuous optic nerve
  - **iv** Transverse venous sinus stenosis

CSF = cerebrospinal fluid; CT = computed tomography; MRI = magnetic resonance imaging.
[a] Reprinted with permission from Friedman DI, et al, Neurology.[34] © 2013 American Academy of Neurology.
[b] A diagnosis of pseudotumor cerebri syndrome is definite if the patient fulfills criteria A–E. The diagnosis is considered probable if criteria A–D are met but the measured CSF pressure is lower than specified for a definite diagnosis.

and potentially problematic. Papilledema may not be present in patients with preexisting optic atrophy, in cases of recurrence, or in patients with mild disease who were not evaluated for disc edema at symptom onset (which may have been years prior).

Of the 165 participants in the IIHTT, 67 had a self-reported history of migraine, which is more than twice the expected prevalence in the general population.[37,38] This may ultimately lead to uncertainty about the etiology of headaches in patients with pseudotumor cerebri syndrome in the long-term. However, the visual disturbances of pseudotumor cerebri syndrome are different from those that occur in migraine.

Transient obscurations of vision are brief episodes of visual loss in one or both eyes that are often precipitated by arising after bending over. They may also be provoked by eye movement or occur spontaneously. The visual loss may be complete ("black out" or "white out") or partial, often described as cloudy or foggy. The episodes last seconds to a few minutes (shorter than typical migraine aura) and may occur many times during the day. These episodes were one of the most disabling symptoms reported by participants in the IIHTT, likely because of their unpredictability.[42] Diplopia in pseudotumor cerebri syndrome is binocular, meaning that the patient sees double only when viewing from both eyes simultaneously. Reflecting abducens palsy, most patients with double vision experience horizontal diplopia that is worse at a distance and is usually constant. It is extraordinarily uncommon for diplopia to occur in the absence of papilledema in the initial presentation of this condition. Other visual symptoms include subjective visual loss (eg, blurred vision, scotomas, dimness, decreased peripheral vision) and visual distortion (if associated macular edema is present). Flashes of light (photopsia) lasting seconds to hours may be similar to those experienced by patients with migraine and are generally provoked by headache, postural change, darkness, fatigue, eye closure, or watching television.[43] The daily occurrence of photopsia was more common in patients with pseudotumor cerebri syndrome than in controls.[43] However, patterned positive visual phenomena, such as fortification spectra or scintillating scotomata, do not occur in pseudotumor cerebri syndrome. Eye pain does not reliably distinguish pseudotumor cerebri syndrome from migraine or controls.[43] Functional (psychogenic) visual loss may occur and, in one study, was more common in patients with IIH who did not have papilledema.[44,45]

Other symptoms of pseudotumor cerebri syndrome may be quite similar to those of spontaneous intracranial hypotension. Tinnitus can occur with either condition, although pulse-synchronous tinnitus suggests pseudotumor cerebri syndrome. Hearing loss or a "high altitude" sensation, neck pain, dizziness, and back pain are common to both disorders.

Prolonged elevated intracranial pressure from pseudotumor cerebri syndrome may cause bony erosion at the skull base with a subsequent empty sella and CSF rhinorrhea or otorrhea. Because patients with skull base CSF leaks from pseudotumor cerebri syndrome have largely "self-decompressed," their CSF pressures tend to be only minimally elevated prior to intervention, and papilledema is absent.[46,47] Similarly, rupture of spinal diverticula from increased intracranial pressure may lead to spontaneous intracranial hypotension, which reverts to a high-pressure syndrome when the spinal leak is repaired (CASE 6-2).

KEY POINTS

- When present, the headache of pseudotumor cerebri syndrome is heterogeneous in phenotype, severe, and disabling.
- The presence of pulse-synchronous tinnitus and transient obscurations of vision supports a diagnosis of pseudotumor cerebri syndrome.
- A history of migraine was over twice as common in participants in the Idiopathic Intracranial Hypertension Treatment Trial as in the general population.
- Elevated CSF pressure in patients with pseudotumor cerebri syndrome may lead to skull base CSF leaks or intracranial hypotension.

CASE 6-2

A 46-year-old woman presented with a history of orthostatic headaches that had begun at least 10 years prior to her initial evaluation. The headaches occurred after being upright for 6 to 7 hours and gradually increased to a 7 out of 10 in severity. The pain was located at the top of her head, was sharp in quality, and was associated with nuchal aching; it was daily and constant, relieved only with sleep and traveling to high altitude. Associated symptoms included phonophobia, constant tinnitus, and pulsatile tinnitus (whooshing) when arising in the morning. She also experienced occipital headaches with intrascapular tension and a burning neck pain. The previous year, she had woken up 2 days in a row with a "wet ear" with a halo of blood and clear liquid on the pillowcase. Her headaches worsened after this, although no CSF leak was found on imaging. She took topiramate 100 mg/d for headache prevention.

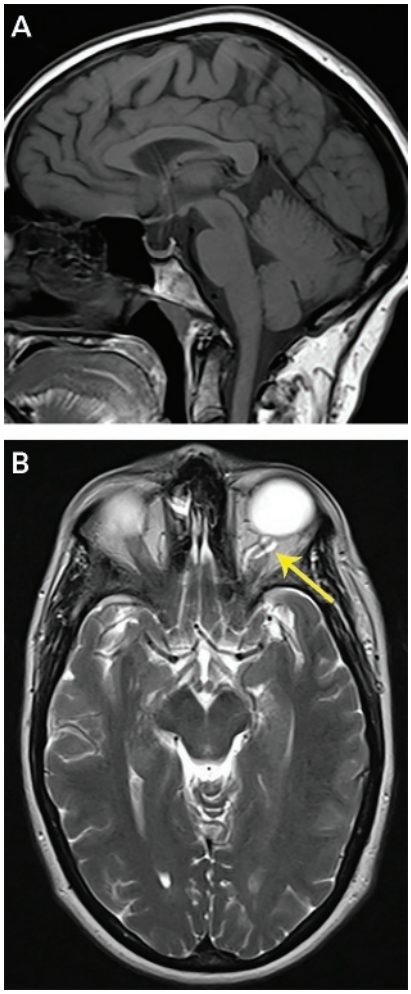

FIGURE 6-4
MRI of the patient in CASE 6-2. *A*, Sagittal T1-weighted image shows an expanded and partially empty sella. *B*, Axial T2-weighted image reveals flattening of the posterior sclerae and a tortuous optic nerve (*arrow*) with distention of the perioptic subarachnoid space (*left eye shown*).

Lumbar puncture 5 years prior for suspected intracranial hypotension showed an opening pressure of 17 cm CSF. A CT myelogram showed multiple perineural cysts but no CSF leak; her headaches resolved for a month after a nontargeted lumbar epidural blood patch. MRI 2 years prior to her current evaluation had shown an expanded and partially empty sella, flattening of the posterior sclerae, and distension of the perioptic subarachnoid space with normal ventricles and brain parenchyma (FIGURE 6-4). She had Ehlers-Danlos syndrome type A.

Examination revealed a body mass index of 28 kg/m^2 and normal fundi with spontaneous venous pulsations. The Trendelenburg test reduced the headache severity from a 7 out of 10 to a 5 out of 10 in 10 minutes.

An epidural blood patch was performed to target a large perineural cyst at T10-T11 (FIGURE 6-5) with short-lived relief. Topiramate was discontinued for potentially exacerbating intracranial hypotension. She had subsequent blood patches with relief for 5 to 9 weeks. However, 10 days after her last blood patch, she developed a different headache that worsened when lying flat. She awakened with a headache that resolved within 10 to 15 minutes of being upright, then the previous orthostatic headache began 4 hours later. She had gained weight (13.6 kg [30 lb]) after stopping topiramate and related a "lifelong" history of transient visual obscurations upon standing.

Her examination showed mild bilateral papilledema (FIGURE 6-6) with absent spontaneous venous pulsations. A trial of acetazolamide was somewhat helpful although poorly tolerated with nausea and cognitive dysfunction, and therapeutic lumbar punctures were required. She was not a candidate for optic nerve sheath fenestration because of good vision, and shunting was undesirable because of its general limitation for headache treatment and potential for increased complications related to Ehlers-Danlos syndrome. Magnetic resonance venography (MRV) revealed a dominant right transverse sinus with a focal narrowing or arachnoid granulation. The left transverse sinus was small with a focal stenosis. Venous manometry showed a gradient of more than 20 mm across the stenotic area in the right transverse sinus, which was successfully stented, albeit with difficulty due to a congenital fenestration in the sinus. She improved considerably after the procedure, but she continued to have mild symptoms of both high and low CSF pressure during the day.

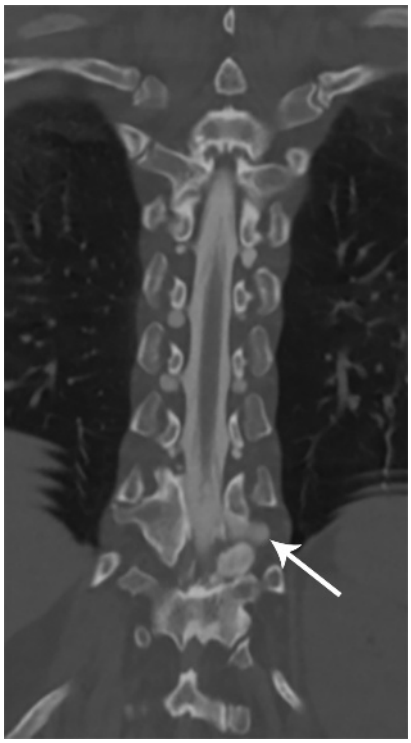

FIGURE 6-5
CT myelography of the patient in CASE 6-2 showing a large, irregular nerve sheath diverticulum at T10-T11 on the left side (*arrow*).

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PAGE 1084

Diagnosis

The diagnosis of pseudotumor cerebri syndrome is based on the presence of papilledema or abducens nerve palsy, neuroimaging findings, lumbar puncture opening pressure, and CSF analysis. The status of the patient's vision helps determine the appropriate therapy.

VISION EVALUATION. The importance of visual assessment in pseudotumor cerebri syndrome cannot be overemphasized. Any patient with headache and visual symptoms needs, at a minimum, a measurement of visual acuity in each eye, assessment of visual fields, pupil examination to look for an afferent pupillary defect or poor pupillary reaction, and a fundus examination. Patients with suspected pseudotumor cerebri syndrome should have a complete ophthalmologic evaluation with a stereoscopic viewing of the optic discs and perimetry. Fundus photography, optical coherence tomography, and fluorescein angiography or orbital ultrasound (if the diagnosis of papilledema is uncertain) are helpful to document the disc appearance for subsequent comparison.

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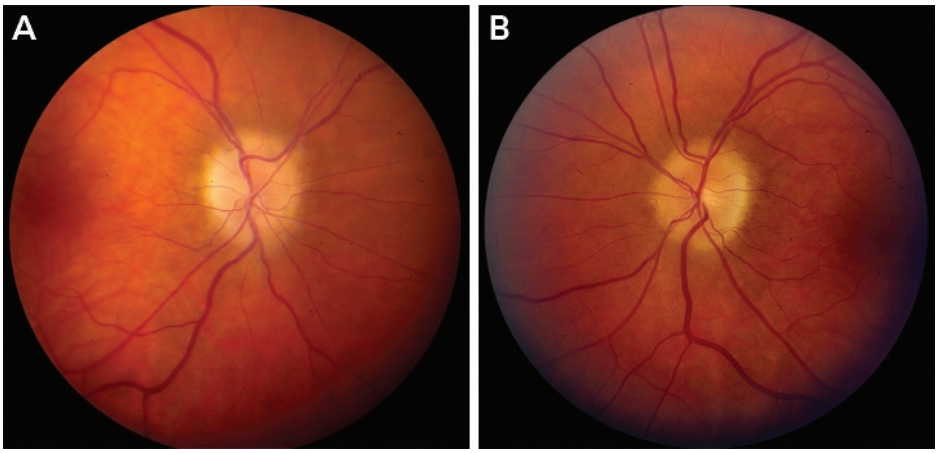

FIGURE 6-6
Fundus image of the patient in CASE 6-2 shows mild optic disc edema in both eyes (*A, right eye; B, left eye*).

COMMENT

This complex case has features of both intracranial hypotension and intracranial hypertension. Considering her brain MRI findings, most likely, the patient's initial problem was intracranial hypertension, with a secondary self-limited skull base leak (otorrhea) and spinal manifestations of intracranial hypotension. Ehlers-Danlos syndrome predisposed her to developing spinal diverticula and a CSF leak. She initially had a good response to epidural blood patches, but her weight gain after discontinuing topiramate caused the intracranial hypertension to recur, producing a "mixed" CSF pressure headache syndrome.

NEUROIMAGING. MRI of the brain with contrast is the imaging test of choice.[48] Orbital images are helpful, although most intraorbital findings can be seen on a high-quality brain image. The T1-weighted midline sagittal images may demonstrate an expanded/empty sella or tonsillar descent. T2-weighted axial images best show flattening of the posterior sclerae, which is assessed at the level where the optic nerves exit the globe. Other findings include distention of the optic nerve sheath complex with enlargement of the perioptic subarachnoid space, tortuosity of the optic nerves, protrusion of the optic nerve head into the vitreous cavity (papilledema), and widening of the foramen ovale. Skull base CSF leaks with meningoceles and meningoencephaloceles may occur.[48]

Brain magnetic resonance venography (MRV) is usually performed simultaneously with MRI to exclude venous sinus thrombosis and determine whether venous sinus stenosis is present. In urgent settings or if MRI is unavailable or contraindicated, contrast-enhanced brain CT with CT venography may be performed.[49]

LUMBAR PUNCTURE. A lumbar puncture is required for the diagnosis. CSF pressure–lowering agents should be discontinued for 24 to 36 hours prior to the lumbar puncture. For the most accurate reading, the opening pressure should be measured with the patient in the lateral decubitus position with the legs at least partially extended; studies in both children and adults suggest that the leg position does not appreciably alter the opening pressure in most cases, but the difference of approximately 10 mm CSF may be meaningful in some patients who have pressures at the upper end of normal.[50]

CSF pressures of 250 mm or greater in adults or 280 mm or greater in children are considered abnormal.[51] Body mass index has a negligible effect on CSF opening pressure, but sedation and Valsalva maneuvers may significantly increase it.[51] Valsalva maneuvers performed during a lumbar puncture can double the opening pressure, which is applicable to patients who are anxious or crying during the procedure.[52] Deeper levels of sedation can also increase the opening pressure, possibly related to hypercapnia, and sedation should be avoided whenever possible in adults and older children.[51] A low-dose benzodiazepine or anxiolytic is preferred if sedation is needed. In children requiring sedation, performing the lumbar puncture immediately after a sedated MRI helps to reduce the number of times that sedatives are administered.[51] No studies support the concept that headache relief following CSF removal proves that intracranial hypertension is the etiology. Also, no evidence suggests that a "large volume" lumbar puncture is warranted, and it may instead cause a spinal headache. A reasonable strategy is to remove enough CSF to achieve a closing pressure in the middle of the normal range.

OTHER TESTS. An evaluation for sleep apnea is recommended in all patients with pseudotumor cerebri syndrome who are obese. As sleep apnea can also occur in individuals of a normal weight, inspection of the pharynx (Mallampati score) and employing a standardized questionnaire to assess sleep apnea risk are also recommended for patients who are not obese and in whom an underlying cause is not identified.

A thorough medical and medication history is needed that specifically inquires about weight gain; medications taken prior to symptom onset (eg, retinoids, tetracycline and related compounds, lithium, treatment for

KEY POINTS

- A comprehensive ophthalmic examination, including perimetry, is of prime importance for patients with suspected or confirmed pseudotumor cerebri syndrome. Confrontation visual field testing is inadequate to detect subtle defects, but the presence of a visual field abnormality on confrontation testing is highly concerning for significant visual loss.
- Body mass index has a negligible effect on lumbar puncture opening pressure.
- The position of the legs during a lumbar puncture has little impact (approximately 10 mm CSF) on the opening pressure, although the most accurate measurement is produced with the patient relaxed and legs extended.
- Sedation and Valsalva maneuvers can substantially increase the CSF opening pressure during a lumbar puncture.
- If the CSF pressure is elevated, remove enough CSF to achieve a closing pressure in the mid-normal range.
- Evaluate patients with pseudotumor cerebri syndrome for obstructive sleep apnea. This process may include screening questionnaires, asking the patient (and bed partner) about sleep apnea symptoms, assessing the Mallampati score, and polysomnography. Treatment of sleep apnea often helps lower the intracranial pressure.

malignancy); and a history of anemia, thyroid disease, or renal disease (TABLE 6-7). Women are evaluated for manifestations of polycystic ovary syndrome, which may warrant an endocrinology consultation. One series showed a high percentage of laboratory abnormalities in patients with IIH such as elevated C-reactive protein (51%), thrombophilia (31%), increased plasma cortisol levels (29%), and elevated lactate dehydrogenase (20%).[53]

Treatment

Patients with asymptomatic papilledema and normal visual function may be followed closely once the diagnosis is established. Causes of pseudopapilledema, such as tilted optic nerves and optic disc drusen, should be excluded. Weight loss is recommended for appropriate patients, and the papilledema usually resolves over time.

The IIHTT demonstrated that acetazolamide was superior to placebo in improving the visual field, papilledema grade, visual quality of life, and general quality of life in adults with IIH and mild visual field loss. The medical regimen was combined with a weight loss program with a goal of losing at least 6% of a patient's body weight.[54] Thus, acetazolamide initiated at 500 mg twice daily and gradually increasing the dosage to 2000 mg twice daily as needed/tolerated is recommended for treatment of such patients.

Other diuretics (not studied in the IIHTT) may be employed in patients who cannot tolerate acetazolamide, including methazolamide, furosemide, bumetanide, or thiazide diuretics. Spironolactone, ethacrynic acid, or triamterene may be used in patients who are allergic to carbonic anhydrase inhibitors, loop diuretics, and thiazide diuretics. Small case series support the use of IM octreotide to induce remission of IIH.[55] Although pregnant women were excluded from participation in the IIHTT, clinical experience supports the use of acetazolamide during pregnancy.[56]

Patients with more extensive visual field loss than was studied in the IIHTT may need additional treatments to reverse visual loss. Therapies may include optic nerve sheath fenestration, a temporary lumbar drain, shunting (ventriculoperitoneal shunting is preferred over lumboperitoneal shunting because of a lower rate of failure and complications), or venous sinus stenting.[57–59] Currently, no evidence-based guidelines recommend one treatment over another, although a randomized trial comparing optic nerve sheath fenestration, maximal medical management, and ventriculoperitoneal shunting is expected to commence in 2018 and is listed on *ClinicalTrials.gov*.[60,61] Other options for patients with sight-threatening disease include IV acetazolamide, IV furosemide, and corticosteroids as temporizing agents. More than one modality may be needed for patients with progressive visual loss or fulminant disease.[62] Weight loss, which may include bariatric surgery, is recommended for long-term management in patients who are obese.[63]

While headache disability improved overall in the IIHTT, no benefit of acetazolamide with regard to headache disability was found compared to placebo. Moreover, no correlation was found between the lumbar puncture opening pressure and headache disability.[38] Therefore, additional treatments may be needed for headache management. No evidence-based guidelines exist for headache treatment in pseudotumor cerebri syndrome, so strategies are similar to those used for primary headache disorders based on the headache phenotype.[64] Among preventive treatments, topiramate and zonisamide have the

potential benefit of facilitating weight loss and have mild carbonic anhydrase activity. Their concurrent use with acetazolamide is generally well tolerated, although symptomatic hypocarbia sometimes occurs. Some enrollees in the IIHTT were treated with a low dose of amitriptyline (up to 50 mg/d) for headache prevention, which did not impede their overall weight loss during the trial; the small number of participants precluded analysis of effectiveness.[38] Medications with weight gain or fluid retention as common side effects must be used with caution and close monitoring. OnabotulinumtoxinA treatment may be useful for patients with a chronic migraine phenotype. No role exists for long-term corticosteroid treatment as corticosteroids result in weight gain, may increase the risk of venous sinus thrombosis, and their discontinuation provokes rebound intracranial hypertension.[65] Most patients will also require acute headache treatments. Indomethacin has a modest CSF pressure–lowering effect but may have intolerable gastrointestinal side effects.[66] Among the nonsteroidal anti-inflammatory drugs, those with a longer duration of action may be less likely to cause medication overuse headache (eg, naproxen, diclofenac). Opioids are occasionally needed initially, but are best avoided in the long-term. Triptans may be used for migrainous headaches.

Medications associated with the development of pseudotumor cerebri syndrome should be discontinued. However, discontinuation alone may not be enough to reverse the process, and therapies to lower the CSF pressure are recommended.[67]

Follow-up and Prognosis

The clinical team caring for patients with pseudotumor cerebri syndrome includes, at a minimum, a neurologist and an ophthalmologist, or a neuro-ophthalmologist. Other disciplines may be involved, such as neurosurgeons, oculoplastic surgeons, neuroradiologists, neurointerventionalists, dietitians, endocrinologists, sleep medicine specialists, headache medicine specialists, and gynecologists. Ongoing communication between team members and the patient's primary care physician facilitates a unified treatment approach. After the initial diagnosis is made, patients need close visual monitoring to incorporate testing mentioned in the diagnosis section of this article. Office visits gradually become less frequent as the patient improves or stabilizes.

Most patients have a good visual outcome, but severe visual loss may occur in up to 10% of patients.[68] In the IIHTT, male sex, high-grade papilledema (often with optic disc hemorrhages), frequent transient obscurations of vision, decreased visual acuity at baseline, and treatment assignment to placebo were associated with a poor prognosis.[69–71] Other poor prognostic factors include profound anemia, renal failure, uncontrolled systemic hypertension, and elevated inflammatory markers. Optic neuropathy with or without coexisting outer retinal changes in the macula (chorioretinal folds, hyperopic shift, hemorrhages, macular edema, subretinal fluid, or neovascularization) as measured by optical coherence tomography correlated with a poor visual outcome in patients with baseline acuity of 20/25 or worse in one study.[71] Transverse sinus stenosis and other MRI changes have no predictive value.[72] Recurrence is possible and is associated with weight gain.[73,74]

Persistent headaches are a major source of morbidity and contribute greatly to decreased quality of life in patients with pseudotumor cerebri syndrome.[42] Both vision-specific and overall quality of life was impaired in

KEY POINTS

- A randomized treatment trial comparing maximal medical therapy with and without ventriculoperitoneal shunting or optic nerve sheath fenestration was funded by the National Eye Institute and is expected to begin enrollment in 2018.
- Although headache disability improved overall in the Idiopathic Intracranial Hypertension Treatment Trial, no benefit of acetazolamide treatment was shown compared to placebo in Headache Impact Test-6 scores. Lowering the CSF pressure does not always result in improvement in headaches; no correlation existed between Headache Impact Test-6 score and lumbar puncture opening pressure at baseline or at 6-month follow-up.
- Many patients with pseudotumor cerebri syndrome require headache treatment in addition to intracranial pressure–lowering therapies. Preventive therapies should be selected based on headache phenotype with attention to side effect profile.
- A team approach is needed for the management of patients with pseudotumor cerebri syndrome, with a neurologist (or neuro-ophthalmologist) directing the coordination of care.

KEY POINTS

- **The visual prognosis in patients with pseudotumor cerebri syndrome is generally good, but up to 10% of patients have permanent severe visual loss. Male sex, high-grade papilledema, profound anemia, renal failure, and uncontrolled systemic hypertension are risk factors associated with a poor visual outcome. Patients who present with loss of visual acuity require aggressive treatment.**

- **Headaches may persist after the CSF pressure is controlled and pseudotumor cerebri syndrome seems otherwise quiescent. This may be related to central sensitization occurring early in the course.**

patients in the IIHTT who had only mild visual impairment prior to the initiation of treatment. Blurred vision, diplopia, transient obscurations of vision, neck pain, a high risk of obstructive sleep apnea, and interference with driving all contributed to reduced visual quality of life in the study. Depression and anxiety are more common in patients with IIH than in age- and weight-matched controls, are frequent comorbid conditions with headache, and may need to be addressed.[75] Thus, a patient-centered, individualized, and multifaceted approach to management is needed.

CONCLUSION

Spontaneous intracranial hypotension is likely underdiagnosed in practice, particularly when the disorder is long-standing and the typical clinical and neuroimaging features recede; patients may have headaches for decades before the diagnosis is considered. Neurologists and headache specialists are more likely to encounter such patients in practice, as individuals with classic symptoms and abnormal imaging are frequently diagnosed and treated by other specialists (eg, neurosurgeons, neuroradiologists). Careful inquiry regarding the onset of symptoms for potential minor trauma, aspects of the headache and other associated symptoms vis-à-vis a postural or circadian component, worsening with Valsalva maneuvers, and assessment of joint hypermobility may be enlightening. In addition to those who have a classic clinical presentation, spontaneous intracranial hypotension should be suspected in patients with headaches that are daily from onset, refractory to "everything," and in those with chronic headaches that do not fit a particular phenotype. The management of patients with spontaneous intracranial hypotension requires collaboration with neuroradiologists and neurosurgeons with expertise in the disorder. Identification of the leak site is often elusive, and the treatment is challenging.

Pseudotumor cerebri syndrome remains a sight-threatening disorder that continues to be missed acutely because fundoscopy was not performed, emphasizing the need for ophthalmoscopic evaluation of all patients being evaluated for headache. A recent study from a large neuro-ophthalmology center indicated that misdiagnoses of IIH are common, largely related to misinterpretation of the fundus findings; as with spontaneous intracranial hypotension, patient care requires a team approach.[2]

The IIHTT provided evidence supporting the use of high-dose acetazolamide, up to 4 g/d, in patients with mild visual field loss. However, data from the IIHTT also indicate that controlling the intracranial pressure alone may not improve headache disability, so neurologists have an important role to play in the management of this symptom that so greatly impacts quality of life. The upcoming surgical trial for patients with moderate to severe visual loss from IIH will be a welcome addition to our evidence base for treatment.

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DISCLOSURE

Continued from page 1066

Dr Friedman has received personal compensation for serving on the board of directors of the American Headache Society, as a contributing author for *MedLink Neurology*, and on the editorial board of *Neurology Reviews*. Dr Friedman has received personal compensation as a consultant for Avanir Pharmaceuticals, Inc; Biohaven Pharmaceutical; ElectroCore, LLC; Eli Lilly and Company; Promius Pharma, LLC; and Teva Pharmaceutical Industries, Ltd and as a speaker for Allergan; Amgen Inc; Avanir Pharmaceuticals, Inc; ElectroCore, LLC; Supernus Pharmaceuticals, Inc; and Teva Pharmaceutical Industries, Ltd. Dr Friedman has received research/grant support from Autonomic Technologies, Inc; Axon Optics; Eli Lilly and Company; Merck & Co, Inc; and Zosano Pharma Corporation. Dr Friedman has served as an expert witness in legal cases involving idiopathic intracranial hypertension.

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Headache in Pregnancy

By Matthew S. Robbins, MD, FAAN, FAHS

ABSTRACT

PURPOSE OF REVIEW: **Headache disorders are extraordinarily common and disproportionately impact women of childbearing age. This article reviews the importance of proper diagnosis, natural history, and management of headache disorders in pregnant and postpartum women.**

RECENT FINDINGS: **Red flags for secondary headache specifically among pregnant women include elevated blood pressure and lack of a previous headache history, as well as a prolonged duration of the headache attack in those with a prior history of migraine. Migraine improvement is typical for most pregnant women, but the prognosis for women who have migraine with aura or chronic migraine is less predictable. Migraine is now an established risk factor for the development of preeclampsia. Recent data suggest hazards for compounds containing butalbital and possibly a better safety profile for triptans than previously believed during pregnancy. Peripheral nerve blocks and noninvasive neurostimulation devices are procedural and emerging therapies that have promising safety profiles for pregnant women with headache disorders.**

SUMMARY: **Acute headache occurring in pregnancy and the postpartum period is a red flag requiring diagnostic vigilance. Migraine frequency in women typically improves during pregnancy, although this trend is less certain when aura is present and after delivery. Acute and preventive treatment plans during pregnancy and lactation are plausible but may require shifts in therapeutic hierarchy. Relatively safe oral, parenteral, and procedural therapies are available for pregnant women. Noninvasive neuromodulation devices are already available and will likely play a greater role in the coming years. Migraine is associated with medical and obstetrical complications during pregnancy, and women with frequent migraine attacks may need to be considered high risk.**

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RELATIONSHIP DISCLOSURE:
Dr Robbins has received personal compensation for serving as a section editor for *Current Pain and Headache Reports* and serves (without compensation) on the board of directors and as a member-at-large of the American Headache Society and as associate editor of *Headache: The Journal of Head and Face Pain*. Dr Robbins has received book royalties from John Wiley & Sons.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Robbins discusses the unlabeled/investigational use of medications and devices for the treatment of headache disorders in pregnant and breast-feeding women, including all analgesics, neuromodulation devices, preventive therapies, and triptans.

INTRODUCTION

Primary headache disorders such as migraine are extraordinarily common in women of childbearing age. The importance of the diagnosis and management of headache in pregnant and postpartum women is underscored by the high rate of secondary headache disorders in this population based on hormonal, vascular, homeostatic, and procedural factors. In addition, treatment decisions must consider both maternal and fetal or newborn health. This article first approaches the diagnosis of headache in pregnancy and carefully distinguishes primary from secondary headache disorders that are state specific. The article then reviews

migraine, the most common headache disorder, and how it may be managed during pregnancy. The diagnosis and management of headache in the peripartum and postpartum state is then addressed, followed by a review of headache management during lactation. Finally, the impact of migraine on pregnancy itself is discussed, with a focus on adverse labor and delivery outcomes, including preeclampsia.

HEADACHE DIAGNOSIS IN PREGNANCY

Many traditional red flags in the diagnosis of headache that raise alarms for secondary causes have been well described.[1] These factors include systemic symptoms or signs, focal neurologic signs or symptoms including papilledema, an older age of onset, an abrupt onset of severe headache (thunderclap), a pattern change at variance with a preexisting headache disorder, precipitation by Valsalva maneuver or exertion, or a postural headache. However, recent evidence suggests that new headache in pregnancy and in the puerperium (within 6 weeks postpartum) is also a red flag for secondary headache.[2,3] Specific clinical clues heightening the suspicion for secondary headache disorders in pregnancy and the puerperium are listed in TABLE 7-1.

Secondary headache disorders that may have a predilection for occurrence during pregnancy and the puerperium fall under many different categories. Symptomatic headache attributed to cerebrovascular disorders may occur with an increased incidence in women during this time and include aneurysmal subarachnoid hemorrhage, acute ischemic or hemorrhagic stroke, cerebral venous thrombosis, cervical artery dissection, and reversible cerebral vasoconstriction syndrome (RCVS) (FIGURE 7-1). Congenital or space-occupying lesions such as a Chiari malformation, a third ventricle colloid cyst, or a neoplasm may present during labor when Valsalva maneuvers can provoke transient rises in intracranial pressure. CASE 7-1 illustrates a patient who developed headache attributed to pituitary disease, which may also manifest more commonly in pregnant women. Disorders of homeostasis can also feature headache during pregnancy or the postpartum state, including acute severe hypertension with or without preeclampsia, eclampsia, and posterior reversible encephalopathy syndrome (PRES) (FIGURE 7-3). Finally, derangements of intracranial pressure may also develop during this period, including idiopathic intracranial hypertension that may present or worsen in the setting of weight gain associated with pregnancy. Post–dural puncture headache after epidural or combined epidural and spinal anesthesia is a common cause for postpartum headache. Pneumocephalus may also occur with epidural or spinal anesthesia when air is introduced into the intrathecal space, migrates cranially, and leads to a sudden headache, typically with onset during or shortly after insertion of an epidural or spinal needle and catheter.

A 2015 study addressed acute headache diagnosis in pregnancy and included 140 women who presented to acute care with severe headache requiring inpatient neurologic consultation.[2] In this sample, primary headache was diagnosed in 65% of patients, and secondary headache was diagnosed in 35% of patients. The most common diagnosis overall was migraine at 59.3%, and the second most common disorder (and the most common in the secondary headache disorder category) was hypertensive disorders of pregnancy, which mostly featured preeclampsia but also included PRES, eclampsia, acute arterial hypertension, and RCVS. In this study, a number

KEY POINTS

- Recent evidence suggests that new headache in pregnancy and in the puerperium (within 6 weeks postpartum) is a red flag for secondary headache.
- Among women with a history of headache, a changed feature of a longer attack duration was associated with a secondary headache disorder diagnosis.
- A diagnostic strategy for acute headache in pregnant women should feature liberal use of noncontrast MRI and monitoring for preeclampsia, particularly in those with an elevated blood pressure and without a headache history.

TABLE 7-1 **Clinical Clues in the Diagnosis of Secondary Headache Disorders in Pregnant and Postpartum Women**[a]

Clinical Clue	Diagnosis	Timing
Orthostatic headache pattern	Post-dural puncture headache	Postepidural anesthesia (hours to days)
Relapsing thunderclap headaches	Reversible cerebral vasoconstriction syndrome (RCVS)	Postpartum more often than antepartum
Single thunderclap headache	Aneurysmal subarachnoid hemorrhage	Antepartum and postpartum
	RCVS	Postpartum more often than antepartum
	Cerebral venous thrombosis	Antepartum and postpartum
	Cervical artery dissection	Postpartum
	Pituitary apoplexy	Antepartum more often than postpartum
	Pneumocephalus	Postepidural anesthesia (immediate)
Hypertension	Preeclampsia/eclampsia	Antepartum more often than postpartum
	Posterior reversible encephalopathy syndrome (PRES)	Antepartum more often than postpartum
	RCVS	Postpartum more often than antepartum
Visual loss	Preeclampsia/eclampsia	Antepartum more often than postpartum
	PRES	Antepartum more often than postpartum
	Pituitary apoplexy	Antepartum more often than postpartum
	Idiopathic intracranial hypertension	Antepartum more often than postpartum
	Cerebral venous thrombosis	Antepartum and postpartum
Seizures	Eclampsia	Antepartum more often than postpartum
	Cerebral venous thrombosis	Antepartum and postpartum
	PRES	Antepartum more often than postpartum
	RCVS	Postpartum more often than antepartum
Horner syndrome	Cervical artery dissection	Postpartum
Papilledema	Cerebral venous thrombosis	Antepartum and postpartum
	Idiopathic intracranial hypertension	Antepartum more often than postpartum
	Space-occupying lesion (eg, neoplasm)	Antepartum and postpartum
Focal neurologic findings	Ischemic stroke	Antepartum and postpartum
	Intracranial hemorrhage	Antepartum and postpartum
	Cerebral venous thrombosis	Antepartum and postpartum
	PRES	Antepartum more often than postpartum
	RCVS	Postpartum more often than antepartum

[a] Modified with permission from Glover RL, Headache.[3] © American Headache Society.

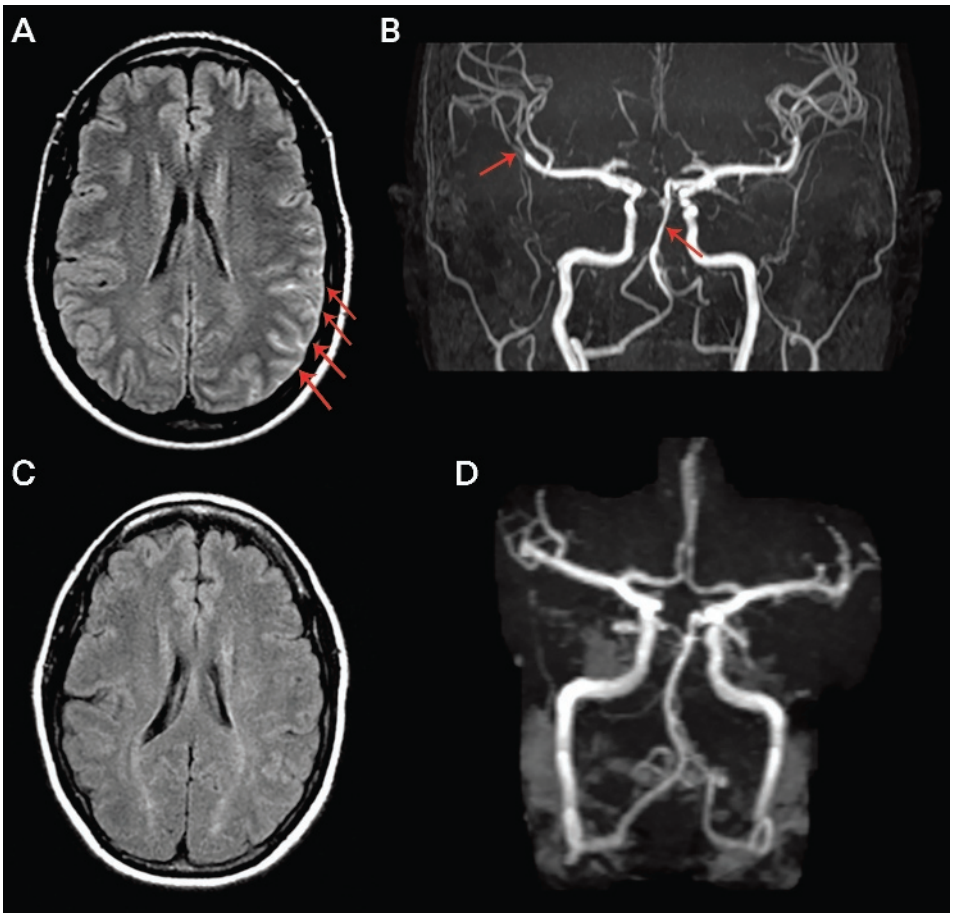

FIGURE 7-1
MRI and magnetic resonance angiogram (MRA) in a patient with acute postpartum headache. A 32-year-old woman at 3-weeks postpartum presented with relapsing thunderclap headaches followed by abulia that gradually resolved with nimodipine and IV magnesium. Initial brain MRI with fluid-attenuated inversion recovery (FLAIR) sequences (*A*) revealed left convexity subarachnoid hemorrhage (*arrows*). *B*, Initial brain MRA demonstrated multifocal areas of vasoconstriction including the middle cerebral artery branches and distal basilar artery (*arrows*) as well as attenuated flow in the anterior cerebral arteries. Repeat brain MRI (*C*) and MRA (*D*) demonstrated improvement of the convexity subarachnoid hemorrhage and resolution of the multifocal areas of vasoconstriction. Convexity subarachnoid hemorrhage can occur in association with reversible cerebral vasoconstriction syndrome.

of factors were associated with primary versus secondary headache, including asthma, hypertension, any past psychiatric diagnosis, and any past headache history.[2] Among women with a history of headache, a changed feature of a longer attack duration was associated with a secondary headache disorder diagnosis in this group. Acute attack features associated more with primary headache included phonophobia only. Attack features associated with secondary headache included the presence of seizures, elevated blood pressure, fever, and an abnormal neurologic examination. In multivariate analysis, a lack of headache history was associated with a nearly fivefold risk of secondary headache, and elevated blood pressure was associated with a 17-fold risk of secondary headache. The study suggested that a diagnostic strategy for acute headache in pregnant women should feature liberal use of noncontrast MRI and monitoring for

KEY POINTS

- Migraine without aura typically improves or remits altogether in most women when pregnant, with improvement or remission observed in nearly 47% of women during the first trimester, in 83% of women during the second trimester, and in 87% of women during the third trimester.
- Migraine with aura is less likely to improve during pregnancy than migraine without aura. New-onset migraine with aura and even aura without headache may occur in the later stages of pregnancy.
- Management of migraine during pregnancy always starts with preconception counseling whenever feasible.
- Nonpharmacologic therapies should always be emphasized as an important aspect of migraine management, especially during pregnancy.
- Migraine prophylactic medication may be unnecessary in pregnancy because of the generally good prognosis and should be avoided because of teratogenic concerns.
- Butalbital compounds that are used in combination with acetaminophen or aspirin and caffeine have recently been associated with congenital heart defects and are generally not recommended.

CASE 7-1

A 23-year-old woman in her first pregnancy presented with 3 days of a sudden-onset severe headache in a fixed bifrontal location. Her history included rare attacks of migraine without aura during her teenage years, but her current symptoms were atypical of her remote migraine attacks. She described a perturbation in her binocular peripheral vision that was not demonstrable on neurologic examination, and fundoscopy, visual field testing, and pupillary reflexes were all normal.

MRI revealed an expanded sella with a fluid level and optic chiasm compression suggestive of pituitary apoplexy (FIGURE 7-2[4]). Automated perimetry revealed a bitemporal hemianopsia, and her serum prolactin level was 395 ng/mL (with the laboratory's normal range for pregnant women being 10 ng/mL to 209 ng/mL).

Because of visual loss, she required transphenoidal resection, which was uncomplicated. She was prescribed levothyroxine thereafter and peripartum hydrocortisone around the time of her otherwise uncomplicated cesarean delivery.

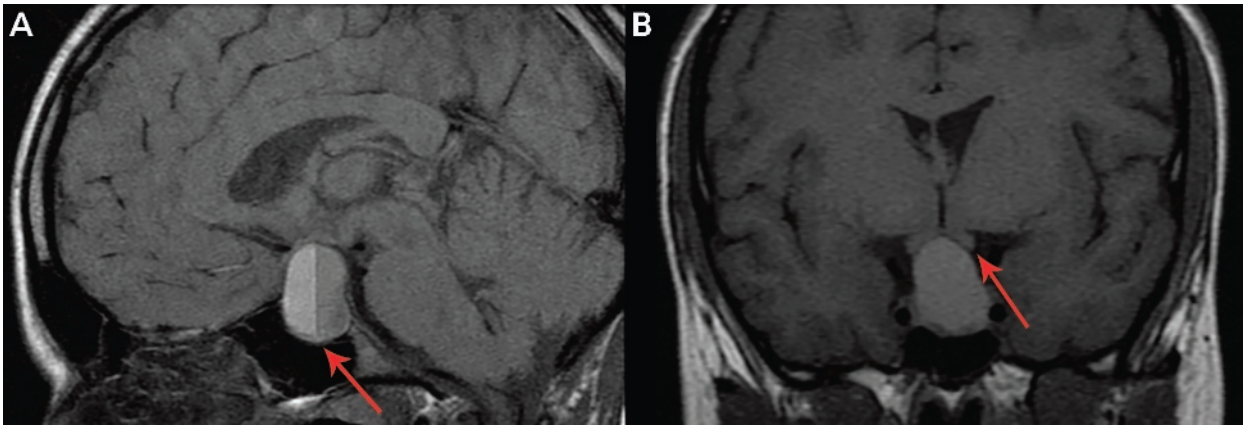

FIGURE 7-2

MRI of the patient in CASE 7-1. Sagittal (*A*) and coronal (*B*) noncontrast T1-weighted brain MRI showing a 1.7 cm by 1.8 cm by 2.5 cm suprasellar mass containing a fluid level (*A, arrow*) with upward compression of the optic chiasm (*B, arrow*). The findings were consistent with pituitary apoplexy, and the pathology revealed a lactotroph-secreting adenoma with hemorrhage.

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COMMENT

Pituitary apoplexy can present with acute headache that can be of gradual onset or thunderclap and can occur with increased frequency in pregnant women because of physiologic expansion of the gland during the antepartum period, which is attributed to lactotroph cellular activity and hyperemia.

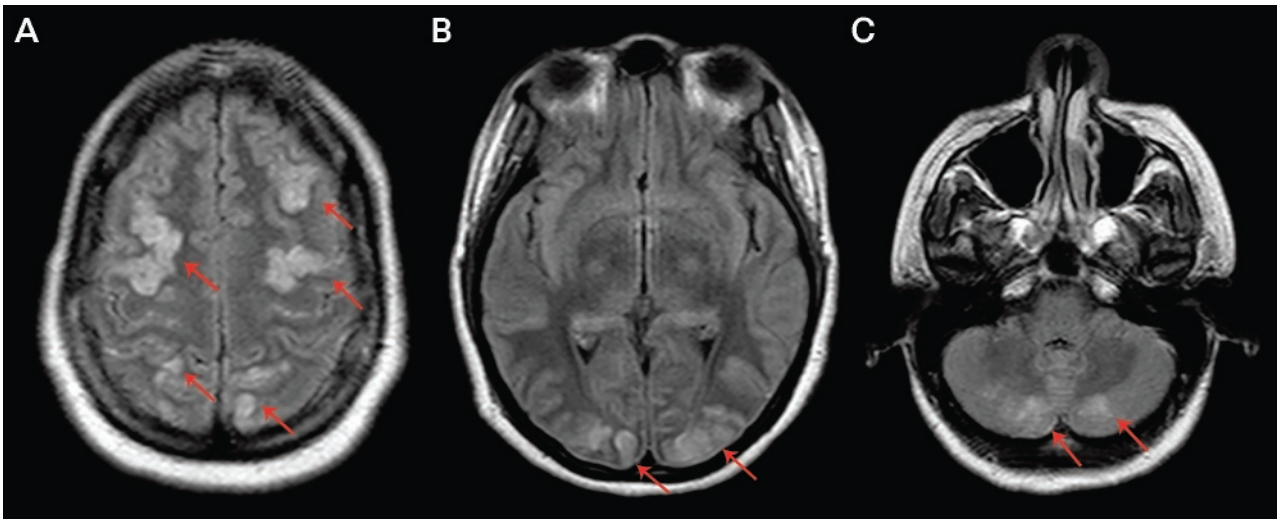

FIGURE 7-3

MRI in acute postpartum headache. A 23-year-old woman 4 days postpartum presented with progressive severe headache and generalized seizures. Axial fluid-attenuated inversion recovery (FLAIR) MRI revealed hyperintensities (*arrows*) throughout the bilateral cerebral (*A*, *B*) and cerebellar (*C*) hemispheres that resolved on follow-up imaging, consistent with posterior reversible encephalopathy syndrome.

preeclampsia, particularly in those with an elevated blood pressure and without a headache history.[2]

PROGNOSIS OF MIGRAINE IN PREGNANCY

Although migraine often improves during pregnancy, the epidemiology of migraine suggests that its enormous prevalence and incidence in women during their childbearing years renders it a frequent clinical problem during pregnancy. During childbearing years, migraine prevalence peaks to nearly 25%, and migraine incidence peaks at nearly 20 per 1000 person-years according to data from the American Migraine Prevalence and Prevention Study.[5,6] Migraine without aura typically improves or remits altogether in most women when pregnant, with improvement or remission observed in nearly 47% of women during the first trimester, in 83% of women during the second trimester, and in 87% of women during the third trimester.[7] Migraine improvement during pregnancy is related to increasing levels of estradiol during the gestational period, as well as the lack of cycling related to the menstrual cycle where estrogen withdrawal can serve as a major migraine trigger. However, more than 26% of pregnant women with migraine do report some degree of moderate or severe headache-related disability during their early pregnancy.[8]

Migraine with aura is less likely to improve during pregnancy than migraine without aura. New-onset migraine with aura and even aura without headache may occur in the later stages of pregnancy. In one study, among 91 women who had any primary headache disorder, 39.6% presented with aura while pregnant, and 69.4% of these women had no previous aura attacks.[2] Potential mechanisms driving the different prognosis of migraine with aura relative to migraine without aura include increased endothelial reactivity during pregnancy, as well

as a high estrogen to progesterone ratio, which may actually lower the threshold for cortical spreading depression.[9–11]

MANAGEMENT OF MIGRAINE IN PREGNANCY

Migraine treatment in pregnancy can be challenging because of concerns for both maternal and fetal well-being. Management of migraine during pregnancy always starts with preconception counseling whenever feasible. All women of childbearing age who are prescribed any therapy for migraine should know what the risks are if they are planning to become pregnant and should contact their physician immediately if an unexpected pregnancy occurs.

Nonpharmacologic therapies should always be emphasized as an important aspect of migraine management, especially during pregnancy. Recognizing and avoiding commonly reported migraine attack triggers such as diet and especially sleep disturbance may be particularly important during pregnancy, when previously stable routines may be disrupted.[12,13] Proactively addressing risk factors for migraine progression and comorbidities is also crucial since many of these factors are modifiable.[14] Medication overuse, excessive caffeine intake, psychiatric and pain comorbidities, obesity, sleep disturbance, and persistent frequent nausea may all be treatable risk factors for migraine progression or worsening. Nonpharmacologic treatments, many of which are evidence-based and safe during pregnancy, are highly recommended and include relaxation strategies, biofeedback, and cognitive-behavioral therapy.[15] Emphasizing the good prognosis for migraine in pregnancy is also helpful to relieve some of the anxiety for women planning to conceive, particularly for those who have episodic migraine without aura. Direct communication with the obstetrician is also helpful in the coordination of care for pregnant women with migraine.

For migraine management with medications, therapies can be divided into acute and prophylactic strategies. Acute treatments may need to be stepwise or stratified, and this plan should be discussed with the patient in advance of conception. Migraine prophylactic medication may be unnecessary in pregnancy because of the generally good prognosis and should be avoided because of teratogenic concerns. Finally, a pregnant woman who has an intractable migraine attack or status migrainosus should know what a backup plan might be during pregnancy to minimize worry and to have a safe and effective treatment strategy in place.

Treating migraine in pregnancy with medication is challenging as no single medication is entirely free of any potential teratogenic effects. The US Food and Drug Administration (FDA) has recently phased out the pregnancy risk letter category system for medications and has replaced it with the new pregnancy and lactation labeling rule, which provides more qualitative description of the risks during pregnancy and lactation.[16] The FDA letter category system was useful as a hierarchical system, but these ratings will soon become outdated.

TABLE 7-2 reviews acute treatments and their safety concerns in pregnant women. The safest acute treatments may include acetaminophen and metoclopramide, which may be given both enterally or parenterally. However, even these agents carry potential risks including the later development of attention deficit hyperactivity disorder in children with antepartum acetaminophen exposure, and maternal cardiac conduction changes and extrapyramidal symptoms with metoclopramide exposure. Opiates are typically not indicated to treat migraine, but if necessary as a rescue therapy, oxycodone may be the safest specific drug within this class to use. However, major safety concerns for opioids

include neonatal respiratory suppression as well as maternal and fetal dependence. Butalbital compounds that are used in combination with acetaminophen or aspirin and caffeine have recently been associated with congenital heart defects and are generally not recommended.[17] Nonsteroidal anti-inflammatory drugs may have a niche in the second trimester, but this must always be prescribed in concert with the patient's obstetrician, as they have trimester-specific teratogenic profiles that generally prohibit their use in the first and third trimesters.

Triptans had all been rated FDA category C. The postmarketing registry maintained for sumatriptan demonstrated a birth defect rate of 4.2% (95%

Acute Headache Therapies and Their Potential Safety Concerns in Pregnant Women TABLE 7-2

Agent or Class	US Food and Drug Administration (FDA) Class[a]	Some Potential Risks and Comments
Acetaminophen	B	Attention deficit hyperactivity disorder
Lidocaine	B	Safety data largely from peripheral injection and not IV use, central nervous system depression
Ondansetron	B	Cleft palate
Dopamine antagonists (metoclopramide)	C (B)[b]	Prolonged QTc interval on ECG, extrapyramidal symptoms
Opiates (oxycodone)	C (B)[c]	All cross placenta, neonatal respiratory suppression (dependence [maternal and fetal])
Butalbital compounds	C	Congenital heart defects
Triptans	C	Preterm labor, uterine atony, postpartum hemorrhage
Bupivacaine	C	Maternal cardiac conduction abnormalities
Prednisone, methylprednisolone (dexamethasone)	C (D)[d]	Orofacial clefts, intrauterine growth restriction, some cross placenta
Nonsteroidal anti-inflammatory drugs	C (first trimester/second trimester)	First trimester: inhibit implantation, cardiac abnormalities, gastroschisis
	D (third trimester)	Third trimester: premature ductus arteriosus closure, oligohydramnios, periventricular hemorrhage
Magnesium sulfate	D	Bone loss[a]
Valproate	X	Neural tube defects, clefts, lower IQ and developmental delay, autism, cardiovascular and genitourinary abnormalities
Dihydroergotamine	X	Uterine ischemia, increased uterine contractility, prematurity

ECG = electrocardiogram; IQ = intelligence quotient; IV = intravenous; QTc = corrected QT interval.
[a] Although the FDA ratings have not been continued past 2015, for now they remain a useful hierarchical scheme in the organization of drug safety in pregnant women.
[b] Class B refers only to metoclopramide.
[c] Class B refers only to oxycodone.
[d] Class D refers only to dexamethasone.

confidence interval, 2.6% to 6.5%), which is in line with the general population.[18] A recent meta-analysis that analyzed prenatal triptan use included one case-control study and five cohort studies that totaled 4208 triptan exposures.[19] When comparing women with migraine exposed to triptans versus women with migraine not exposed to triptans, no significant increases were found in malformation rates (odds ratio of 0.84 [0.61 to 1.16]), prematurity (odds ratio of 0.90 [0.35 to 2.30]), or spontaneous abortions (odds ratio of 1.27 [0.58 to 2.79]). Compared to healthy nonmigraine controls, women exposed to triptans had a higher risk of spontaneous abortions (odds ratio of 3.54 [2.24 to 5.59]). Women with migraine not exposed to triptans compared to healthy controls had a higher rate of malformations (odds ratio of 1.41 [1.11 to 1.80]). A more recent prospective observational study of 432 pregnant women exposed to triptans demonstrated no increase of major birth defects, spontaneous abortions, preterm delivery, and preeclampsia in comparison to a nonmigraine cohort.[20] It may be that women with more severe migraine in pregnancy who have been studied take triptans, and the majority of evidence suggests triptans intrinsically may not adversely impact labor and delivery outcomes, but more studies among pregnant women stratified by migraine severity may provide further clarity.

Prophylactic medications for migraine during pregnancy also have variable safety profiles (TABLE 7-3). Medications that may be safe based on limited human and animal studies include pindolol, memantine, and cyproheptadine but have not been investigated extensively in rigorous clinical trials. Magnesium supplementation is often used as a preventive treatment in nonpregnant women and may be safe during pregnancy. However, the association of prolonged maternal IV magnesium sulfate exposure with fetal bone demineralization has raised concerns about the safety of magnesium oxide used daily in pregnant women, and further investigations are certainly indicated. Beta-blockers are generally thought to be safe and are commonly used for the treatment of hypertension in pregnancy but may be associated with intrauterine growth restriction. Antiepileptic drugs such as topiramate and valproic acid are avoided during pregnancy because of their more significant teratogenicity.

Interventional therapies and noninvasive neurostimulation devices have become prominent in recent years in the treatment of headache disorders, particularly migraine.[21] Such treatments include injectable therapies such as botulinum toxin, peripheral nerve blocks, trigger point injections, and sphenopalatine ganglion blocks. Three neuromodulation devices have been approved by the FDA for the treatment of migraine: a transcutaneous supraorbital nerve stimulator that is approved as a prophylactic and for acute treatment, a single-pulse transcranial magnetic stimulation device that is approved for both the acute treatment of migraine with aura attacks and as a preventive therapy, and noninvasive vagus nerve stimulation that has been approved for the acute treatment of episodic cluster headache attacks as well as for the acute treatment of migraine. These therapies have excellent safety profiles[22–24] and should be appropriate for pregnant women to use, although, of these devices, only limited investigations have been reported in pregnant women with single-pulse transcranial magnetic stimulation. A postmarketing study in Europe for both acute and prophylactic treatment with single-pulse transcranial magnetic stimulation included three patients who used the device while pregnant. All three patients used the device with good success as an acute treatment while pregnant and did not develop any known adverse delivery outcomes.[23]

Botulinum toxin had been previously rated by the FDA as a category C drug. It has a high molecular weight and theoretically should not cross the placenta, and reported cases of botulism have not been associated with adverse fetal outcomes. The pharmaceutical database, including patients in clinical trials and postmarketing studies, has reported 232 pregnancies, of which migraine was a clinical treatment diagnosis in 22 women. The majority of these botulinum toxin exposures were from 3 months preconception through the first trimester. The rate of fetal loss was 20.9% in comparison to 35.4% in the US population. The rate of major birth defects was 2.7% compared to the 3% US population birth defect rate.[25] However, most physicians still avoid using botulinum toxin during pregnancy because of safety concerns.[26]

Preventive Headache Therapies and Their Potential Safety Concerns in Pregnant Women TABLE 7-3

Agent	Class	US Food and Drug Administration (FDA) Class[a]	Potential Risks and Comments
Magnesium oxide	Nutraceutical	Not ranked	Neonatal hypotonia, bone demineralization associated with IV use
Riboflavin	Nutraceutical	Not ranked	Largely unknown in typical migraine doses of 400 mg/d
Memantine	*N*-methyl-D-aspartate (NMDA) receptor antagonist	B	Unknown
Cyproheptadine	Antihistamine/serotonergic	B	Unknown
Propranolol (pindolol)	Beta-blocker	C (B)[b]	Intrauterine growth restriction
Amitriptyline	Tricyclic antidepressant	C	Limb reduction, cardiac defects, neonatal withdrawal
Verapamil	Calcium channel blocker	C	Intrauterine growth restriction, fetal bradycardia, tocolysis
Gabapentin	Antiepileptic	C	Unknown, but crosses placenta
OnabotulinumtoxinA	Neurotoxin	C	Largely unknown
Aspirin	Cyclooxygenase inhibitor	C/D	Safe <150 mg/d
Candesartan	Angiotensin receptor blocker	D	Renal agenesis, oligohydramnios, craniofacial and limb deformities
Topiramate	Antiepileptic	D	Oral cleft, hypospadias, low birth weight
Valproic acid	Antiepileptic	X	Neural tube defects, clefts, lower IQ and developmental delay, autism, cardiovascular and genitourinary abnormalities

IQ = intelligence quotient; IV = intravenous.

[a] Although the FDA ratings have not been continued past 2015, for now they remain a useful hierarchical scheme in the organization of drug safety in pregnant women.

[b] Class B refers only to pindolol.

Occipital and trigeminal pericranial nerve blocks are a treatment used for migraine, cluster headache, and other headache disorders as an acute therapy as well as for short-term prevention and are appealing to use in pregnancy because of their peripheral administration and presumed safety. Most headache specialists are comfortable using peripheral nerve blocks during pregnancy.[27] It seems prudent to use lidocaine instead of bupivacaine because of its more favorable teratogenicity profile. One case series that examined 13 pregnant women who received a total of 27 peripheral nerve blocks for migraine or chronic migraine showed efficacy for both status migrainosus and short-term prophylaxis. The treatment seemed to be safe, although one patient developed a brief vasovagal attack, and two patients with no acute pain reduction ultimately developed preeclampsia and had postpartum resolution of their headache.[28] CASE 7-2 illustrates a patient in whom peripheral nerve blocks were utilized for status migrainosus in the second trimester.

CASE 7-2

A 33-year-old woman presented for preconception migraine management. She had a history of episodic migraine without aura that had been treated effectively with rizatriptan and naproxen. Preconception counseling included the natural history of migraine in pregnancy and the risks, benefits, and alternatives of antimigraine therapies in pregnancy.

She intentionally became pregnant for the first time, and once pregnant, acetaminophen and metoclopramide were prescribed for acute attack therapy. In the first trimester, her headache frequency was 1 to 2 days per week, but at 24 weeks gestational age she developed status migrainosus for 5 consecutive days and presented in follow-up.

Neurologic examination was normal, but because she had never experienced such a prolonged attack previously, a noncontrast brain MRI and magnetic resonance venogram (MRV) were performed and were normal. A 3-day course of prednisone helped only temporarily and her symptoms returned. Bilateral greater occipital, auriculotemporal, supraorbital, and supratrochlear nerve blocks with lidocaine were performed with definitive relief after 1 day. Migraine attacks diminished in frequency thereafter, and she had an uncomplicated spontaneous vaginal delivery at term.

COMMENT

This patient underwent preconception counseling, which is the most ideal way to frame risks and benefits and implement treatment plans including rescue therapies. As a prolonged attack duration is a specific red flag for pregnant women with a history of migraine, neuroimaging was obtained and fortunately was normal. Nerve blocks are an appealing therapy for status migrainosus or short-term migraine prevention in pregnancy because of their peripheral administration and favorable safety profile. The remainder of her migraine course in pregnancy with amelioration in the third trimester was typical of women who have migraine without aura.

PERIPARTUM AND POSTPARTUM HEADACHE

Women presenting with acute headache in the peripartum and postpartum period also require high diagnostic vigilance for secondary headache causes. Different clinical clues may also be associated with more specific secondary headache diagnoses during this period (TABLE 7-1). One large study of postpartum headache evaluated 985 women prospectively and documented a rate of headache at 39% including incapacitating headache at 4%.[29] Median onset was 2 days postpartum, with primary headache diagnosed in more than 75% of women. Post–dural puncture headache occurred in about 5% of women. Risk factors for postpartum headache included known dural puncture, previous headache history, multiparity, and increasing age. Another study retrospectively examined 95 women with more acute postpartum headache and revealed a mean onset of 3.4 days postpartum. The rate of secondary headache was 53%, most commonly featuring preeclampsia/eclampsia (24%) and post–dural puncture headache (16%), and potentially life-threatening causes of cerebrovascular etiology were also encountered.[30]

A recent study of 63 consecutive neurologic consultations for acute postpartum headache revealed an even higher rate of secondary headache (73.0%), of which post–dural puncture headache (45.7%), postpartum preeclampsia (26.1%), and cerebrovascular headache disorders (21.7%) were the most common diagnoses.[31]

However, headaches associated with spinal or epidural anesthesia could also be attributed to pneumocephalus as well as post–dural puncture headache. Post–dural puncture headache is more common and results from leakage of CSF, typically featuring an orthostatic headache pattern that, in comparison with a postpartum migraine attack, typically emerges within 24 hours of delivery and features a lack of side predominance of the head pain.[31] If performed, neuroimaging may reveal brain sag, pachymeningeal enhancement, subdural fluid collections, pituitary hyperemia, and dilation of venous sinuses. Treatment typically includes conservative measures such as IV fluids and nonspecific analgesics. IV caffeine sodium benzoate may also be used. If initial conservative therapies fail, a lumbar epidural autologous blood patch is typically effective.

Post–dural puncture headache is distinguished from pneumocephalus, which may also develop when the loss of resistance to air technique is used by anesthesiologists. This secondary headache results when air is introduced intrathecally and migrates cranially, leading to obstruction or compression of pain-sensitive intracranial structures, and may feature a thunderclap headache within seconds or minutes of the anesthetic procedure. Treatment also may be conservative but can require use of 100% oxygen inhalation to improve the rate of reabsorption of intrathecal air. CT reveals hypodensities in the ventricles, cisterns, and subarachnoid space (FIGURE 7-4). MRI may reveal hypointensities in the same regions on gradient echo sequences.[32]

HEADACHE AND LACTATION

Over half of all women who have migraine will have an attack postpartum, so the management of postpartum headache, particularly in breast-feeding women, is an important clinical problem. Treatment of headache during lactation requires special consideration of the effects of the medication on the patient and the effects the treatment may have on the breast-fed baby. Lactation may be protective by inducing amenorrhea and reducing the cycling estradiol levels that may trigger migraine attacks in susceptible women, but this is not universal. All

KEY POINTS

- The majority of evidence suggests triptans intrinsically may not adversely impact labor and delivery outcomes, but more studies among pregnant women stratified by migraine severity may provide further clarity.
- Occipital and trigeminal pericranial nerve blocks are a treatment used for migraine, cluster headache, and other headache disorders as an acute therapy as well as for short-term prevention and are appealing to use in pregnancy because of their peripheral administration and presumed safety.
- Headaches associated with spinal or epidural anesthesia could take two forms: post–dural puncture headache and pneumocephalus.
- Over half of all women who have migraine will have an attack postpartum, so the management of postpartum headache, particularly in breast-feeding women, is an important clinical problem.
- Of the triptans, eletriptan is likely the most compatible medication with breast-feeding based on its low milk to plasma ratio.
- The evaluation of a pregnant or postpartum woman with suspected preeclampsia is also confounded by migraine serving as a preeclampsia risk factor. The distinction is crucial as migraine and preeclampsia are managed differently, with antepartum severe preeclampsia managed by expedited delivery.

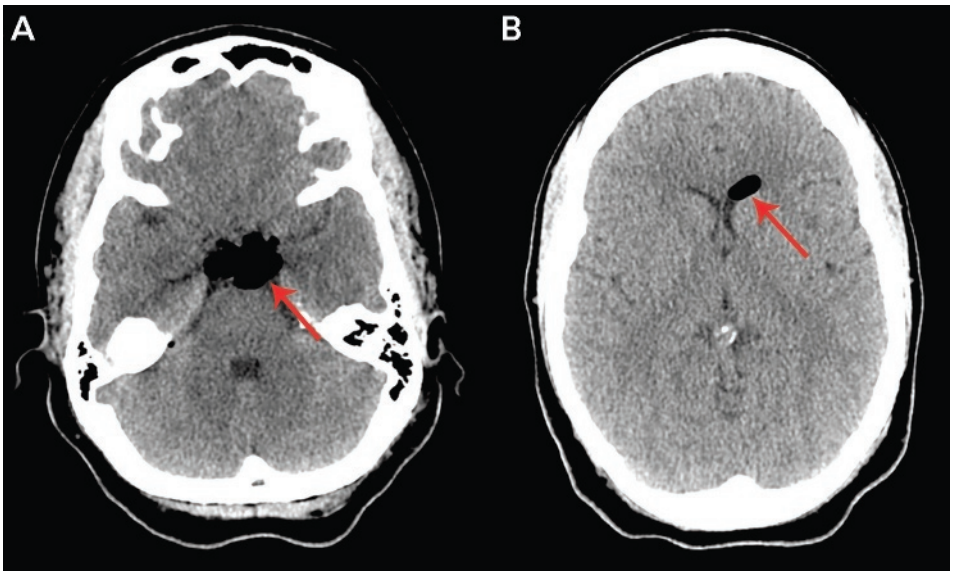

FIGURE 7-4
Head CT performed in a patient with thunderclap headache during anesthesia for labor. A 30-year-old woman who was in labor at term and otherwise healthy experienced a thunderclap headache coinciding with the lack of resistance to air during needle insertion in combined lumbar spinal-epidural anesthesia. Axial head CT revealed hypodensities (*arrows*) in the prepontine cistern (*A*) and left lateral ventricle (*B*) consistent with pneumocephalus.

medications can be graded by a milk to plasma ratio and, generally, a less than 10% value is a safe threshold for drugs that do not concentrate in breast milk. However, other factors include the lipophilicity, small size, low protein binding, and oral administration of drugs. Other issues related to lactation include the prematurity of a baby where a brain of a newborn may be more susceptible to any central nervous system–sedating properties of drugs used. In addition, the timing of medication may also be important, and patients can be advised to discard pumped milk after taking any medication that may have side effects to the breast-fed baby.[33]

TABLE 7-4 illustrates medications that have favorable safety profiles in breast-feeding women. For acute treatments, acetaminophen and ibuprofen generally are the safest nonspecific medications in lactation. Of the triptans, eletriptan is likely the most compatible medication with breast-feeding based on its low milk to plasma ratio. Antiemetics also are generally safe, particularly ondansetron and promethazine. If a patient requires a corticosteroid, prednisone may be the most compatible in comparison to other drugs of its class. No prophylactic therapy is perfectly safe for lactation, but many have more favorable lactation profiles, including the tricyclic antidepressants amitriptyline and nortriptyline; gabapentin; beta-blockers including propranolol and timolol; riboflavin; and magnesium. OnabotulinumtoxinA is probably compatible with breast-feeding given its peripheral administration and large molecular size.

IMPACT OF MIGRAINE ON PREGNANCY

The impact of migraine on pregnancy itself is another important consideration in women. A systematic review has revealed that many cardiovascular or cerebrovascular complications of pregnancy in women with migraine are apparent, including gestational hypertension, preeclampsia, ischemic stroke,

heart disease, and venous thromboembolism.[34] More specific labor and delivery complications have been examined in two population studies in Taiwan[35] and Hungary,[36] and both studies consistently showed an elevated risk of preeclampsia in pregnant women with migraine. It is not clear if pregnant women who have "active migraine" during pregnancy are at a particularly higher risk of adverse delivery outcomes. One single-center retrospective study in a sample enriched with pregnant women with chronic migraine and status migrainosus presentations during pregnancy found that rates of preeclampsia, preterm delivery, and low birth weight were markedly elevated compared to historical controls from the same population.[37]

Preeclampsia and migraine are interrelated clinical problems in pregnant women. Phenotypic overlap occurs in the symptomatology as both disorders may feature severe headache that can be throbbing, have otherwise typical migraine-associated features, and also feature varied visual phenomenology that can be specific to preeclampsia or migraine aura.[2] The evaluation of a pregnant or postpartum woman with suspected preeclampsia is also confounded by migraine serving as a preeclampsia risk factor. The distinction is crucial as migraine and preeclampsia are managed differently, with antepartum severe preeclampsia managed by expedited delivery. It is not known whether migraine influences how preeclampsia is clinically expressed or if its prognosis is different in those with migraine. In addition, little is known about postpartum preeclampsia and its relationship with migraine. Recent evidence from a multicenter randomized placebo-controlled trial suggests that the use of low-dose aspirin as a preventive therapy against preterm preeclampsia in pregnant women at higher risk is safe and effective, and it may also be effective as a migraine preventive agent, particularly in women who have migraine with aura.[38]

CONCLUSION

The occurrence of headache in pregnant and postpartum women is a frequent clinical consideration. Acute headache that occurs in pregnancy and the

Medications Used to Treat Headache and Their Relative Safety in Breast-feeding Women[a] TABLE 7-4

Therapy Category	Considered Safe	Use With Caution	Contraindicated
Acute	Acetaminophen, ibuprofen, caffeine, aspirin (≤162 mg/d), eletriptan, sumatriptan, ondansetron, prednisone, lidocaine, bupivacaine	Naproxen, indomethacin, ketorolac, other triptans, codeine and opioids, metoclopramide, prochlorperazine, butalbital, dexamethasone	Dihydroergotamine, aspirin (higher doses)
Preventive	Propranolol, timolol, amitriptyline, nortriptyline, verapamil, onabotulinumtoxinA, magnesium, riboflavin	Topiramate, valproic acid, metoprolol, candesartan	Atenolol, nadolol

[a] Lactation safety concerns also include timing of administration as well as neurologic health of the baby, including prematurity.

postpartum period is a red flag that requires high diagnostic vigilance. Although migraine prognosis is largely favorable in pregnancy, the prognosis of migraine with aura is not certain, and postpartum migraine attacks are common even in the presence of lactation. Acute and preventive treatment plans during pregnancy and lactation are plausible but often require shifts in therapeutic hierarchy. Many relatively safe rescue therapies exist for pregnant women with migraine including oral or IV corticosteroids, antiemetics, and peripheral nerve blocks. Noninvasive neuromodulation devices are already available and likely will play a greater role in migraine treatment in pregnant women in the coming years, assuming no unexpected safety data emerge. Migraine is associated with medical and obstetrical complications during pregnancy, particularly preeclampsia. Close coordination and communication between neurologists and obstetricians is crucial in the diagnosis and management of primary and secondary headache disorders in pregnant and postpartum women.

USEFUL WEBSITE

DRUGS AND LACTATION DATABASE (LACTMED)
The LactMed database from the National Institutes of Health US National Library of Medicine provides information related to medication effects on breast-feeding.
toxnet.nlm.nih.gov/newtoxnet/lactmed.htm

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REVIEW ARTICLE

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Dr Gelfand has received personal compensation for serving on the medical advisory board of eNeura Inc; as associate editor for *JAMA Neurology;* and as a consultant for Biohaven Pharmaceutical, Eli Lilly and Company, and Zosano Pharma Corporation.
Continued on page 1136

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Gelfand discusses the unlabeled/investigational use of all listed medications for the treatment of headache in children and adolescents, with the exceptions of almotriptan oral tablets, sumatriptan/naproxen combination tablets, and zolmitriptan nasal spray for adolescents 12 to 17 years of age for the treatment of acute migraine as well as topiramate in adolescents 12 to 17 years of age for migraine prevention. Rizatriptan is labeled for acute migraine treatment in children age 6 and older.

Pediatric and Adolescent Headache

By Amy A. Gelfand, MD

ABSTRACT

PURPOSE OF REVIEW: This article provides the practicing neurologist with a comprehensive, evidence-based approach to the diagnosis and management of headache in children and adolescents, with a focus on migraine.

RECENT FINDINGS: Four triptans are now labeled by the US Food and Drug Administration (FDA) for acute migraine treatment in adolescents, and rizatriptan is labeled for use in children age 6 and older. For preventive migraine treatment, the Childhood and Adolescent Migraine Prevention trial demonstrated that approximately 60% of children and adolescents with migraine will improve with a three-pronged treatment approach that includes: (1) lifestyle management counseling (on sleep, exercise, hydration, caffeine, and avoidance of meal skipping); (2) optimally dosed acute therapy, specifically nonsteroidal anti-inflammatory drugs and triptans; and (3) a preventive treatment that has some evidence for efficacy. For the remaining 40% of children and adolescents, and for those who would not have qualified for the Childhood and Adolescent Migraine Prevention trial because of having continuous headache or medication-overuse headache, the clinician's judgment remains the best guide to preventive therapy selection.

SUMMARY: Randomized placebo-controlled trials have been conducted to guide first-line acute and preventive migraine treatments in children and adolescents. Future research is needed to guide treatment for those with more refractory migraine, as well as for children and adolescents who have other primary headache disorders.

INTRODUCTION

Headache is one of the most common neurologic symptoms that brings a child or adolescent to the neurologist's office. The clinician's first task is to separate those few children who have a dangerous underlying secondary cause of headache from the majority who have a primary headache disorder such as migraine. A thorough history and neurologic examination are usually the only tests needed to make this distinction, although in some instances neuroimaging, CSF examination, EEG, or other tests may be needed. This article aims to help practicing neurologists develop an approach to pediatric

headache history taking, identify red flags for secondary headaches in children, recognize diagnostic features of primary headache disorders in this age group, and recommend evidence-based treatment strategies.

APPROACH TO PEDIATRIC HEADACHE HISTORY TAKING

Children are remarkably good headache historians. Having a planned, systematic approach to pediatric headache history taking is essential. One advantage in pediatric headache history taking is that a parent/guardian will almost always be in the room. The parent/guardian can provide detailed information about the child's birth and development, the presence or absence of early episodic syndromes that may be associated with migraine,[1] and any family history of migraine (which is helpful as migraine often occurs in those with a family history). There may also be an opportunity to take a direct headache history from a first-degree relative when the parent/guardian is biologically related to the child. Parents may not recognize that their "normal headaches" are, in fact, migraine. For example, a woman who develops pounding headaches each month before her menses and must lie down in a dark room may only learn that she has migraine when she attends her child's neurology visit. Only 48% of adults with migraine in the United States have ever received a migraine diagnosis by a physician,[2] so it would not be surprising to uncover a parent with undiagnosed migraine.

Having a parent/guardian in the room during history taking can also be a challenge. In his or her desire to help the child, the parent/guardian may be inclined to try to provide the child's headache history themselves. Below are suggested strategies for facilitating pediatric headache history taking (in neurodevelopmentally typical children).

Step 1: Assign Seats

Have the child or adolescent sit closest to the clinician. The parent/guardian can sit to the side of his or her child. This seating arrangement sends the message that the patient is the focus of the visit. The parent/guardian is there to help and support, not to take over.

Step 2: Set Expectations at the Outset

Introducing the headache history taking process at the outset of the visit can help to set everyone's expectations. While making eye contact with the child or adolescent, the clinician can say something to the effect of, "I am going to ask you a number of questions about your headaches. I tend to ask my questions to you, because it's your head, and you know best. However, if there's anything you're not sure about, feel free to ask your [parent/guardian(s)] for help. I'm sure they'd be happy to help you out. At the end, if there's anything I missed that you think is important, I'll give you an opportunity to add it in, and your [parent/guardian(s)] will have an opportunity as well."

This brief speech sets up the expectation that the history taking is going to predominantly be a conversation between the clinician and the child or adolescent, but that there will be an opportunity for the parent/guardian(s) to add in his or her important perspective. It also reassures the child that if he or she cannot remember something or is not sure about something, the parent/guardian is right there to offer support.

Step 3: Take the Headache History

The history taking can then generally proceed as it would with an adult. As the headache neurologist Peter J. Goadsby, MD, PhD, is fond of saying, "Good headache histories are taken, not given." Having a systematic, structured approach to headache history taking will allow the clinician to come to a clear diagnosis. Some age-specific points are included below.

VERY YOUNG CHILDREN. Children younger than age 6 may have difficulty providing the details of their headache history. In this age group, parents/guardians likely will need to provide a fairly large proportion of the history. Having children draw a picture of themselves and how they feel during a headache can be diagnostically helpful.[3] The tissue paper on the examining table can be a ready source of drawing paper for impromptu art production.

PREADOLESCENT SCHOOL-AGED CHILDREN. Time can be a challenging concept for this age group, hence details such as duration and frequency (ie, How long do the headaches last? How many times a week or a month do they happen?) may still need to come from the parent/guardian. Medication names and dosages likely also will come from the adult caregiver.

ADOLESCENTS. Adolescence spans a tremendous developmental range. Some children at 12 years of age will be able to give their entire history, right down to their sumatriptan dose, while others at 17 years of age will still be shrugging and looking to their parents. As a generality, however, adolescents can give a complete headache history, and parental assistance will likely be minimal. It is acceptable to ask the parent/guardian to step out of the room for a few moments to allow for a confidential discussion with the teen around sensitive issues such as alcohol and drug use.

RED FLAGS FOR SECONDARY HEADACHE PATHOLOGY IN CHILDREN AND ADOLESCENTS

This section focuses on features to watch out for in the child or adolescent who experiences recurrent headaches at home and presents to the neurology clinic for outpatient evaluation. "First or worst" headaches (eg, the singular thunderclap headache that occurs with subarachnoid hemorrhage) are more likely to present in the emergency department. Red flags for secondary headache pathology in children and adolescents tend to overlap with secondary headache evaluation in adults, with the exception of select epidemiologic diagnostic considerations in older adults and some pediatric-specific nuances. For more information, refer to the article "Secondary Headache Syndromes" by Denise E. Chou, MD,[4] in this issue of *Continuum*.

Headaches Occurring When Supine or With Valsalva Maneuver

While children with migraine might occasionally have a headache that wakes them from sleep at night, a regular pattern of headaches occurring at night while supine or occurring exclusively with Valsalva maneuver or cough suggests elevated intracranial pressure and the possibility of a mass, which warrants further investigation.

Headaches With Exercise, Sexual Activity, or Cough

While primary headache disorders may occur with exercise, sexual activity, or cough,[1] they are diagnoses of exclusion, and generally neuroimaging is needed to exclude secondary causes of these types of headaches.

KEY POINT

● New headaches, or new types of headaches, are more concerning for secondary pathology than old headaches.

Recurrent Thunderclap Headaches

Thunderclap headaches (ie, those that come on suddenly and are maximal in intensity at onset) occurring in a flurry of attacks over the course of a few days or weeks can suggest reversible cerebral vasoconstriction syndrome (RCVS).[1]

New-onset Headaches With Accompanying Concerning Features

New-onset headaches with accompanying features suggestive of meningitis, encephalitis, or a focal neurologic process (eg, seizure, movement disorder, altered mental status) or signs of systemic illness or infection) require further evaluation.

Visual Symptoms not Characteristic of Migraine Aura

Focal childhood epilepsy syndromes can mimic migraine with visual aura. Panayiotopoulos syndrome is an epilepsy syndrome with a peak age of onset of 3 to 6 years. The child may describe colored spinning balls or other visual hallucinations.[5] In contrast, visual symptoms in migraine aura are usually "negative" (eg, scotomata or the black and white jagged curvilinear outline of a fortification spectrum).[1] Autonomic symptoms such as nausea, vomiting, and pallor are typical in Panayiotopoulos syndrome. Autonomic seizures can last for 30 minutes or more and may end with altered consciousness, nystagmus, and convulsion. The total number of seizures in Panayiotopoulos syndrome is low, and patients typically have fewer than five lifetime seizures from Panayiotopoulos syndrome. A second epilepsy syndrome, idiopathic childhood occipital epilepsy of Gastaut, usually starts around 8 to 11 years of age. Children may describe colored spinning objects or visual hallucinations/illusions followed by severe headache and sometimes vomiting. Visual episodes are stereotyped, coming on within seconds and typically lasting just a couple of minutes.[5] By contrast, visual aura in migraine typically develops slowly over minutes and lasts for at least 5 minutes.[1] The occipital lobe seizures in Gastaut epilepsy are typically frequent and brief.[5] Usually, the clinical description is enough to reassure the clinician that the child does not have epilepsy, but if question remains, an EEG is indicated.

Headaches Worsening When Upright

Headaches that worsen with standing may suggest spontaneous intracranial hypotension or post–dural puncture headache if a recent lumbar puncture has occured.[1]

Headaches Accompanied by Diplopia, Transient Visual Obscurations, Decreased Visual Acuity, or Visual Field Deficits

Headaches accompanied by diplopia, transient visual obscurations, decreased visual acuity, or visual field deficits are suggestive of intracranial hypertension, including idiopathic intracranial hypertension (pseudotumor cerebri). Children on medications known to cause this disorder or adolescent females with an elevated body mass index are most likely to be affected. Note that an opening pressure of 280 mm CSF or more is needed to make this

diagnosis in children who are obese or sedated, compared to 250 mm CSF or more in adults or in children who are not obese or sedated.[6]

Brief Side-locked or Site-locked Headaches Associated With Symptoms of Endocrine Pathology

Functional or structural pituitary lesions can generate secondary headaches that are brief and sometimes phenotypically mimic trigeminal autonomic cephalalgias.[7] Abnormalities of growth, galactorrhea, or symptoms of hypothyroidism/hyperthyroidism can be suggestive of pituitary pathology. Trigeminal autonomic cephalalgias are side-locked and site-locked headaches; however, these disorders are rare in children, so before finalizing such a diagnosis, an MRI of the brain, with special attention to the pituitary, should be obtained.

Focal Neurologic Examination Findings

On initial presentation for headache, all children and adolescents need a thorough neurologic examination including funduscopic examination. Focal findings, unless long-standing and previously explained (eg, a well-documented right hemiparesis from a known left middle cerebral artery perinatal stroke), require neuroimaging.

Immunocompromised Child or Adolescent

Children with a history of cancer, immunosuppressive therapy, a congenital or acquired immunodeficiency, or on anticoagulation will likely need neuroimaging to exclude secondary pathology before finalizing a primary headache diagnosis, even in otherwise typical headache syndromes.

PEDIATRIC HEADACHE FEATURES NOT RED FLAGS FOR SECONDARY PATHOLOGY

Recognizing headache features that are common in children can help to avoid unnecessary testing.

Occipital Headache Location

In the emergency department setting, occipital headache in children has been associated with brain tumors.[8,9] However, the children with tumors in those studies also had objectively abnormal neurologic examinations. In the clinic setting, the child who has recurrent occipital headaches but a normal neurologic examination and headaches that are otherwise consistent with migraine does not appear to be at increased risk of secondary pathology.[10] Occipital headache alone is not necessarily a reason to image.

Headaches Accompanied by Nasal Congestion, Itchy Eyes, or Ear Pressure

"Sinus headache" is one of the most common misdiagnoses given to adult and pediatric patients who have migraine.[11,12] This misdiagnosis can result in unnecessary courses of antibiotics, unnecessary sinus surgeries, and delays in diagnosis and appropriate treatment of migraine. Cranial autonomic symptoms are common in pediatric migraine; in fact, the majority of patients will have at least one cranial autonomic symptom (FIGURE 8-1),[13,14] and their presence should not dissuade the clinician from making a diagnosis of migraine. These symptoms result from activation of trigeminal nociceptive afferents and parasympathetic efferent outflow in cranial nerves VII and

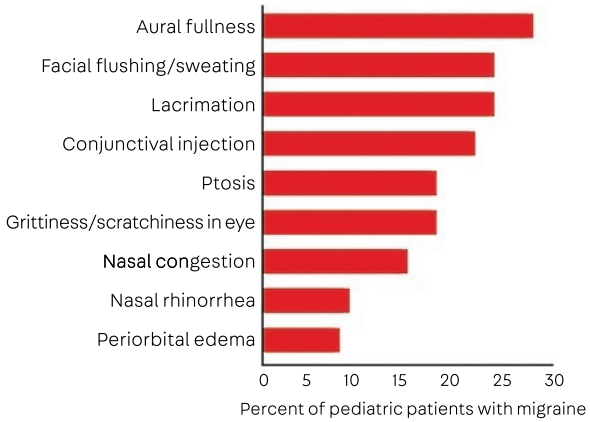

FIGURE 8-1
Frequency of cranial autonomic symptoms in patients with pediatric migraine.
Reprinted with permission from Gelfand AA, et al, Neurology.[13] © 2013 American Academy of Neurology.

VIII.[15] The list of cranial autonomic symptoms recognized in the *International Classification of Headache Disorders, Third Edition* (*ICHD-3*) is as follows[1]:

- **Conjunctival injection and/or lacrimation**
- **Nasal congestion and/or rhinorrhea**
- **Eyelid edema**
- **Forehead and facial sweating**
- **Forehead and facial flushing**
- **Sensation of fullness in the ear**
- **Miosis and/or ptosis**

PRIMARY HEADACHE DISORDERS AFFECTING CHILDREN AND ADOLESCENTS

Many different primary headache disorders can affect children and adolescents.

Migraine

While sometimes thought of as an adult disorder, migraine can occur in children and adolescents.

EPIDEMIOLOGY, DIAGNOSIS, AND IMPACT. Migraine is common in children and adolescents. By age 10, the prevalence of migraine in children is approximately 5%, and it increases further over the course of adolescence (FIGURE 8-2).[16] Prior to puberty, migraine affects boys and girls equally.[16] By late adolescence, migraine affects more girls than boys, ultimately approximating the 3:1 ratio seen in adult women and men.[16,17] (Refer to the open access online version of the *ICHD-3* for a complete listing of the diagnostic criteria of migraine in children and adolescents.[1])

Chronic migraine, referring to headache occurring 15 days or more per month for 3 months or more, of which 8 or more meet criteria for migraine,[1] is also common in children and adolescents. Among children ages 5 to 12 years,

KEY POINT

- **By age 10, migraine prevalence in children is approximately 5%. This means that by fifth grade, almost every classroom contains at least one child with migraine.**

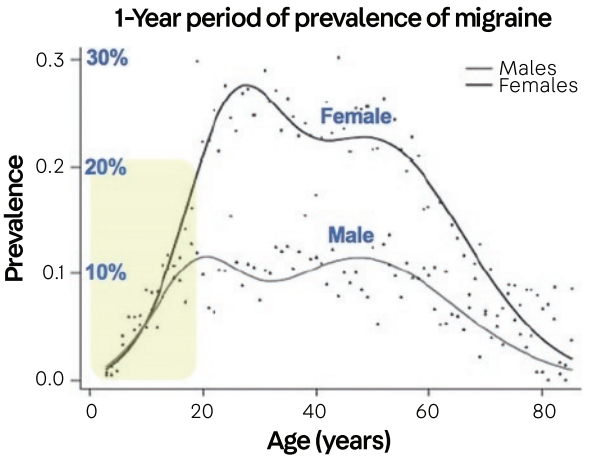

FIGURE 8-2
Migraine prevalence by age and sex.
Modified with permission from Victor TW, et al, Cephalalgia.[16]

chronic migraine prevalence is 0.6%.[18] In adolescents 12 to 17 years of age, the prevalence of chronic migraine is 0.8% to 1.8%.[19] Children from socioeconomically disadvantaged backgrounds are 4 times more likely to experience chronic migraine.[18]

Children with migraine miss more school and perform more poorly in school than their headache-free peers. A dose effect occurs, wherein children with chronic migraine tend to miss more school than those with episodic migraine.[18] In the recent Childhood and Adolescent Migraine Prevention (CHAMP) trial, a National Institutes of Health (NIH)–funded multisite migraine prevention study for participants ages 8 to 17 years, the 361 participants missed 165 full days of school and 124 partial days of school during the 4-week run-in period alone.[20] In children with migraine, nausea during migraine attacks is the strongest predictor of missing school (odds ratio of 5.7; 95% confidence interval, 2.6-12.4).[18] Migraine has a tremendous capacity to cause disability and to negatively impact a child's schooling.

Measuring and quantifying migraine-associated disability in children and adolescents is important for determining the appropriate level of treatment intervention and for following treatment response over time. The Pediatric Migraine Disability Assessment (PedMIDAS) questionnaire is a six-question validated instrument for measuring headache-related disability in children and adolescents.[21] A version can be downloaded for free at *cincinnatichildrens.org/service/h/headache-center/pedmidas*.[22]

PHENOTYPE OF MIGRAINE IN CHILDREN. As in adults, children and adolescents with migraine can experience premonitory symptoms and postdrome symptoms in addition to ictal phase symptoms of migraine,[23] although the most common symptoms experienced by these age groups may differ from adults. Premonitory symptoms precede the headache phase of migraine by hours or even a day or two and include symptoms such as neck pain, mood change, food cravings, photophobia/phonophobia, and increased yawning. Postdrome symptoms follow the headache phase and include fatigue, a "washed out" feeling, and brain fog. (Refer to the articles "The Migraine Premonitory Phase" and "The Migraine Postdrome" by Nazia Karsan, MBBS, MRCP; Pyari Bose, MD, MRCP; and Peter J. Goadsby, MD, PhD,[24,25] in this issue of *Continuum*.) Symptoms in the premonitory and postdrome phase scan impact function and contribute to migraine-related disability.

PREMONITORY PHASE OF PEDIATRIC AND ADOLESCENT MIGRAINE. Premonitory symptoms are seen in approximately two-thirds of children and adolescents with migraine.[23] Fatigue, irritability/mood change, neck stiffness, and facial changes are the most commonly reported premonitory symptoms in this age group.[23,26]

MIGRAINE TRIGGERS VERSUS PREMONITORY SYMPTOMS. Patients can sometimes misinterpret a premonitory symptom as a migraine trigger. For example, if the brain has already entered the premonitory phase and become excessively sensitive to light, the person might erroneously conclude that bright lights triggered the headache. Importantly, in a randomized double-blind trial, chocolate was no more likely to trigger a migraine attack than was the control substance.[27] This was true regardless of whether the person thought chocolate was a trigger for them. Food craving, often for sweet foods, is a known premonitory phase migraine symptom, hence migraine may cause chocolate eating rather than chocolate causing migraine.

ICTAL PHASE OF PEDIATRIC AND ADOLESCENT MIGRAINE. The pathophysiology of migraine in children is likely similar to that in adults. Calcitonin gene-related peptide (CGRP) levels are elevated in pediatric migraine attacks just as they are in adult migraine attacks (FIGURE 8-3).[28] However, the phenotype of migraine in the developing brain has some unique features.

PHENOTYPIC FEATURES OF MIGRAINE THAT DIFFER IN CHILDREN AND ADOLESCENTS VERSUS ADULTS. Migraine duration in children can be shorter, particularly in children younger than 7 years of age.[29] In the *ICHD-3*, the lower margin of duration for untreated or unsuccessfully treated attacks in children is 2 hours versus 4 hours in adults.[1] It is not known why migraine tends to be shorter in the developing brain; however, one possibility might be that younger children are more likely to take naps, and sleep seems to be helpful in terminating migraine attacks.[29] The majority (more than 80%) of children and adolescents report bilateral migraine headache. This is the phenotype through late adolescence.[30]

EPISODIC SYNDROMES THAT MAY BE ASSOCIATED WITH MIGRAINE. Previously referred to as childhood periodic syndromes, certain disorders that tend to affect young children more often than adults have been associated with migraine and may represent early life manifestations of migraine genes in the

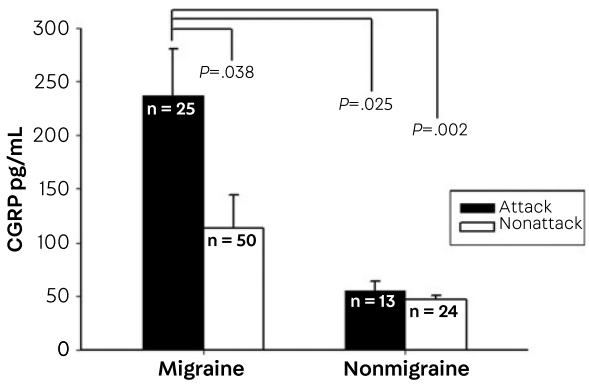

FIGURE 8-3
Calcitonin gene-related peptide (CGRP) levels in children with migraine versus children with nonmigraine headache both during headache and when without headache.
Reprinted with permission from Fan PC, et al, Cephalalgia.[28]

KEY POINTS

- **The Pediatric Migraine Disability Assessment questionnaire is a six-question validated instrument for measuring headache-related disability in children and adolescents.**
- **Common premonitory symptoms in pediatric migraine include fatigue, irritability/mood changes, neck stiffness, and facial change.**
- **Differentiating premonitory symptom from migraine triggers can be challenging.**
- **Chocolate does not appear to be a migraine trigger.**

developing brain. These include infant colic, benign paroxysmal torticollis, benign paroxysmal vertigo, cyclic vomiting syndrome, and abdominal migraine.[1]

INFANT COLIC. Excessive crying in an otherwise healthy and well-fed infant (infant colic) affects 5% to 19% of babies. While all babies cry, these babies cry more and often inconsolably. Children with migraine are more likely to have been colicky as babies,[31,32] women with migraine are more likely to have a baby with colic,[33] and babies with colic are more likely to grow up to have migraine without aura as adolescents.[34] It has been hypothesized that babies with migraine genetics may be more sensitive to stimuli than other babies, and that they express this sensitivity to stimuli through excessive crying at the end of the day.[33] Data suggest that colicky babies are more sensitive to sound and smell and cry most in the evenings and at night.[35] Excessive crying is associated with caregiver frustration and shaken baby syndrome[36,37]; hence, it is important that colic's etiology is ultimately understood so that these infants can be managed appropriately.

BENIGN PAROXYSMAL TORTICOLLIS. Starting in infancy, children with benign paroxysmal torticollis experience periodic attacks of head tilt, nausea/vomiting, and fussiness. For those children old enough to crawl or walk, ataxia may also be present. Some children have accompanying gross motor delay, which may be secondary to the effects of torticollis and ataxia that decrease the amount of time the child has to develop gross motor skills.[38] The calcium channel gene mutation *CACNA1A*, one of the genes associated with familial hemiplegic migraine, has been found in some individuals with benign paroxysmal torticollis.[39] Benign paroxysmal torticollis is rare, and referral to child neurology for diagnostic confirmation and treatment is recommended.

BENIGN PAROXYSMAL VERTIGO. Starting around preschool age, children with benign paroxysmal vertigo experience periodic attacks of dizziness typically lasting for several minutes. They may drop to the floor and have nystagmus. Epilepsy is on the differential. The natural history is to outgrow the episodes after several years.[40]

CYCLIC VOMITING SYNDROME. Cyclic vomiting syndrome typically occurs in elementary school–aged children and presents as periodic attacks of frequent vomiting. Accompanying abdominal discomfort and anorexia may be present. Inborn errors of metabolism can mimic this phenotype and should be considered in children who have developmental delay or regression, encephalopathy with attacks, or attacks clearly triggered by fasting or illness.[41] Adolescents with a cyclic vomiting phenotype should be asked about cannabis use and whether they take long showers or bathe in hot water during vomiting attacks, as cannabinoid hyperemesis syndrome is a diagnostic mimic.[42] Adults can also have cyclic vomiting syndrome. Antiemetics, triptans, and the neurokinin-1 receptor antagonist aprepitant[43] may be helpful in treating this disorder. L-carnitine and coenzyme Q10 supplementation may also be helpful.[41]

ABDOMINAL MIGRAINE. School-age children with abdominal migraine have periodic attacks of abdominal pain that is dull or "just sore" in quality. It tends

to be diffuse in location, and this feature is helpful in distinguishing it from abdominal pathology that tends to have localized pain. Associated pallor, anorexia, nausea, and vomiting may be present. Adults can also have abdominal migraine. Antiemetics, triptans, and dihydroergotamine may be helpful in treating this disorder.[44]

KEY POINT

● Cannabinoid hyperemesis syndrome can mimic cyclic vomiting syndrome in adolescents.

POSTDROME PHASE OF PEDIATRIC AND ADOLESCENT MIGRAINE. In one study, 82% of children and adolescents experienced postdrome symptoms. The most common symptoms were thirst, somnolence, visual disturbances, and food cravings.[45] In the vast majority of patients, postdrome symptoms resolved within 12 hours. Additional research in this area is needed. One advantage to migraine preventive treatment is that acute treatments focus on treating ictal phase symptoms and do not necessarily avoid the premonitory or postdromal symptoms and their associated disability. Preventing the attack entirely is optimal for minimizing disability.

TREATMENT OF PEDIATRIC AND ADOLESCENT MIGRAINE

Migraine treatment consists of two broad categories: preventive treatments (ie, things done to attempt to decrease migraine frequency) and acute treatment (ie, things done to attempt to decrease or stop acute symptoms).

Lifestyle Aspects of Migraine Prevention

Maintaining regularity and homeostasis is generally helpful in individuals with migraine. However, change is the rule in childhood and adolescence, and thus adolescence can be a challenging time for controlling migraine frequency. Physical, cognitive, and emotional growth are ongoing. Changes in schedule are near ever-present in this age group. While children with migraine are sometimes accused of "faking" a headache to get out of school, empirically they are no more likely to present to the emergency department for headache during a school month than a summer month.[46] The only exceptions are that (in the Northern Hemisphere) adolescents are more likely to present in September and January—the 2 months of the year when they go through significant changes in sleep and activity schedules as they transition from holiday schedules back to school. It therefore seems to be "changes in daily schedules and transitions" that are related to migraine frequency, rather than school itself.[46]

Several areas related to lifestyle regularity are worth discussing with children and adolescents and their families. In the CHAMP study, counseling around lifestyle aspects of migraine management was done at each month's study visit, which may have contributed to the excellent response seen in approximately 60% of the placebo arm.[47]

SLEEP. An optimal sleep schedule for a child or adolescent with migraine is one that includes adequate sleep (TABLE 8-1[48]) and bedtime and wake-up times that do not differ significantly from weekday to weekend. Achieving these goals can be particularly difficult for adolescents. Adolescents have a physiologic sleep phase delay wherein their brains do not want to go to sleep until later at night and want to sleep in.[49] High school schedules rarely accommodate adolescent neurobiology. While the American Academy of Pediatrics recommends that high schools begin no earlier than 8:30 AM,[50] only

17.7% of schools actually do.[51] Adolescents often sleep little during the week and try to make up for it over the weekend. Difficulty falling asleep Sunday night before the school week begins or inadequate sleep Sunday night may contribute to Monday being the most migrainous day of the week.[52] Clinicians can advocate for appropriate school start times with their local school districts. Consider excusing patients from their first period classes if it is necessary for improving migraine management.

HYDRATION. Increasing water intake is associated with improved headache severity and quality of life measures in adults with headaches.[53,54] In one study, 55% of all children and adolescents 6 to 19 years of age were mildly dehydrated based on tests of urine concentration.[55] *Headachereliefguide.com* is a website developed by pediatric headache experts that gives patients and families information about migraine in children and adolescents.[56] Children can go to the site to determine their individual water needs based on their sex, weight, the weather, and their level of physical activity for the day.

CAFFEINE. Caffeine withdrawal can provoke migraine. The clinician can determine whether the adolescent should avoid caffeine entirely or maintain a regular, modest, age-appropriate intake.

AVOIDING MEAL SKIPPING. Fasting can provoke headache.[57,58] For adolescents with migraine, the issue is usually inadequate time in the morning to eat breakfast (see above on start times for high schools). Portable breakfasts such as fruit and cheese can help.

EXERCISE. In an adult study where individuals with migraine were randomly assigned to either topiramate or aerobic exercise for 40 minutes (15 minute warm-up, 20 minute exercise, 5 minute cooldown) 3 times per week, both groups improved equally.[59] Prescribing exercise to a child seems generally healthier than prescribing topiramate, so it is worth spending some time discussing strategies for the child to get adequate physical activity.

TABLE 8-1

American Academy of Sleep Medicine Recommendations for Sleep in Children and Adolescents[a]

Age of Children/Adolescents	Recommended Hours of Sleep
3–5 years of age	10–13 hours of sleep per 24 hours (including naps)
6–12 years of age	9–12 hours of sleep per 24 hours
13–18 years of age	8–10 hours of sleep per 24 hours

[a] Data from Paruthi S, et al, J Clin Sleep Med.[48]

Behavioral Preventive Treatments for Pediatric and Adolescent Migraine

Cognitive-behavioral therapy, in combination with preventive medication, has been shown to help adolescents with chronic migraine in the 10 to 17 year age group improve more than medication plus lifestyle advice.[60] The course of therapy needed to provide benefit may be relatively short. Improved adherence may be part of the mechanism by which cognitive-behavioral therapy improves migraine frequency. For example, while it is one thing for the doctor to say, "keep a regular sleep schedule," it is another thing entirely for the adolescent and family to actually apply that advice. Coming up with strategies to facilitate regular sleep and good sleep hygiene is just one example of the type of skill building that can be achieved as part of cognitive-behavioral therapy. However, accessing cognitive-behavioral therapy can be challenging for patients and families.

Examples of barriers to accessing cognitive-behavioral therapy include stigma around anything called "therapy," inadequate insurance coverage for biobehavioral services, and inadequate numbers of providers trained in cognitive-behavioral therapy for headache in children and adolescents.

Overcoming barriers to cognitive-behavioral therapy is important.[61] Families can call their insurance company or third-party payer for a list of in-network providers in their area. The primary care pediatrician or family practice provider may have a list of appropriate providers in the family's area. Ultimately, technology-based solutions will likely be needed to fill the accessibility gap, such as telemedicine and cognitive-behavioral therapy smartphone apps. Several online programs already exist for cognitive-behavioral therapy for insomnia.

Pharmacologic Preventive Treatment

The CHAMP trial published in 2017 has helped to reframe the approach to migraine prevention in children and adolescents.[47] In this NIH-funded multisite trial designed to identify a first-line preventive for pediatric migraine prevention in children and adolescents ages 8 to 17 years, participants could have episodic or chronic migraine, although approximately three-fourths of the participants had episodic migraine.[20] A PedMIDAS score of 10 or more was an inclusion criterion in CHAMP, as this was thought to be the minimum amount of disability at which a pharmacologic preventive would be indicated.

The three treatment arms of the CHAMP trial were amitriptyline (goal dose of 1 mg/kg), topiramate (2 mg/kg), and placebo. During the course of the CHAMP study, topiramate became the first migraine preventive to be labeled by the US Food and Drug Administration (FDA) for migraine prevention in adolescents 12 to 17 years of age, based upon an earlier study of topiramate in this age group.[62]

The CHAMP trial was ultimately stopped early for futility. In all three treatment arms, approximately 60% of the participants met the primary end point of a 50% or more reduction in headache days 24 weeks after starting preventive therapy.[47] Adverse events were more commonly seen in the amitriptyline and topiramate arms than in the placebo group. Topiramate currently remains FDA-labeled for migraine prevention in adolescents 12 to 17 years of age, and no preventive therapies labeled for children younger than age 12 exist.

KEY POINTS

- **Combine cognitive-behavioral therapy with pharmacologic preventive treatment for chronic migraine in children and adolescents ages 10 to 17 years.**
- **First-line pharmacologic preventives for pediatric and adolescent migraine should have a side effect profile comparable to that of placebo.**
- **In the United States, 504 plans allow children and teenagers to have necessary accommodations at school for management of a medical condition, such as migraine. All children and adolescents with migraine should have an annual letter from their doctor stating their diagnosis and supporting accommodations for their 504 plan.**

Several factors may have contributed to the high placebo response rate seen in the CHAMP trial.[63] One is the possibility of active cointerventions. In addition to pharmacologic prevention, all participants received:

- **Lifestyle migraine management advice on sleep, exercise, hydration/eating, and caffeine. This advice was reinforced at monthly study visits. Attending to these aspects of prevention may have contributed to participants doing well.**
- **Optimal acute therapy: All participants received evidence-based optimal acute therapy, specifically nonsteroidal anti-inflammatory drugs (NSAIDs) and triptans, dosed appropriately and with use frequency guidance so as to avoid medication overuse. In adults, inadequate acute treatment efficacy is associated with an increased risk of progressing from episodic to chronic migraine.[64] Thus, optimizing treatment of acute attacks may itself have a preventive role.**

Of note, however, these interventions alone were not enough to decrease headache frequency, at least over the 4-week baseline run-in period. Participants' odds of having a headache in the fourth week of the run-in period were no lower than in the first week of the run-in period.[20] It seems that providing a preventive treatment was essential for bringing about headache frequency reduction. As treatment efficacy in the three arms was comparable, but adverse events were higher in the medication arms, these data suggest that first-line preventive treatments for pediatric migraine should have a side effect profile that is comparable to that of placebo.[63]

Preventive treatments with preferable side effect profiles include:

- **Melatonin 3 mg nightly: In an adult randomized placebo-controlled trial of melatonin 3 mg versus amitriptyline 25 mg versus placebo for migraine prevention, melatonin was more effective than placebo and similar in effect to amitriptyline. Melatonin had a side effect profile similar to placebo and better than amitriptyline.[65]**
- **Riboflavin 400 mg/d: In an adult randomized placebo-controlled trial of riboflavin versus placebo, riboflavin was superior to placebo and had excellent tolerability.[66]**
- **Cognitive-behavioral therapy: Evidence of efficacy has been shown,[60] and side effects would be expected to be minimal, although time and cost are considerations, and accessibility may be an issue.**
- **Low-dose prescription medications: For example, amitriptyline 10 mg nightly may have a favorable side effect profile, and there is some[67] evidence in adults for migraine preventive efficacy at low doses.**

The treatments suggested may help the approximately 60% of children and adolescents with migraine who would have met CHAMP inclusion criteria.

However, two important populations of patients remain: the approximately 40% of CHAMP-eligible children and adolescents with migraine who do not respond to first-line therapy, and those who would not have qualified for CHAMP (TABLE 8-2[68]) and to whom its results therefore do not necessarily generalize.

It has been observed that the children and adolescents most in need of effective migraine prevention (ie, those with continuous headache, high levels of migraine-related disability, or medication overuse) were the very ones excluded from CHAMP.[63]

In managing these two populations of patients, we still do not have adequate data to guide our treatment selection. Therefore, clinical experience and extrapolation from adult data will have to serve as stand-ins. For these

patients, migraine preventive treatments that have been shown to be effective in adults and can be considered to treat children and adolescents include: propranolol, amitriptyline, topiramate, candesartan, venlafaxine, memantine, and sodium valproate. In treating adolescent girls of reproductive age, it is important to note that topiramate, sodium valproate, and angiotensin receptor antagonists (eg, candesartan) have known teratogenicity.[69–71]

Acute Migraine Treatment in Children and Adolescents

This section focuses on treating pediatric acute migraine in the outpatient setting,[72] as this is where the majority of attacks are treated.

CONSIDER THE ENVIRONMENT. Children will often naturally seek out dark, quiet spaces when they have migraine. This should be encouraged. They should also be encouraged to take frequent small sips of water to remain hydrated. If they are in a place where they can get to sleep, sleep may be useful in terminating a migraine attack.

As acute medications are most effective when taken while pain is still mild,[73] which tends to be early in an attack, families and adolescents should work out strategies to ensure the medications are available and on hand. At school, adolescents who are old enough to administer their own medications might keep them in a purse or a locker. Younger children will need to go to the nurse's office or get help from an adult to administer medication. Arrangements for excusing them from class in such settings should be put in place ahead of time.

In the United States, 504 plans allow children and teenagers to have necessary accommodations at school for management of a medical condition, such as migraine. All children and adolescents with migraine should have an annual letter from their doctor stating their diagnosis and supporting accommodations for their 504 plan (**SDC 8-1**, *links.lww.com/CONT/A253*).

NONORAL ROUTES OF MEDICATION ADMINISTRATION. During acute migraine or exacerbations of chronic migraine, nausea/vomiting may make oral administration of medications challenging. Vomiting can sometimes be a very prominent part of the migraine attack in young children. In an urgent care or emergency department setting, IV administration is possible. However,

Main Exclusion Criteria for Childhood and Adolescent Migraine Prevention Trial[a] **TABLE 8-2**

A	Continuous headache
B	Accompanying medication overuse, defined as unwilling to avoid taking nonspecific analgesics/nonsteroidal anti-inflammatory drugs >3 times per week or triptans >6 times per month
C	Pediatric Migraine Disability Assessment score of ≥140
D	Current use of disallowed medications such as opioids, barbiturates, benzodiazepines, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, antipsychotics, antimanics, nutraceuticals, sedatives, muscle relaxants, tramadol
E	Psychiatric disease such as major depression, generalized anxiety disorder

[a] Data from Hershey AD, et al, Headache.[68]

ideally patients have the tools they need to treat successfully at home. Nasal spray or nasal powder formulations are available for some triptans, dihydroergotamine, and the NSAID ketorolac. Some children are accepting of nasal administration while others find the sensation unpleasant. Nasal absorption may be variable. The suppository route allows for excellent and rapid absorption. Prochlorperazine is available as a suppository and can be helpful for all aspects of migraine, including nausea/vomiting. Other medications can be compounded into a suppository form, including chlorpromazine, dihydroergotamine, and sumatriptan. Young children are often very accepting of a suppository; teenagers are less likely to be enthusiastic. Sumatriptan is available as a 6 mg auto injector, and smaller dosages can be drawn up in a syringe. Certain other medications can also be given by injection (eg, dihydroergotamine or ketorolac). Neurostimulation devices, such as transcranial magnetic stimulation devices or the transcutaneous electrical nerve stimulation device, could be useful acutely, although patients may not have access to these devices. The antiemetic granisetron is available as a transdermal patch. With a little trial and error, usually a nonoral treatment plan can be found.

PILL SWALLOWING. Younger children may not yet have the ability to swallow pills. Some acute migraine treatments are available as liquids, melts, or nasal sprays. Starting around age 8, neurodevelopmentally typical children can start working on pill-swallowing techniques. Practicing pill swallowing using small chocolate chewable candies or similar treats can be helpful and is often a good way to get the child to comply with the process.

ACETAMINOPHEN. Acetaminophen has been studied in a randomized, double-blind, placebo-controlled trial and was found to be effective for acute migraine in children 4 years and older.[74] Dosing is 15 mg/kg orally. Acetaminophen is available over the counter in the United States in a flavored liquid formulation at a concentration of 160 mg/5 mL. There are also 160 mg melts for older children, and 325 mg to 500 mg tablets are available over the counter. An IV formulation of acetaminophen is available and could be useful in the emergency department setting.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS. Ibuprofen has been studied in randomized, double-blind, placebo-controlled trials and found to be effective for acute migraine treatment in children.[74] Children as young as age 4 years were included in one of these studies.[74] Dosing is 7.5 mg/kg to 10 mg/kg,[74,75] generally to a maximum of 600 mg to 800 mg orally up to every 6 hours. Ibuprofen is broadly used to treat pain and fever in pediatric patients, including in infants 6 months of age and older. It is available over the counter in the United States in flavored liquid formulation at a concentration of 100 mg/5 mL. For slightly older children, 100 mg melts are available. Once children are able to swallow pills, they can take the 200 mg over-the-counter tablets with which most parents/guardians are familiar.

Naproxen has a longer half-life than ibuprofen and is perhaps better studied for acute migraine treatment in adults. Combining naproxen with sumatriptan increases the likelihood of being pain free at 2 hours and decreases the likelihood of recurrent headache from 2 to 24 hours in adults.[76] Naproxen

combined with sumatriptan has been studied in adolescents and was found to be safe and effective.[77] Naproxen dosing is 5 mg/kg to 10 mg/kg, generally to a maximum of 660 mg (3 of the 220 mg over-the-counter tablets) orally up to every 12 hours. For younger children, naproxen is available by prescription as a liquid at a concentration of 125 mg/5 mL.

Ketorolac is available as oral tablets, nasal spray, and by injection (IM/IV). In the emergency department setting, ketorolac was not as effective as prochlorperazine at treating acute pediatric migraine.[78] Some patients with significant nausea/vomiting may appreciate the option of the nasal spray formulation.

Diclofenac is available as a tablet. The individual child or adolescent with migraine might try several different NSAIDs before settling on the one that seems most effective.

TRIPTANS. Triptan medications were developed specifically for treatment of acute migraine. Seven are available on the market in the United States. Of these, four are FDA-labeled for acute migraine treatment in adolescents 12 to 17 years of age: almotriptan (oral), zolmitriptan (nasal spray), rizatriptan (melt), sumatriptan/naproxen (oral); and one medication, rizatriptan (melt), is labeled for use in children age 6 and older. TABLE 8-3 shows FDA-labeled dosing when available and shows the author's dosing recommendation where it is not.[79–87]

PRESCRIBING A TRIPTAN TO A CHILD OR ADOLESCENT. If a child's or adolescent's migraine attacks are not responsive to NSAIDs or are inadequately responsive, then a triptan is indicated. The majority of triptan contraindications are rare in pediatric patients as children tend to be healthy from a vascular standpoint. Those with a history of stroke or peripheral vascular disease would not be candidates. Blood pressure should be checked to ensure the child does not have uncontrolled hypertension. Children and adolescents who are on selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) generally do not need to have their access to triptans restricted. The action of triptans is specifically at 5-HT_{1B} and 5-HT_{1D} receptors, whereas serotonin syndrome results from overactivation predominantly at 5-HT_{2A} receptors. The potential for serotonin syndrome developing from combining SSRIs/SNRIs with triptans has been examined, and the risk appears to be quite low. Pharmacists concerned about this possibility can be referred to the 2010 position paper from the American Headache Society.[88]

Sumatriptan oral tablets will often be the first triptan tried in this age group simply because it is tier 1 on most insurance plans. For children younger than age 6 who require triptans, consider referral to a pediatric headache subspecialist.

For children and adolescents with chronic migraine who may have daily or even continuous headache, it is also reasonable to consider triptans for treating these headache exacerbations. While triptans are most likely to be effective if taken when pain is still mild,[73] which tends to be early on in an attack, they can still be effective when pain is moderate or severe,[76] and it is in these settings that youths with continuous headache would most likely use them. Children with chronic migraine are less likely to respond to triptans than those with episodic migraine, but many still do.[89] Counseling about frequency of use is

KEY POINTS

- Four triptans are labeled by the US Food and Drug Administration for acute migraine in adolescents 12 to 17 years of age: almotriptan (oral), zolmitriptan (nasal spray), rizatriptan (melt), and sumatriptan/naproxen (oral); and one medication, rizatriptan (melt), is labeled for use in children age 6 and older.
- Children and adolescents who are on selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors generally do not need to have their access to triptans restricted.

needed to ensure the patient does not develop medication-overuse headache[47]; generally, limiting triptan use to 2 days per week helps avoid this. Combining a triptan with naproxen may both improve the likelihood of efficacy and reduce the likelihood of developing medication-overuse headache.[76,90] For more information on prescribing triptans, refer to the article "Acute Treatment of Migraine" by Bert B. Vargas, MD, FAAN, FAHS,[91] in this issue of *Continuum*.

DIHYDROERGOTAMINE. This migraine-specific ergot derivative can be given to children via a nasal spray, IM injection, or IV. Nausea is the most common significant side effect and is most likely to occur with IV administration as the C_{max} (peak serum concentration) is higher.[92] Nonetheless, given how common nausea is in migraine already, premedicating with an antiemetic is

TABLE 8-3 Triptan Dosing in Children and Adolescents[a]

Medication	<40 kg (88 lb)	≥40 kg (88 lb)	Notes
Sumatriptan tablet	12.5–25 mg	50–100 mg	Combined sumatriptan/naproxen is labeled by the US Food and Drug Administration (FDA) for ages 12 to 17 years: 10 mg/60 mg to 85 mg/500 mg[77]
Sumatriptan nasal spray[79–82]	5 mg	10–20 mg	Studied in children aged 6 and older; labeled in Europe for ages 12 to 17 years
Sumatriptan nasal powder	11 mg	11–22 mg	Not specifically studied in children
Sumatriptan subcutaneous injection	0.1 mg/kg	4–6 mg	Doses <6 mg will typically need to be drawn up in a syringe
Rizatriptan (melt or tablet)[83,84]	5 mg	10 mg	Doses are FDA labeled for ages 6 to 17 years, by weight
Zolmitriptan tablet[85]	2.5 mg	5 mg	
Zolmitriptan nasal spray[86]	2.5 mg	5 mg	FDA labeled for ages 12 to 17 years
Almotriptan tablet[87]	6.25 mg	12.5 mg	FDA labeled for ages 12 to 17 years
Naratriptan tablet	1 mg	2.5 mg	Some studies of naratriptan for menstrual migraine included girls 15 years of age or older
Frovatriptan tablet	1.25 mg (1/2 tablet)	2.5 mg	Not specifically studied in children
Eletriptan tablet	20 mg	40–80 mg	Not specifically studied in children

[a] The doses listed are intended to be single doses given once in a 24-hour period. While giving a second dose of a triptan 2 hours after the first may be safe, additional efficacy has not been demonstrated.

prudent regardless of route of administration. Contraindications to dihydroergotamine in children mirror those of triptans.

DOPAMINE RECEPTOR ANTAGONISTS. Dopamine receptor antagonists can be particularly helpful for children and adolescents who have prominent nausea. Prochlorperazine 0.15 mg/kg IV (maximum 10 mg) is more effective than ketorolac 0.5 mg/kg IV (maximum 30 mg) for treating pediatric acute migraine in the emergency department setting.[78] Chlorpromazine has been studied in adults for acute migraine and can be used in children as well.[72] Coadministration of diphenhydramine with these medications can decrease the likelihood of akathisia.[93]

CASE 8-1 and CASE 8-2 demonstrate approaches to treatment of migraine in children and adolescents.

Tension-type Headache

Tension-type headache can occur in both children and adolescents.

EPIDEMIOLOGY. Prevalence estimates for tension-type headache in children and adolescents vary greatly, with some studies estimating 5% to 11%[94,95] and others estimating 29% to 58%.[96] While tension-type headache seems to be relatively common in the general pediatric and adolescent population, it is generally rare in the clinic. In an adult study, only 3% of patients coming to see their primary care doctor for recurrent headaches had tension-type headache, and 94% had migraine or probable migraine.[97] Tension-type headache affects boys and girls equally.[98]

DISABILITY. Tension-type headache in children and adolescents is generally not as disabling as migraine. Adolescents with tension-type headache have lower PedMIDAS scores than those with migraine.[98] In a study of adolescents, the vast majority of those with tension-type headache had little to no disability from it (ie, Grade 1 PedMIDAS scores).[98] Children with tension-type headache are no more likely than their headache-free peers to have below average school performance and are less likely to miss school than are children with migraine.[18] Nausea and vomiting are not present in tension-type headache, which helps to limit its disability. The presence of nausea in children with headaches has high specificity for a diagnosis of migraine.[42,43,53,71,99,100]

DIAGNOSIS. In the appendix of the *ICHD-3*, tension-type headache is classified as entirely featureless—ie, no photophobia, phonophobia, nausea, or vomiting.[1] Hence, the diagnosis is clearest when the headache disorder is entirely featureless.

EARLY CHILDHOOD SYNDROMES. The childhood episodic syndromes that may be associated with migraine do not seem to be associated with tension-type headache, suggesting that the pathophysiology and genetic underpinnings of migraine and tension-type headache in children are distinct. For example, while children with migraine are more likely to have a history of infant colic, children with tension-type headache are not.[32] Similarly, history of abdominal migraine is higher in children with migraine than in controls, but not in children with tension-type headache.[101]

TREATMENT OF PEDIATRIC TENSION-TYPE HEADACHE. No randomized, double-blind, placebo-controlled trials have been conducted to guide treatment in

KEY POINTS

- While tension-type headache exists in the general pediatric population, it is not a common reason for clinical presentation.
- Nausea is not present in tension-type headache. The presence of nausea in children with headaches has high specificity for a diagnosis of migraine.

CASE 8-1

An 8-year-old boy presented to the neurology clinic with his parents after being referred by his pediatrician for evaluation of 6 months of recurrent headaches. The headaches occurred once a week and typically occurred after school. The patient reported a "booming" pain all over his head, including the occiput. During the headaches he lay down on the couch and asked his siblings to be quiet. He experienced an upset stomach and vomited on a few occasions. He was otherwise healthy and developmentally typical. He was colicky as an infant. His parents reported that no one in the family had headaches "like his," but on further questioning his mother said she experienced headaches before her periods and that she had to lie down in a dark room and take ibuprofen.

His Pediatric Migraine Disability Assessment (PedMIDAS) score was 11, indicating mild headache-related disability. The boy's family had tried giving him acetaminophen, which was helpful sometimes, but it was not helpful for the more severe headaches or the ones with vomiting. His general and neurologic examinations were normal, and his weight was 30 kg (66 lb).

Acute Treatment Options for an 8-year-old 30 kg (66 lb) Patient	Goal Dose[a]	If Patient Can Swallow Pills	If Patient Cannot Swallow Pills
Ibuprofen 7.5–10 mg/kg	300 mg	1.5 tablets of the 200 mg over-the-counter tablet	15 mL of 100 mg/5 mL over-the-counter solution or 3 of the 100 mg over-the-counter junior strength chewable tablets
Naproxen 5–10 mg/kg	300 mg	275 mg prescription tablet or 220 mg over-the-counter tablet	12 mL of 125 mg/5mL prescription solution
Sumatriptan nasal spray	5 mg	1 spray to nare	1 spray to nare
Rizatriptan melt	5 mg	5 mg melt	5 mg melt
Sumatriptan oral	25 mg	25 mg tablet	Not applicable

[a] Goal dose refers to the oral acute treatment dose. Ibuprofen can be dosed every 6 hours as needed, and naproxen can be dosed every 12 hours as needed. While it is safe to give a second dose of a triptan 2 hours after the first if headache persists, no data suggest that this improves efficacy. Generally, this author recommends one dose of a triptan in a 24-hour period.

COMMENT

This boy has episodic migraine. No red flags were identified on the history or the examination to suggest that he needed neuroimaging. For preventive treatment, the patient should be counseled regarding the importance of regular sleep, exercise, meals, and hydration. Based on his age, 9 to 11 hours of sleep per night is recommended. His individualized water intake goal is 40 oz to 72 oz per day (see *headachereliefguide.com*[56]). His PedMIDAS score is high enough to consider offering preventive treatment. He has never been on a preventive treatment before, and based on the results of the Childhood and Adolescent Migraine Prevention (CHAMP) trial, a preventive treatment that has some expectation of benefit and a side effect profile that is similar to that of placebo should be selected. For acute treatment, a nonsteroidal anti-inflammatory drug might help him more than acetaminophen. Optimal evidence-based therapy is a nonsteroidal anti-inflammatory drug plus a triptan. Rizatriptan is labeled by the US Food and Drug Administration (FDA) in his age group. Sumatriptan tablets may be required first-line triptan therapy based on insurance requirements. If he does not yet swallow pills, now is a good time to start practicing. For episodes that are more severe, he may need a nonoral route of administration. Sumatriptan nasal spray has been studied in his age group and would be a reasonable option. Refer to the following table for acute treatment dosing examples for this 30 kg (66 lb) child. The family should be given a letter for the school supporting 504 plan accommodations for migraine. Follow-up should be in 6 to 8 weeks to reinforce lifestyle management and assess the efficacy of his first trial of preventive therapy.

pediatric and adolescent tension-type headache. Not all patients require pharmacologic prevention. Physical exercise or counseling from a nurse or physical therapist may help.[102] Riboflavin 50 mg/d may decrease the frequency of tension-type headache in children.[103] A small uncontrolled study suggests melatonin 3 mg nightly may be efficacious in pediatric tension-type headache prevention as well as in migraine.[104]

Posttraumatic Headache

According to the *ICHD-3*, posttraumatic headache must begin within 7 days of head trauma to be attributed to that injury (or within 7 days of regaining

CASE 8-2

A 16-year-old girl presented for evaluation of headaches. She used to get headaches a couple of times per month, but the frequency increased 6 months ago, and she had experienced pain "all the time" for the last 6 months. About 3 times a week the pain increased in intensity for several hours to the point that she had to go to bed. During these periods, she preferred to be in a dark, quiet room. Sometimes she became nauseated but did not vomit. The rest of the days, the headache was milder, and she was not nauseated or bothered by lights and sounds and could go about her activities. Her Pediatric Migraine Disability Assessment (PedMIDAS) score was 90, indicative of severe headache-related disability. Her pediatrician treated her with topiramate 50 mg twice daily for 2 months, but she did not find it helpful. She took ibuprofen 400 mg for the thrice weekly exacerbations, but it did not help. Her general and neurologic examinations were normal, and her weight was 60 kg (132 lb).

COMMENT

This is a teenaged girl with chronic migraine. Although some of her headache days do not meet migraine criteria, she has at least 15 days of headache per month, of which 8 or more days meet criteria for migraine, and she therefore meets *International Classification of Headache Disorders, Third Edition* criteria for chronic migraine.[1] She does not need both a migraine and a tension-type headache diagnosis. She would not have qualified for the Childhood and Adolescent Migraine Prevention (CHAMP) trial as she has continuous headache. The patient should be counseled that the combination of cognitive-behavioral therapy and medication seems to be most effective for treating chronic migraine in her age group. Lifestyle management advice is also indicated. All the preventive options discussed in the section on preventive therapy would be reasonable to consider in her case, except for topiramate, which she has already tried. For acute therapy, ibuprofen dosing could be optimized to 600 mg orally at headache onset, with repeated dosing up to every 6 hours as needed if headache persists. She also should be given a triptan and counseled to only use it up to 2 days per week. A sumatriptan 50 mg tablet taken with a naproxen 500 mg tablet would be a very reasonable starting point for her. A letter supporting the 504 plan accommodations for school and close clinic follow-up in 6 to 8 weeks round out her treatment plan.

consciousness and/or stopping medications that might impair pain perception).[1] It remains to be seen whether this 7-day cutoff is biologically meaningful in adults or in children and adolescents. The topic of concussion and its management is a burgeoning and important area of research and is beyond the scope of this article. In brief, the phenotype of posttraumatic headache in children and adolescents can be featureful (ie, migrainous) or featureless (ie, similar to tension-type headache). In the absence of randomized trials guiding posttraumatic headache treatment in this age group, treating the headache based on the underlying phenotype seems reasonable.

New Daily Persistent Headache

New daily persistent headache occurs when a headache begins out of the blue on a specific, recalled date and continues unabated for at least 3 months.[1] Some evidence suggests this disorder may occur more commonly in adolescents than in adults.[105] It is best thought of as a syndromic description, as multiple etiologies may exist that can lead to a new daily persistent headache phenotype.[106] The headache can resemble migraine or tension-type headache. Additional research is needed to determine how best to treat adolescents with new daily persistent headache. In the meantime, it seems reasonable to manage these patients based on phenotype.

Primary Stabbing Headache

Approximately 3% to 5% of children and adolescents present to headache clinic because of primary stabbing headache.[107] However, of children younger than age 6 presenting to headache clinic, as many as 12% are presenting because of primary stabbing headache.[108]

Primary stabbing headache is characterized by brief attacks of sharp pain. Duration is typically just a few seconds, although some children may experience attacks lasting several minutes.[1,108,109] The pain is typically described as a stab or series of stabs.[107,109] It can be quite severe.[109] Some children will be brought to their knees by the pain. Perhaps it is the particularly high pain intensity of primary stabbing headache when it occurs in the young developing brain that makes it a more common reason for children and adolescents to come to clinical attention, although not all children report severe pain intensity.[108]

The location of the pain can be anywhere in the head and can be unilateral or bilateral.[108,109] Location can change from attack to attack or be fixed. In adults, fixed location is seen in approximately one-third of patients[110]; however, it is less clear how often fixed headache location occurs in children, making it difficult to assess how clear of an indication for neuroimaging this is, particularly as young children require anesthesia for MRI scans. The complete absence of cranial autonomic symptoms is important in distinguishing primary stabbing headache from trigeminal autonomic cephalalgias.[1] Migratory location is also a helpful feature in distinguishing primary stabbing headache from a trigeminal autonomic cephalalgia. Boys and girls seem equally likely to be affected.[109,111] Onset can be in childhood or adolescence,[107–109,111] but younger than age 6 seems to be more common (CASE 8-3).[108,111] The underlying pathophysiology of primary stabbing headache is unknown; however, given that attack locations often vary within an individual, peripheral mechanisms seem less likely.[107,111] Intermittent

KEY POINTS

- **Primary stabbing headache is a particularly common reason for clinical presentation in children younger than the age of 6 years.**
- **Primary stabbing headache pain intensity can be severe in children.**

dysfunction in central nociceptive processing or brain immaturity leading to central hyperexcitability have been proposed.[107,108]

Usually, attacks are rare and short enough that they do not require any specific treatment. Reassurance about the benign nature of the headaches is typically all that families need. However, preventive treatment may be considered in cases where the attacks are frequent and distressing. Indomethacin is useful for some adult patients.[107,110] Some patients will respond to nightly melatonin.[112,113] In young children who are less than 20 kg (44 lb), melatonin 1 mg to 3 mg nightly may be sufficient. Gummy, melt, or liquid/edible melatonin formulations are available.

Trigeminal Autonomic Cephalalgias

Trigeminal autonomic cephalalgias are rare in children but do occur. Data in the pediatric and adolescent age range are limited to case reports. In the developing brain, the phenotype of a developing trigeminal autonomic cephalalgia may not yet cleanly divide out as cluster headache, paroxysmal hemicrania, hemicrania continua, or short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)/short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) (CASE 8-4).

Hypnic Headache

Hypnic headache is almost unheard of in children. Hypnic headache, or "alarm clock headache," is largely a disorder of older adults and is thought to be related to age-related decline in function in the suprachiasmatic nucleus of the hypothalamus.[1] However, it is possible that there could be developmental

CASE 8-3

A 3-year-old girl was brought to the headache clinic by her parents for evaluation of brief but extremely intense stabs of head pain that had been occurring multiple times per day for the last 3 months. When attacks occurred, she grabbed her head and started to cry. The location of the attacks was sometimes on the right, sometimes on the left, and could be frontal or temporal. No associated cranial autonomic symptoms were present.

General and neurologic examinations were normal, and her weight was 17 kg (37.5 lb). Her development had been normal, and she was otherwise healthy. The parents wanted to know what was causing the headaches and how to make them go away. A trial of melatonin 2.5 mg gummy nightly resolved her attacks within a week.

COMMENT

Primary stabbing headache is a surprisingly common reason children, particularly young children, present to pediatric headache clinic. Absence of cranial autonomic symptoms helps to differentiate it from trigeminal autonomic cephalalgias. It usually does not require treatment but may when attacks are frequent or particularly painful.

abnormalities in the structure or function of the hypothalamus that could lead to this disorder occurring in children. A case series of five children with hypnic headache has been reported. The children ranged in age from 7 to 11 years, with three boys and two girls. Two responded to treatment with melatonin.[114] Given that pediatric hypnic headache is remarkably rare, consider referral to a pediatric headache specialist.

CONCLUSION

Headache is common in children and adolescents. Most children who come to see the neurologist for headaches will have a primary headache disorder, with migraine being most common in this setting. For acute migraine treatment, acetaminophen and NSAIDs have been studied in children age 4 and older and have been found to be effective. Triptans are also effective in children and adolescents. Four triptans are now FDA-labeled for acute migraine treatment in adolescents, and rizatriptan is labeled for use in children age 6 and older. Unless there is a contraindication, children and adolescents whose migraine attacks do not respond to NSAIDs should be offered a triptan.

For preventive migraine treatment, the recent CHAMP trial indicates that approximately 60% of children and adolescents with migraine will improve with a three-pronged treatment approach that includes lifestyle management counseling; evidence-based optimally dosed acute therapy, specifically NSAIDs and triptans; and a daily preventive treatment that has some evidence for efficacy and a side effect profile that is similar to that of placebo. For the approximately 40% of children and adolescents who do not respond to a first-line preventive, and for those who have continuous headache and/or medication overuse who would not have qualified for CHAMP, the clinician's

CASE 8-4

A 17-year-old boy presented for evaluation of attacks of side-locked left retro-orbital pain that lasted 1 to 2 hours in duration, occurred 1 to 3 times per day, and were associated with conjunctival injection and lacrimation. Between attacks he was completely pain free. The attacks remitted completely on indomethacin.

COMMENT

The duration and frequency of this boy's attacks would be most suggestive of cluster headache in the adult; however, his absolute response to indomethacin is more suggestive of paroxysmal hemicrania. This is an example of how trigeminal autonomic cephalalgias may be phenotypically variable in the developing brain. The appendix section of the *International Classification of Headache Disorders, Third Edition* classifies these cases as an undifferentiated trigeminal autonomic cephalalgia: "A trigeminal autonomic cephalalgia–like disorder occurring in children and adolescents with characteristics of the disorder not fully developed."[1] More research is needed to understand these rare disorders in the developing brain. Referral to a pediatric headache specialist is recommended for diagnosis and treatment.

best judgment remains the best guide to therapy selection. Future research should focus on this population of children and adolescents who have migraine that is more difficult to treat, as arguably they are the ones most in need of effective preventive therapies.

USEFUL WEBSITE

INTERNATIONAL CLASSIFICATION OF HEADACHE DISORDERS, THIRD EDITION (ICHD-3)
The online version of the *ICHD-3* is a useful resource for accessing a complete listing of the diagnostic criteria of the unusual headache disorders discussed in this article.
ichd-3.org/wp-content/uploads/2018/01/The-International-Classification-of-Headache-Disorders-3rd-Edition-2018.pdf

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DISCLOSURE

Continued from page 1108

Dr Gelfand has received research/grant support from eNeura Inc, the Migraine Research Foundation, the National Institutes of Health/National Center for Advancing Translational Sciences, and the University of California San Francisco Weill Institute for the Neurosciences. Dr Gelfand has received publishing royalties from UpToDate, Inc and has received compensation as a legal consultant.

Cluster Headache and Other Trigeminal Autonomic Cephalalgias

By Mark Burish, MD, PhD

REVIEW ARTICLE

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UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Burish discusses the unlabeled/investigational use of baclofen, corticosteroids, deep brain stimulation, lithium, occipital nerve stimulation, oxygen, sphenopalatine ganglion stimulation, sumatriptan, topiramate, valproate, verapamil, and zolmitriptan for the treatment of cluster headache; indomethacin, topiramate, and verapamil for the treatment of paroxysmal hemicrania; carbamazepine, duloxetine, gabapentin, lamotrigine, lidocaine, oxcarbazepine, and topiramate for the treatment of short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; and celecoxib, gabapentin, ibuprofen, indomethacin, melatonin, occipital nerve stimulation, onabotulinum toxin injections, topiramate, and verapamil for the treatment of hemicrania continua.

ABSTRACT

PURPOSE OF REVIEW: **This article covers the clinical features, differential diagnosis, and management of the trigeminal autonomic cephalalgias (TACs). The TACs are composed of five diseases: cluster headache, paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA), and hemicrania continua.**

RECENT FINDINGS: **New classifications for the TACs have two important updates; chronic cluster headache is now defined as remission periods lasting less than 3 months (formerly less than 1 month), and hemicrania continua is now classified as a TAC (formerly classified as *other primary headache*). The first-line treatments of TACs have not changed in recent years: cluster headache is managed with oxygen, triptans, and verapamil; paroxysmal hemicrania and hemicrania continua are managed with indomethacin; and SUNCT and SUNA are managed with lamotrigine. However, advancements in neuromodulation have recently provided additional options for patients with cluster headache, which include noninvasive devices for abortive therapy and invasive devices for refractory cluster headache. Patient selection for these devices is key.**

SUMMARY: **The TACs are a group of diseases that appear similar to each other and to other headache disorders but have important differences. Proper diagnosis is crucial for proper treatment. This article reviews the pathophysiology, epidemiology, differential diagnosis, and treatment of the TACs.**

INTRODUCTION

The trigeminal autonomic cephalalgias (TACs) are a group of uncommon primary headache disorders that share similar clinical features but differ in frequency, duration, triggers, and treatment (TABLE 9-1[1–6]). All TACs share an intense unilateral pain in a trigeminal nerve distribution associated with ipsilateral cranial autonomic features such as lacrimation, conjunctival injection, nasal congestion, and rhinorrhea. A single attack varies in duration from seconds (as in short-lasting unilateral neuralgiform headache attacks with conjunctival

TABLE 9-1 **Comparison of the Trigeminal Autonomic Cephalalgias**

	Cluster Headache[1]	Paroxysmal Hemicrania[2]	SUNCT/SUNA[3]	Hemicrania Continua[4]
Ratio of female to male	1:3	Slightly more female	1:1.5	2:1
Pain				
Quality	Sharp, stabbing, throbbing	Sharp, stabbing, throbbing	Sharp, stabbing, throbbing	Baseline: aching; exacerbations: sharp, stabbing, throbbing
Severity	Very severe	Very severe	Severe	Baseline: mild to moderate; exacerbations: moderate to severe
Attacks				
Frequency (per day)	1–8[a]	5–50	1 to hundreds	Constant
Duration (minutes)	15–180	2–30	0.01–10[b]	Baseline: 3 months or more; exacerbations: 30 minutes to 3 days
Ratio of episodic to chronic	90:10	35:65	10:90	15:85[c]
Associated features				
Restlessness	90%	80%	65%	70%
Circadian periodicity	82%[5]	Rare	Rare	Rare
Triggers				
Alcohol	Yes	Yes	No	Yes
Nitroglycerin	Yes	Yes	No	Rare
Neck movements	No	Yes	Yes	No
Cutaneous	No	No	Yes	No
Treatment response				
Oxygen	70%	No effect	No effect	No effect
Sumatriptan 6 mg subcutaneous	90%	20%	Rare effect	No effect
Indomethacin	Rare effect	100%	No effect	100%

SUNA = short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms; SUNCT = short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

[a] Cluster headache frequency is officially one headache every other day up to eight per day.[6]

[b] SUNCT and SUNA duration is 1 to 600 seconds.

[c] For hemicrania continua, the ratio of episodic to chronic refers to the ratio of remitting to unremitting attacks.

injection and tearing [SUNCT] and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms [SUNA]) to months (as in hemicrania continua). Inversely, the frequency of attacks varies from hundreds per day (as in SUNCT/SUNA) to constant (as in hemicrania continua) (FIGURE 9-1). The distinction between the TACs is important for the practicing physician because of the distinction in therapies. Treatments that are highly effective in one disorder may be completely ineffective in another. Paroxysmal hemicrania and hemicrania continua are exquisitely sensitive to indomethacin, while cluster headache, SUNCT, and SUNA are not.

Cluster headache is the most common of the TACs at a prevalence of 1 in 1000 and is the best studied. For this reason, much of this article focuses on cluster headache. SUNCT and SUNA have very similar traits and treatments and are generally discussed together, and SUNCT may in fact be a subset of SUNA.[6] Hemicrania continua has been reclassified as a TAC in the most recent *International Classification of Headache Disorders, Third Edition* (*ICHD-3*),[6] and thus will be discussed here (it was previously classified as *other primary headaches*).

KEY POINT

- **The trigeminal and autonomic systems are connected through the trigeminal autonomic reflex.**

PATHOPHYSIOLOGY

The exact mechanisms of the TACs have not been elucidated. However, three brain systems are particularly prominent in the TACs based on clinical, anatomic, and molecular data and include the pain system (especially the trigeminovascular system), the cranial autonomic system, and the hypothalamus (FIGURE 9-2).[7–12] Indeed, cluster headache can be treated by stimulation of the occipital nerve (part of the trigeminovascular system), the sphenopalatine ganglion (part of the cranial autonomic system), or the posterior hypothalamus. It is plausible to think that all three systems are linked through the trigeminal autonomic reflex, hypothalamic-trigeminal nucleus connections, and hypothalamic-autonomic connections.[13,14] Our knowledge of these systems has primarily come from studies in cluster headache, although small studies have been performed that support similar mechanisms in the other TACs.

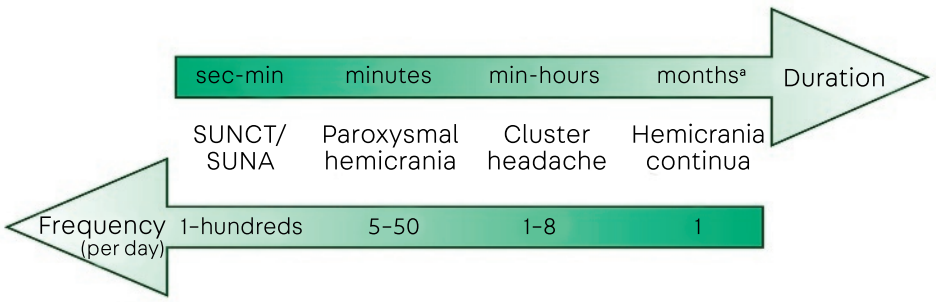

FIGURE 9-1

Timing of individual attacks in trigeminal autonomic cephalalgias. Listed are typical durations of individual attacks and frequencies of attacks per day. Considerable overlap exists between the disorders. Of note, the frequency of cluster headache is officially between one attack every other day and eight per day.[6]

SUNA = short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms; SUNCT = short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

[a] While a hemicrania continua headache lasts months, flares in hemicrania continua pain can last minutes to days.

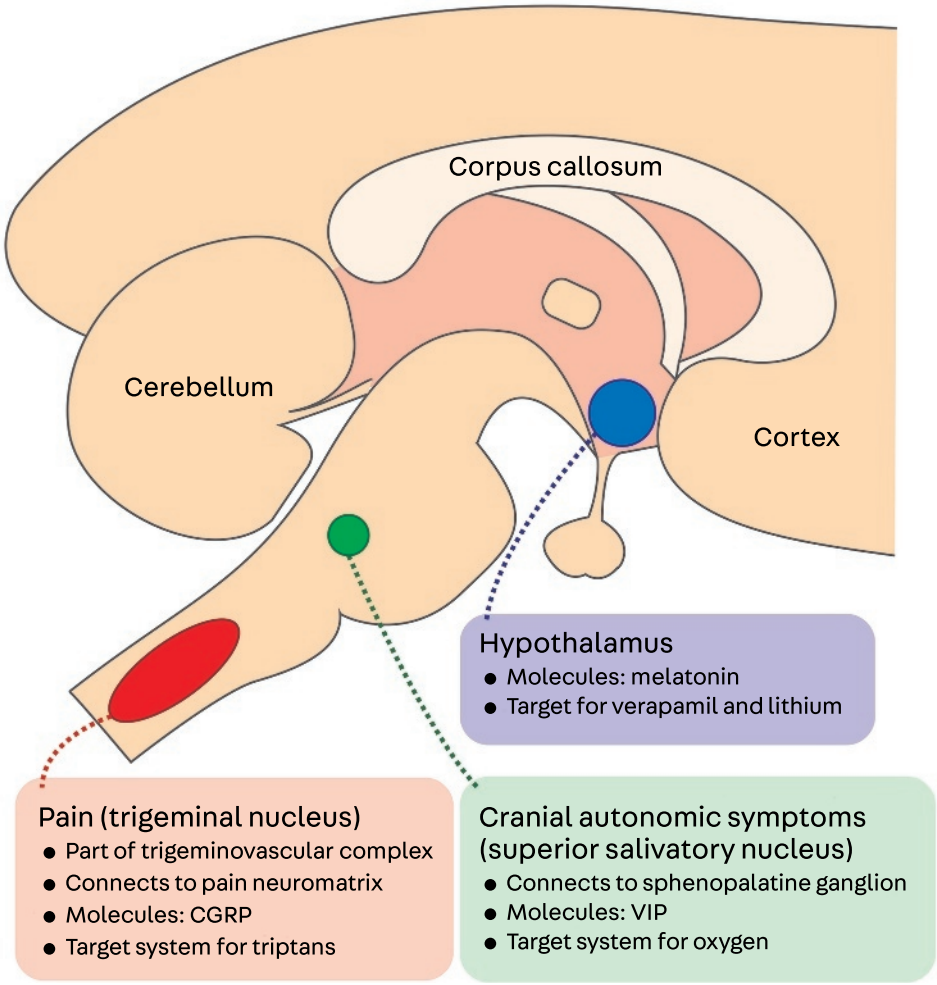

FIGURE 9-2

Pathogenesis of trigeminal autonomic cephalalgias. At least three systems are involved including the pain system (the trigeminal nerve, trigeminovascular complex, and general pain system called the pain neuromatrix), the cranial autonomic system (the superior salivatory nucleus and sphenopalatine ganglion), and the hypothalamus. Human studies have shown alterations in several molecules, and animal research has suggested that cluster headache medications work on different systems as shown.

CGRP = calcitonin gene-related peptide; VIP = vasoactive intestinal peptide.

The trigeminovascular system is the pain component of TACs and starts with the ophthalmic or V1 branch of the trigeminal nerve, which receives inputs from the forehead, eye, dura, and large cranial vessels. The ophthalmic branch projects to several nociceptive nuclei in the brainstem and upper cervical cord (together these nuclei are known as the trigeminocervical complex, which includes the occipital nerve), then to the thalamus, and finally to the pain neuromatrix (a collection of brain areas that modulate many types of pain). Functional MRI (fMRI) and anatomic MRI studies have shown changes in the pain neuromatrix in patients with cluster headache.[15] Interestingly, rare cases of secondary cluster headache have been reported from meningiomas, carotid dissections, and venous sinus thromboses, which are all inputs to the trigeminovascular system.[16,17] The trigeminovascular system has several

signaling molecules including calcitonin gene-related peptide (CGRP), which is elevated during a cluster attack.[7]

The autonomic system is responsible for lacrimation, conjunctival injection, and other cranial autonomic features. Most of these features involve either parasympathetic overactivation or sympathetic inactivation. The autonomic areas in TACs include a pathway from the superior salivatory nucleus to the sphenopalatine ganglion. By placing an electrode over the sphenopalatine ganglion in patients with cluster headache, a cluster attack can be triggered or aborted by changing the stimulation parameters.[18] The autonomic system has several signaling molecules, including vasoactive intestinal peptide, which is elevated during a cluster attack.[7]

The hypothalamus may explain many of the other clinical features of the TACs, and research suggests a large role for the hypothalamus in all the TACs. The hypothalamus includes the circadian system and aggression areas, which may explain the clocklike regularity of cluster headache and the restlessness seen in patients with TACs. Positron emission tomography (PET) has shown activation of the posterior hypothalamus at the beginning of a cluster attack that was triggered by nitroglycerin.[19] Activation of the hypothalamus has also been seen in functional imaging of paroxysmal hemicrania, hemicrania continua, and SUNCT/SUNA. Molecules modulated by the hypothalamus, such as melatonin, are altered in patients with cluster headache.[8] Ultimately, the hypothalamus appears to be the first area activated during a cluster attack, followed by trigeminovascular and autonomic activation.

A possible genetic basis also exists for these disorders; familial cases are rare but have been reported for all the TACs. A genome-wide screen of 259 patients with cluster headache and 267 controls failed to find any individual genes, and the conclusion was that the genetics of cluster headache is complex.[20] Similar to migraine, multiple susceptibility genes likely exist for the TACs.

KEY POINTS

- Functional imaging has shown activation of the posterior hypothalamus at the onset of a cluster headache attack.
- Cluster headache is 3 times more common in men, with a typical age of onset between 20 and 40 years of age. The two forms of cluster headache are an episodic version, where patients have a headache-free period of more than 3 months, and a chronic version, where the headache-free period is less than 3 months.
- The pain in cluster headache is excruciating, anecdotally worse than migraine, childbirth, or kidney stones.

CLUSTER HEADACHE

Cluster headache is a unilateral headache syndrome with ipsilateral cranial autonomic features and/or restlessness and is intensely unpleasant, with pain that is anecdotally worse than migraine, childbirth, or kidney stones. It is unusually responsive to oxygen.

Epidemiology

Cluster headache is 3 times more common in men, with a typical age of onset between 20 and 40 years of age. The two forms of cluster headache are an episodic version, where patients have a headache-free period of more than 3 months, and a chronic version, where the headache-free period is less than 3 months. Most (90%) patients with cluster headache have the episodic version, although up to 33% of patients can change from episodic to chronic and vice versa.[21] Data on the natural history of cluster headache are limited, but patients with longer headache cycles and shorter headache-free periods seem more likely to progress to chronic cluster headache.

Clinical Features

The criteria for cluster headache are shown in TABLE 9-2.[6] Cluster headache is characterized by unilateral pain with ipsilateral cranial autonomic features and/or restlessness, with an individual attack lasting 15 to 180 minutes and

occurring up to 8 times per day.[6] Typically, patients have one to three attacks per day lasting 45 to 90 minutes. In the episodic version, patients typically have one to two headache cycles per year, with each headache cycle usually lasting 6 to 12 weeks. These episodic headache cycles often start and end with milder and less frequent headaches, as if the disease is ramping up and backing down.

In addition to the defined criteria, several other features are very common in patients with cluster headache and can aid in the diagnosis. First, an abrupt onset to a cluster headache attack occurs, and pain escalates to maximal intensity over 5 to 15 minutes; a similarly abrupt cessation to an attack occurs. Second, many patients can trigger a cluster attack within 1 to 2 hours of drinking alcohol or, as one patient put it, "before I finish my glass of wine." Other triggers include nitroglycerin, heat/exercise, high altitude (such as plane flights), and strong smells like solvents and cigarette smoke. Interestingly, the triggers have no effect during the headache-free period. Third, most patients will receive substantial but short-lasting relief from subcutaneous sumatriptan and high-flow oxygen;

TABLE 9-2 ***ICHD-3* Diagnostic Criteria for Cluster Headache[a]**

Cluster Headache

- **A** **At least five attacks fulfilling criteria B–D**
- **B** **Severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15–180 minutes (when untreated)**
- **C** **Either or both of the following**:
  - **1** At least one of the following symptoms or signs, ipsilateral to the headache:
    - **a** Conjunctival injection and/or lacrimation
    - **b** Nasal congestion and/or rhinorrhea
    - **c** Eyelid edema
    - **d** Forehead and facial sweating
    - **e** Miosis and/or ptosis
  - **2** A sense of restlessness or agitation
- **D** **Occurring with a frequency between one every other day and eight per day[b]**
- **E** **Not better accounted for by another *ICHD-3* diagnosis**

Episodic Cluster Headache

- **A** **Attacks fulfilling criteria for cluster headache and occurring in bouts (cluster periods)**
- **B** **At least two cluster periods lasting from 7 days to 1 year (when untreated) and separated by pain-free remission periods of ≥3 months**

Chronic Cluster Headache

- **A** **Attacks fulfilling criteria for cluster headache and criterion B below**
- **B** **Occurring without a remission period, or with remissions lasting <3 months, for at least 1 year**

ICHD-3 = International Classification of Headache Disorders, Third Edition.

[a] Reprinted with permission from Headache Classification Committee of the International Headache Society, Cephalalgia.[6] © 2018 International Headache Society.

[b] During part but less than half of the active time course of cluster headache, attacks may be less frequent.

however, if these are not effective, an indomethacin trial may be considered to rule out other TACs.

The most peculiar feature of cluster headache, however, may be its clocklike regularity. A circadian pattern is seen with cluster headaches, with most patients having headaches at defined times of the night. In episodic cluster headache, a circannual pattern is also seen, with most patients having headaches every year or every other year in spring and autumn. For example, a patient may report getting a headache every day in April at 2:00 AM, then may report the headache resolving for 2 years, only to return the next April at 2:00 AM. Circadian patterns are present in 82% of patients with cluster headache[1] but are quite rare in the other TACs.

Differential Diagnosis and Workup

Despite the well-defined criteria, a diagnostic delay of several years may be seen for cluster headache as many patients are referred back and forth between primary care physicians, dentists, ophthalmologists, otolaryngologists, and other specialists.[22] In this author's personal experience, patients are often told they have sinus headache, perhaps because the headache cycles occur in the spring and fall, are associated with nasal congestion and rhinorrhea, and improve temporarily with antibiotics and a steroid pack (in reality, it is the steroids that are treating cluster headache).

The differential diagnosis of cluster headache includes primary and secondary headache disorders (TABLE 9-3). An indomethacin trial is often warranted to rule out hemicrania continua and paroxysmal hemicrania: approximately one-third of patients with cluster headache have interictal dull pain that mimics hemicrania continua, and an individual cluster attack (15 to 180 minutes) overlaps in duration with a paroxysmal hemicrania attack (2 to 30 minutes). Cluster headache can also be misdiagnosed as migraine, as typical "migrainous features" such as photophobia, phonophobia, facial allodynia, and nausea are seen in up to 50% of patients with cluster headache.[2,23] Patients with cluster headache have also been reported to have auras and premonitory symptoms. Likewise, more than 50% of patients with migraine have cranial autonomic symptoms.[24] The misdiagnosis as migraine seems to occur more frequently in women, as migraine is more common in women, whereas cluster headache is more common in men. Cluster headache is best differentiated from migraine based on shorter duration (fewer than 4 hours), higher frequency (can have more than 1 per day), rapid escalation (reaches peak pain within minutes), and restlessness during the headache.

Given the differential diagnosis, the recommended workup for all patients with cluster headache according to a European Headache Federation consensus includes a brain MRI with dedicated views of the pituitary and cavernous sinus.[25] A magnetic resonance angiogram (MRA) of the head and neck can also be considered, especially if patients fail to respond to typical preventive medications such as verapamil. In some patients, an erythrocyte sedimentation rate for temporal arteritis or referral to ophthalmology, dentistry, or otolaryngology may be appropriate. For patients refractory to treatment, a sleep study and pituitary laboratory studies should be considered. Some patients have reported improvement in their headaches with continuous positive airway pressure (CPAP) for sleep apnea, testosterone treatment for low testosterone, or dopamine agonists for pituitary tumors.[16,17,26]

KEY POINTS

- Cluster headache has well-defined criteria. Other features that are common in cluster headache include rapid escalation and de-escalation of pain, alcohol as a trigger during the headache period (but not during the remission period), a positive response to subcutaneous sumatriptan, a positive response to high-flow oxygen, and a clocklike daily pattern of headaches.
- Cluster headache may include short frequent headaches (mimicking paroxysmal hemicrania) or a mild interictal headache (mimicking hemicrania continua). An indomethacin trial is warranted in these situations.
- Patients with cluster headache may have migrainous features such as photophobia, phonophobia, and nausea. Patients with migraine likewise may have cranial autonomic symptoms.
- The differential diagnosis between cluster headache and migraine can often be made based on the duration, frequency, and associated factors such as restlessness.

TABLE 9-3

Differential Diagnosis of Cluster Headache

Primary Headaches Mimicking Cluster Headache

- **Migraine**
- **Hemicrania continua**
- **Paroxysmal hemicrania**
- **Hypnic headache**

Secondary Headaches Mimicking Cluster Headache

- **Acute-angle glaucoma**
- **Impacted molar tooth**
- **Maxillary sinusitis**
- **Tolosa-Hunt syndrome**
- **Paratrigeminal (Raeder) neuralgia**
- **Temporal arteritis**
- **Trigeminal neuralgia**

Causes of Symptomatic Cluster Headache[a]

- **Neoplastic**
  - Pituitary tumors
  - Meningiomas[b]
  - Glioblastoma
- **Vascular**
  - Carotid or vertebral artery dissection
  - Cerebral arteriovenous malformations
  - Stroke (in setting of moyamoya disease)
  - Subclavian steal syndrome
- **Infectious**
  - Sinusitis
- **Other**
  - Obstructive sleep apnea

[a] Data for symptomatic cluster headaches shown here are from systematic reviews.[16,17] Other symptomatic cluster headaches mentioned in the literature include nasopharyngeal hemangiomas, epidermoid tumors, cavernous hemangiomas, cerebral aneurysms, subdural hematomas, cerebral venous sinus thrombosis, cervical cord and medullary infarcts, and herpes zoster ophthalmicus.

[b] Meningiomas in multiple locations between the cavernous sinus and the upper cervical region have been documented in case reports as causes of secondary cluster headache that resolved with surgical excision.

Management

Treatment for cluster headache includes a combination of acute, transitional, and preventive medications (TABLE 9-4).[27,28] Transitional medications refer to preventive medications that can be uptitrated quickly and used for short periods of time and are most useful in two situations: (1) as the lone preventive for patients with short headache cycles, and (2) as a bridge in patients with longer headache cycles while uptitrating other preventives. In addition to medications, lifestyle changes are recommended in patients with cluster headache, in particular the avoidance of known triggers such as alcohol. Therapies such as acupuncture and chiropractic have not shown benefit.

ACUTE MEDICATIONS. The mainstays of acute treatment of patients with cluster headache are high-flow oxygen and triptans, in particular sumatriptan and zolmitriptan. Oxygen should be administered at 100% via a nonrebreather mask at a rate of 12 L/min to 15 L/min for at least 20 minutes and trialed several times before being considered ineffective. Patients can later titrate the oxygen to find the minimum effective rate. For triptans, quicker routes of administration are preferred, with subcutaneous triptans being the most effective, followed by nasal and then oral formulations.

Recently, noninvasive vagus nerve stimulation has been approved by the US Food and Drug Administration (FDA) for acute prevention of episodic cluster headache. Unfortunately, the currently approved device did not show a clear benefit in chronic cluster headache.[29] Oxygen and noninvasive vagus nerve stimulation can be used safely multiple times per day and are good options for patients who have multiple attacks per day or who are limited in the number of triptan doses per month. In patients who are pregnant or breast-feeding, oxygen and nasal lidocaine are reasonable first-line acute treatments.[30]

TRANSITIONAL MEDICATIONS. The mainstays of short-term prophylaxis are greater occipital nerve blocks (with local anesthetic plus steroids) or a course of oral steroids. The most effective formulations are unknown; multiple types and doses of steroids have been used for greater occipital nerve blocks and for oral steroids.[31] For oral steroids, a taper over 3 weeks is generally recommended because of the risk of osteonecrosis of the hip, especially with prolonged steroid use. The use of steroids should also be limited to 2 to 3 courses per year. Steroids are ideal for patients with brief headache cycles or when uptitrating medications such as verapamil.

PREVENTIVE MEDICATIONS. The drug of choice for cluster headache prevention is verapamil. A typical total daily maintenance dose is generally 480 mg to 720 mg divided into 3 doses. Although data are limited, the immediate-release formulation is generally preferred. Cardiac conduction abnormalities are a feared consequence of high doses of verapamil, usually caused by lengthening the PR interval. A pretreatment ECG and a consideration of ECGs after dose increases is recommended in a survey of cardiologists.[32] A proposed schedule is ECG monitoring before initiation, 10 to 14 days after each dose change, and every 6 months thereafter while on the medication.[33]

Second-line medications for cluster headache include topiramate and lithium. Melatonin has been shown to be helpful and is often used as an adjunct preventive. Other medications with data supporting use as a second- or third-line treatment of cluster headache include baclofen and valproic acid. For episodic

KEY POINTS

- When using triptans to treat cluster headache, quicker routes are better: subcutaneous is more effective than nasal, which is more effective than oral.
- For the acute treatment of cluster headache, oxygen and noninvasive vagus nerve stimulation are good options for patients with multiple attacks per day.

TABLE 9-4 Treatment of Cluster Headache[a]

	American Headache Society Recommendations[27]	European Federation of Neurological Societies Recommendations[28]
Acute		
Oxygen (high flow)	Level A	Level A
Sumatriptan subcutaneous	Level A	Level A
Sumatriptan nasal	Level B	Level A
Sumatriptan oral		
Zolmitriptan nasal	Level A	Level A/level B
Zolmitriptan oral	Level B	Level B
Octreotide subcutaneous	Level C	Level B
Lidocaine nasal	Level C	Level B
Noninvasive vagus nerve stimulation		
Transitional		
Ipsilateral greater occipital nerve block	Level A	
Oral steroids	Level U	Level A
Ergotamine tartrate		Level B
Preventive		
Verapamil	Level C	Level A
Lithium	Level C	Level B
Melatonin	Level C	Level C
Topiramate		Level B
Baclofen		Level C
Valproic acid	Unfavorable[b]	Level C
Refractory		
Sphenopalatine ganglion stimulation	Level B	
Occipital nerve stimulation		
Hypothalamic deep brain stimulation	Unfavorable[b]	

Level A = established as effective; level B = probably effective; level C = possibly effective; level U = data inadequate.
[a] Blank entries indicate that no specific recommendation is provided.
[b] Valproic acid and hypothalamic deep brain stimulation are probably ineffective according to American Headache Society guidelines (level B negative rating).

cluster headache, preventives should be uptitrated early in the headache cycle to an effective dose, using transitional medications if needed. When the patient is headache free for about 2 weeks and is presumably out of their headache cycle, the preventive medication can be downtitrated and discontinued.

REFRACTORY PATIENTS. When extensive medication trials are unsuccessful, a sleep study and pituitary laboratory studies should be considered, as discussed above. For patients who are refractory to treatments, more invasive procedures can be considered. Neuromodulation is generally the preferred technique as it is minimally destructive. Sphenopalatine ganglion stimulation, occipital nerve stimulation, and deep brain stimulation of the hypothalamus have all been proposed as invasive neuromodulation treatments for cluster headache. Patient selection for these procedures is key, and considerations for their use include 2 years of daily or almost daily attacks, extensive medication trials, management by a single provider over at least 1 year, and a psychological evaluation.[34] Current American Headache Society guidelines support the use of sphenopalatine ganglion stimulation (level B evidence: probably effective) but are unfavorable toward deep brain stimulation (level B evidence: probably ineffective).[27] The guidelines also note that not enough studies of occipital nerve stimulation have been performed, but the existing data suggest a benefit. Sphenopalatine ganglion stimulation is available in Europe but not in the United States, although trials have been performed and are awaiting FDA review.

Some of the neuromodulation devices mentioned here are MRI-compatible while others are not. If MRIs are anticipated in the future, this point should be discussed with the implanting surgeon.

KEY POINT

- **Unlike cluster headache, paroxysmal hemicrania has shorter and more frequent attacks, has a slight female predominance, is more likely to be chronic, is less likely to be circadian, can be triggered by neck movements, and responds completely to indomethacin.**

PAROXYSMAL HEMICRANIA

Paroxysmal hemicrania shares many features with cluster headache but is slightly shorter in the duration of attacks. In contrast to cluster headache, it is completely responsive to indomethacin.

Epidemiology and Clinical Features

Paroxysmal hemicrania is less prevalent than cluster headache and is found at a rate of 0.5 per 1000 or less, with onset between 30 and 40 years of age. Unlike cluster headache, this disease may be slightly more common in women, and the chronic version is present in 80% of patients.[3] The criteria for paroxysmal hemicrania (TABLE 9-5) include a headache duration of 2 to 30 minutes and a frequency of greater than five attacks per day for half of the time the disease is active. In one study, the average duration was 26 minutes, and the average frequency was six per day,[35] but up to 50 attacks per day have been reported.

The pain is generally sharp, stabbing, or throbbing and is located in the orbital, supraorbital, and temporal areas. Like cluster headache, the time to peak pain is rapid, usually fewer than 10 minutes, and the headaches are associated with cranial autonomic features, with lacrimation being the most common. Migrainous features are also common during the headaches, and patients can have interictal milder headaches. Unlike in cluster headache, restlessness is less common, and the headaches are rarely circadian. Paroxysmal hemicrania attacks can be triggered by alcohol, neck movements, or pressure over the neck or greater occipital nerves.

Management, Differential Diagnosis, and Workup

Management begins with an indomethacin trial, and patients with paroxysmal hemicrania should have a complete response to indomethacin. Most patients respond to an oral total daily dose between 75 mg and 225 mg[6] and often respond to their effective dose within 24 hours. One proposed indomethacin titration schedule in hemicrania continua, which is likely to be effective in paroxysmal hemicrania as well, is to uptitrate from 25 mg 3 times a day to 75 mg 3 times a day over 1 to 2 weeks, then to stay at 75 mg 3 times a day for another 1 to 2 weeks.[36] A gastroprotective agent such as a histamine receptor 2 antagonist (H2 blocker) or a proton pump inhibitor is advised during the trial to prevent gastrointestinal symptoms. Unfortunately, a substantial number of patients may experience adverse effects of indomethacin, most commonly nausea, dyspepsia, diarrhea, or constipation.[37] Like other nonsteroidal anti-inflammatory medications, a risk of gastrointestinal ulcers, cardiovascular events, kidney toxicity, and increased

TABLE 9-5 *ICHD-3* Diagnostic Criteria for Paroxysmal Hemicrania[a]

Paroxysmal Hemicrania

- **A** **At least 20 attacks fulfilling criteria B–E**
- **B** **Severe unilateral orbital, supraorbital, and/or temporal pain lasting 2–30 minutes**
- **C** **Either or both of the following:**
  - **1** At least one of the following symptoms or signs, ipsilateral to the headache:
    - **a** Conjunctival injection and/or lacrimation
    - **b** Nasal congestion and/or rhinorrhea
    - **c** Eyelid edema
    - **d** Forehead and facial sweating
    - **e** Miosis and/or ptosis
  - **2** A sense of restlessness or agitation
- **D** **Occurring with a frequency of ≥5 per day[b]**
- **E** **Prevented absolutely by therapeutic doses of indomethacin**
- **F** **Not better accounted for by another *ICHD-3* diagnosis**

Episodic Paroxysmal Hemicrania

- **A** **Attacks fulfilling criteria for paroxysmal hemicrania and occurring in bouts**
- **B** **At least two bouts lasting from 7 days to 1 year (when untreated) and separated by pain-free remission periods of ≥3 months**

Chronic Paroxysmal Hemicrania

- **A** **Attacks fulfilling criteria for paroxysmal hemicrania and criterion B below**
- **B** **Occurring without a remission period, or with remissions lasting <3 months, for at least 1 year**

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[b] During part but less than half of the active time course of paroxysmal hemicrania, attacks may be less frequent.

bleeding exists. Indomethacin can also be a source of headaches in rare cases, and patients may report a new headache type after starting the medication.[38] Once the patient's headaches improve, a reduction in the dosage is suggested to find the minimal effective dose, which is often less than a total daily dose of 100 mg.[39] Indomethacin should be titrated off after the expected remission period in episodic paroxysmal hemicrania. For chronic paroxysmal hemicrania, periodic downtitrations of indomethacin can be considered but, unfortunately, guidance is limited; little data exist on the rate at which chronic paroxysmal hemicrania resolves or the rate at which it converts to episodic. In women of childbearing age, consider stopping indomethacin before pregnancy is planned.[40]

Indomethacin's mechanism in paroxysmal hemicrania is unknown. It is an acetic acid derivative similar to diclofenac, but it does have several properties that set it apart from other cyclooxygenase inhibitors. Indomethacin demonstrates increased absorption through the blood-brain barrier compared to other cyclooxygenase inhibitors. It also has effects on hypothalamic and autonomic nuclei, causes a reduction in intracranial pressure, and possesses a unique effect on nitric oxide.[37]

Paroxysmal hemicrania attacks are generally too brief for acute medications, thus management is focused on prevention. For patients who cannot tolerate indomethacin, several other medications have been proposed including cyclooxygenase type 2 inhibitors, verapamil, and topiramate. Sphenopalatine ganglion and greater occipital nerve blocks have also been helpful in case reports.[41] If indomethacin is ineffective, other diseases should be considered. Paroxysmal hemicrania has significant overlap with cluster headache (CASE 9-1) and thus the differential diagnosis is similar, but the differential also includes more short-lived unilateral facial pains such as dental pain, trigeminal neuralgia, and primary stabbing headache. Symptomatic cases of pituitary adenomas causing paroxysmal hemicrania have been reported.[17] Because of this differential diagnosis, the recommended workup for paroxysmal hemicrania according to the European Headache Federation consensus is a brain MRI and arterial imaging of the head and neck.[25]

KEY POINT

- **Indomethacin is not always well tolerated. A gastroprotective medication should be considered. In addition, indomethacin should be downtitrated to find the minimal effective dose, which is often less than a total daily dose of 100 mg.**

SUNCT AND SUNA

SUNCT and SUNA share many features with the other TACs and with trigeminal neuralgia. They are characterized by brief attacks of unilateral pain with autonomic features: SUNCT has both conjunctival injection and lacrimation, and SUNA has one or neither.

Epidemiology and Clinical Features

SUNCT and SUNA, which are similar disorders in terms of clinical features and treatments, have a prevalence of 0.05 to 1 in 1000. Onset is at 40 to 70 years of age, older than other TACs. These headaches are slightly more common in men. SUNCT and SUNA have identical diagnostic criteria with one exception: SUNCT always has the presence of both conjunctival injection and lacrimation, whereas SUNA may have one or neither of these features (TABLE 9-6). Both episodic and chronic versions of these diseases may be seen. Individual attacks are brief (1 to 600 seconds) and must occur once a day but usually occur much more frequently, up to hundreds of times per day. Attacks can occur as a single attack or a series of attacks with no interictal pain, or they can occur in a sawtooth pattern with a background pain lasting minutes that is punctuated by stabs on top. Attacks typically last 1 minute with an average of 59 attacks per day.[4] The pain is maximal in 2 to 3 seconds and is stabbing, sharp, or throbbing. Triggers are

prominent in SUNCT and SUNA, especially tactile stimuli; touching the area of pain, chewing, or brushing the teeth may provoke an attack.

Management, Differential Diagnosis, and Workup

The mainstay of treatment is lamotrigine, which is usually titrated to a total daily dose between 100 mg and 200 mg. Proposed second-line treatments include topiramate or gabapentin. Some providers have also suggested carbamazepine, oxcarbazepine, or duloxetine.[42] Short-term relief can often be obtained with steroids. The most effective medication, however, may be IV lidocaine at a rate of 1 mg/kg/h to 3.5 mg/kg/h.[43] Typical protocols include a 1-week admission by experienced providers with continuous telemetry, and the use of IV lidocaine is contraindicated in patients with cardiac conduction abnormalities. While most patients receive temporary relief with IV lidocaine, a substantial subset of patients with SUNCT and SUNA have received prolonged relief for several months.[43]

The differential diagnosis for SUNCT and SUNA is similar to that for paroxysmal hemicrania. The sawtooth pattern of SUNCT and SUNA, which can

CASE 9-1

A 33-year-old woman with a past history of infrequent tension-type headaches presented for evaluation of a new type of headache that had been occurring for 3 years. She reported extreme pain of the right eye, which lasted approximately 30 minutes and occurred 1 to 5 times per day. The pain had never occurred on the left side. During a headache, her right eye became watery, bloodshot, and sensitive to light. The skin around the right eye felt swollen and hot, and she sat alone and rocked back and forth. One of the headaches invariably occurred at 2:00 AM and woke her up from sleep. These headaches occurred every day for 6 weeks in September and October, then she had only the occasional tension headache until the following September, when the right-sided headaches resumed at 2:00 AM. She had tried naproxen, ibuprofen, and acetaminophen without relief, and hydrocodone "took the edge off a little."

COMMENT

This is a presentation of an as yet undifferentiated trigeminal autonomic cephalalgia. This patient meets most criteria for both cluster headache and paroxysmal hemicrania, as these two conditions overlap in the duration and frequency of the headache attacks. Statistically, female sex makes her more likely to have paroxysmal hemicrania, while the circadian pattern and restlessness are more likely to be cluster headache. An indomethacin trial is warranted in this patient. If ineffective, the patient should be treated for cluster headache.

Patients with trigeminal autonomic cephalalgias can have migrainous features such as photophobia, but they tend to be only ipsilateral to the pain. The restlessness in this patient may not be immediately obvious; while most patients with restlessness will pace or move about the room, some patients will give a history of staying in one place but continuously rocking or moving.

last for several minutes, may be confused with paroxysmal hemicrania or cluster headache. Primary stabbing headache is also on the differential, although primary stabbing headaches lack autonomic features, and the location of pain often changes in subsequent attacks. Trigeminal neuralgia, however, is the most commonly confused disorder for SUNCT and SUNA. Trigeminal neuralgia is also characterized by multiple daily attacks of sharp, unilateral, brief pain in a trigeminal distribution that can be triggered by tactile stimuli. Trigeminal neuralgia is also treated with carbamazepine, oxcarbazepine, and lamotrigine. Trigeminal neuralgia, however, lacks the prominent cranial autonomic features of SUNCT and SUNA. Furthermore, trigeminal neuralgia typically has a refractory period after an attack is triggered where no more attacks can be triggered by tactile stimuli for a brief time. SUNCT and SUNA typically do not have a refractory period.

Symptomatic cases of SUNCT and SUNA have been reported, especially pituitary tumors and posterior fossa tumors. Recommended workup includes MRI brain and arterial imaging of the head and neck.[25] A dedicated view of the trigeminal nerve can also be considered.

HEMICRANIA CONTINUA

Hemicrania continua shares many features with the other TACs and with migraine. Hemicrania continua is characterized by continuous unilateral pain as well as pain flares with autonomic features. It is completely responsive to indomethacin.

Epidemiology and Clinical Features

Only a few hundred cases of hemicrania continua have been reported in the literature and thus the true prevalence is unknown, but hemicrania continua was found in 0.8% of patients who presented with daily headaches.[44] Based on small studies, it appears to be more common in women. The two types of hemicrania continua (TABLE 9-7) are the remitting and unremitting subtypes, with the unremitting subtype appearing to be more common.[5]

Hemicrania continua is characterized by unilateral frontal or temporal pain that is usually sharp or throbbing in nature. Many patients have commented on a foreign body sensation or itching of the affected eye. A baseline persistent headache is present that is usually mild or moderate in intensity and may have few if any autonomic features. The disease is punctuated by headache flares lasting minutes to days that are associated with an increase in ipsilateral cranial autonomic features as well as the presence of nausea, photophobia, or phonophobia. In comparison with other TACs, hemicrania continua has less prominent cranial autonomic features and more prominent migrainous features. Triggers for flares include stress, alcohol, and irregular sleep.[5]

Management, Differential Diagnosis, and Workup

Management starts with an indomethacin trial and, by definition, patients with hemicrania continua should have a dramatic response. Indomethacin treatment is the same as that mentioned above for paroxysmal hemicrania, with a trial up to 75 mg 3 times a day for 1 to 2 weeks, the use of gastroprotective agents, and the downtitration to a minimum effective dose that is usually less than a total daily dose of 100 mg.[39] Remissions have been reported in hemicrania continua, and a withdrawal of indomethacin should be considered every 6 months. If the symptoms are to return, they will generally reappear 12 hours to 2 weeks after indomethacin is stopped.[45]

KEY POINTS

- In comparison to short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms, trigeminal neuralgia does not have prominent cranial autonomic features, and has a refractory period for tactile stimuli.
- Hemicrania continua has more prominent migrainous features and less prominent cranial autonomic features than other trigeminal autonomic cephalalgias.
- Patients with hemicrania continua on indomethacin should be gradually downtitrated approximately every 6 months, as remissions have been reported for hemicrania continua.

TABLE 9-6 *ICHD-3* Diagnostic Criteria for SUNCT and SUNA[a]

Short-lasting Unilateral Neuralgiform Headache Attacks

- **A** At least 20 attacks fulfilling criteria B–D
- **B** Moderate or severe unilateral head pain with orbital, supraorbital, temporal, and/or other trigeminal distribution, lasting for 1–600 seconds and occurring as single stabs, series of stabs, or in a sawtooth pattern
- **C** At least one of the following five cranial autonomic symptoms or signs, ipsilateral to the pain:
  - **1** Conjunctival injection and/or lacrimation
  - **2** Nasal congestion and/or rhinorrhea
  - **3** Eyelid edema
  - **4** Forehead and facial sweating
  - **5** Miosis and/or ptosis
- **D** Occurring with a frequency of at least one a day[b]
- **E** Not better accounted for by another *ICHD-3* diagnosis

Short-lasting Unilateral Neuralgiform Headache Attacks With Conjunctival Injection and Tearing (SUNCT)

- **A** Attacks fulfilling criteria for short-lasting unilateral neuralgiform headache attacks and criterion B below
- **B** Both of the following, ipsilateral to the pain:
  - **1** Conjunctival injection
  - **2** Lacrimation (tearing)

Episodic SUNCT

- **A** Attacks fulfilling criteria for SUNCT and occurring in bouts
- **B** At least two bouts lasting from 7 days to 1 year (when untreated) and separated by pain-free remission periods of ≥3 months

Chronic SUNCT

- **A** Attacks fulfilling criteria for SUNCT and criterion B below
- **B** Occurring without a remission period, or with remissions lasting <3 months, for at least 1 year

Short-lasting Unilateral Neuralgiform Headache Attacks With Cranial Autonomic Symptoms (SUNA)

- **A** Attacks fulfilling criteria for short-lasting unilateral neuralgiform headache attacks and criterion B below
- **B** Not more than one of the following, ipsilateral to the pain:
  - **1** Conjunctival injection
  - **2** Lacrimation (tearing)

CONTINUED ON PAGE 1153

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Episodic SUNA

A **Attacks fulfilling criteria for SUNA and occurring in bouts**

B **At least two bouts lasting from 7 days to 1 year (when untreated) and separated by pain-free remission periods of ≥3 months**

Chronic SUNA

A **Attacks fulfilling criteria for SUNA and criterion B below**

B **Occurring without a remission period, or with remissions lasting <3 months, for at least 1 year**

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[b] During part but less than half of the active time course of short-lasting unilateral neuralgiform headache attacks, attacks may be less frequent.

ICHD-3 Diagnostic Criteria for Hemicrania Continua[a]

TABLE 9-7

Hemicrania Continua

A **Unilateral headache fulfilling criteria B–D**

B **Present for >3 months, with exacerbations of moderate or greater intensity**

C **Either or both of the following:**

1 At least one of the following symptoms or signs, ipsilateral to the headache:

a Conjunctival injection and/or lacrimation

b Nasal congestion and/or rhinorrhea

c Eyelid edema

d Forehead and facial sweating

e Miosis and/or ptosis

2 A sense of restlessness or agitation, or aggravation of the pain by movement

D **Responds absolutely to therapeutic doses of indomethacin**

E **Not better accounted for by another *ICHD-3* diagnosis**

Hemicrania Continua, Remitting Subtype

A **Headache fulfilling criteria for hemicrania continua and criterion B below**

B **Headache is not daily or continuous, but interrupted (without treatment) by remission periods of ≥24 hours**

Hemicrania Continua, Unremitting Subtype

A **Headache fulfilling criteria for hemicrania continua and criterion B below**

B **Headache is daily and continuous for at least 1 year, without remission periods of ≥24 hours**

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For patients who cannot tolerate indomethacin, several other medications have been proposed including other cyclooxygenase inhibitors (ibuprofen, celecoxib), melatonin, gabapentin, verapamil, and topiramate. Some patients have had positive responses to greater occipital nerve blocks, onabotulinum toxin injections, and occipital nerve stimulation.[41]

Should indomethacin result in anything less than a dramatic improvement in the headaches, other diseases should be considered. The differential diagnosis includes other causes of chronic daily headache, and a full discussion is beyond the scope of this review.[46] It is worth noting, however, that a hemicrania continua flare may be indistinguishable from chronic migraine, as they both can be throbbing unilateral pain lasting up to several days with nausea, photophobia, phonophobia, and some autonomic features. Thus, if a patient presents with migrainous strictly unilateral headaches and a continuous unilateral background headache, an indomethacin trial should be considered.

Symptomatic causes of hemicrania continua include cerebral venous sinus thrombosis and brain metastases.[16] The recommended workup for hemicrania continua includes a brain MRI and arterial imaging of the head and neck such as an MRA to assess for structural causes of chronic daily headache.[25] Venous imaging such as a magnetic resonance venogram (MRV) may also be considered if a suspicion exists for venous sinus thrombosis, and an erythrocyte sedimentation rate should be performed if there is a suspicion for temporal arteritis (CASE 9-2).

CASE 9-2

A 40-year-old woman presented for evaluation of headaches that had been occurring intermittently for 8 years and were described as left-sided throbbing headaches associated with sensitivity to light and noise, nausea, nasal congestion, and watering of the left eye. She had approximately two headaches per month, each lasting about 24 hours. Between the headaches she had a moderate amount of pain on the left side but did not have any of the associated features. The constant pain, however, was interfering with her daily life. She had tried ibuprofen, sumatriptan, rizatriptan, propranolol, and venlafaxine without relief. She could not recall the last time she was completely headache free. She also could not recall the headaches ever occurring on the right side.

Brain MRI, magnetic resonance angiogram (MRA) of the head and neck, and magnetic resonance venogram (MRV) of the brain were unremarkable. Indomethacin was started. Within 24 hours of increasing the dose to 50 mg 3 times a day, she was headache free for the first time in 8 years.

COMMENT

This patient meets criteria for hemicrania continua. Hemicrania continua typically has exacerbations of pain with both migrainous and cranial autonomic features. Clues to the diagnosis of hemicrania continua are the constant unilateral headache and the lack of effectiveness of typical migraine treatments. For patients with continuous side-locked headaches, imaging should be performed. Should the side-locked headaches have migrainous and cranial autonomic features and if imaging is negative, an indomethacin trial should be considered.

CONCLUSION

The TACs have similar clinical features and likely a similar pathophysiology but differ in timing and treatment. Familiarity with the diagnostic criteria is key, as patients may experience a delay of years before the correct diagnosis is made.

KEY POINT

- **If indomethacin is not effective after a solid 1- to 2-week course at 75 mg 3 times a day, the diagnosis of hemicrania continua or paroxysmal hemicrania should be reconsidered.**

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Cranial Neuralgias

By Stewart J. Tepper, MD, FAHS

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

ABSTRACT

PURPOSE OF REVIEW: This article describes the clinical features and diagnostic criteria, pathophysiology (when known), and treatment strategies of the major cranial neuralgias.

RECENT FINDINGS: Abnormal vascular loops compressing cranial nerves are the most common known pathogenesis associated with the primary neuralgias.

SUMMARY: The most frequently encountered primary neuralgias are trigeminal neuralgia, occipital neuralgia, and, rarely, glossopharyngeal neuralgia. Nervus intermedius neuralgia is even more rare. All neuralgias merit a careful workup for secondary causes. Drug treatment generally relies on antiepileptic drugs, antidepressants, and baclofen. OnabotulinumtoxinA can be useful in treating some cranial neuralgias. Surgical and invasive treatments include ablation, gamma knife treatment, and microvascular decompression.

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Continued on page 1178

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Tepper discusses the unlabeled/investigational use of all listed medications for the treatment of neuralgias.

INTRODUCTION

Neuralgias of the head constitute a separate chapter in the *International Classification of Headache Disorders, Third Edition* (*ICHD-3*), which lists the major cranial neuralgias discussed in this article. The *ICHD-3* specifies the definition of neuralgia as "pain in the distribution(s) of a nerve or nerves, presumed to be due to dysfunction or injury of those neural structures. Common usage has implied a paroxysmal or lancinating quality, but the term *neuralgia* should not be reserved for paroxysmal pains."[1]

Consideration of the anatomy suggests that afferents for the major cranial nerves of the head (V, VII, IX, and X) are irritated in neuralgias. Occipital neuralgia involves the second cervical nerve root, so cervical components for the back of the head are also listed in this article. The pathology of these cranial neuralgias can be due to almost any type of lesion: compressive, metabolic, or infectious.

A problem of causation exists in naming the cranial and upper cervical neuralgias because many of the traditional neuralgias, such as trigeminal neuralgia, are no longer considered primary, since contributory compressive lesions have subsequently been defined as the most common etiology. Examples are the vascular loop compression found in what was considered primary trigeminal neuralgia and the entrapments demonstrable in occipital neuralgia, both of which are now considered secondary.

The *ICHD-3* addressed the problem as follows:

> For the trigeminal, glossopharyngeal, and intermedius neuralgias, the term classical is reserved for cases where imaging or surgery has revealed

vascular compression of the respective nerve. Strictly speaking, classical neuralgias are secondary (to the neurovascular compression), but it is beneficial to separate them from other causes on the basis of the wider therapeutic options and potentially different nerve pathophysiology.[1]

The *ICHD-3* classifies the secondary trigeminal neuropathies with the term *painful trigeminal neuropathy*, with subsets of herpetic, traumatic, demyelinating, neoplastic, and other (TABLE 10-1).[1]

The optimal approach to a patient presenting with a suspected cranial or upper cervical neuralgia is to assume a secondary cause until proven otherwise. As many as 15% of trigeminal neuralgia cases and painful trigeminal neuropathies are associated with lesions at the cerebellopontine angle, including neoplasms and demyelinating lesions. An epidermoid tumor is the most common tumor associated with trigeminal neuropathic pain, but vestibular schwannomas can present this way as well.[2] Since posterior fossa arteriovenous malformations and mass lesions can also manifest as cranial or cervical neuralgias, an MRI study with and without contrast and a magnetic resonance angiogram (MRA) are both mandatory in the workup of patients with cranial neuralgias.

TABLE 10-1 ***ICHD-3* Classification of Painful Lesions of the Cranial Nerves and Other Facial Pain**[a]

13.1 Pain Attributed to a Lesion or Disease of the Trigeminal Nerve

- **13.1.1 Trigeminal neuralgia**
  - 13.1.1.1 Classical trigeminal neuralgia
    - → 13.1.1.1.1 Classical trigeminal neuralgia, purely paroxysmal
    - → 13.1.1.1.2 Classical trigeminal neuralgia with concomitant continuous pain
- **13.1.2 Painful trigeminal neuropathy**
  - 13.1.2.1 Painful trigeminal neuropathy attributed to herpes zoster
  - 13.1.2.2 Trigeminal postherpetic neuralgia
  - 13.1.2.3 Painful posttraumatic trigeminal neuropathy
  - 13.1.2.4 Painful trigeminal neuropathy attributed to other disorder
  - 13.1.2.5 Idiopathic painful trigeminal neuropathy

13.2 Pain Attributed to a Lesion or Disease of the Glossopharyngeal Nerve

13.3 Pain Attributed to a Lesion or Disease of Nervus Intermedius

- **13.3.1 Nervus intermedius neuralgia**
  - 13.3.1.1 Classical nervus intermedius neuralgia
- **13.3.2 Painful nervus intermedius neuropathy**

13.4 Occipital Neuralgia

ICHD-3 = International Classification of Headache Disorders, Third Edition.

[a] Reprinted with permission from Headache Classification Committee of the International Headache Society, Cephalalgia.[1] © 2018 International Headache Society.

This article describes each of the major cranial and cervical neuralgias, their pathophysiology when known, and treatments, as well as some strategies in proceeding through therapies. The most frequently encountered primary or classical neuralgias are trigeminal neuralgia, occipital neuralgia, and, least common, glossopharyngeal neuralgia. Nervus intermedius neuralgia is even more rare.

As noted, all neuralgias merit a careful workup for secondary causes. Drug treatment generally relies on antiepileptic drugs (AEDs), antidepressants, and baclofen. OnabotulinumtoxinA can be useful to treat some neuralgias. Surgical and invasive treatments include ablation, gamma knife treatment, and microvascular decompression.

KEY POINT

- The *International Classification of Headache Disorders, Third Edition* uses the term classical trigeminal neuralgia for what was previously called primary trigeminal neuralgia.

TRIGEMINAL NEURALGIA

Trigeminal neuralgia is likely to be the most frequently encountered cranial neuralgia for the clinician. Because it is so severe and disabling, precision in diagnosis optimizes treatment planning.

Classification

What neurologists traditionally thought of as trigeminal neuralgia is divided into nine subtypes in the *ICHD-3*. The two divisions are classical trigeminal neuralgia and painful trigeminal neuropathies. As noted in the introduction to this article, classical trigeminal neuralgia was thought to be a primary disorder in the past. Since vascular loops are now thought to account for the majority of the cases, the term *primary* was replaced with *classical*.

The other painful trigeminal neuropathies are also secondary or symptomatic. The secondary causes include acute herpetic, postherpetic, posttraumatic, demyelinating, neoplastic, and other. These trigeminal neuropathies, conventionally thought of as secondary, are now categorized under the specific term *painful trigeminal neuropathies*.[1]

Classical Trigeminal Neuralgia

The *ICHD-3* definition of neuralgia cited at the beginning of the section on trigeminal neuralgia is a very useful place to start in the full understanding of classical trigeminal neuralgia, which is defined as the following:

> A disorder characterized by recurrent unilateral brief electric shock–like pains, abrupt in onset and termination, limited to the distribution of one or more divisions of the trigeminal nerve, and triggered by innocuous stimuli. It may develop without apparent cause or be a result of another diagnosed disorder. Additionally, there may be concomitant continuous pain of moderate intensity within the distribution(s) of the affected nerve division(s).[1]

CLINICAL FEATURES AND EPIDEMIOLOGY. As noted, traditionally, trigeminal neuralgia was described as consisting of lightninglike paroxysmal pains strictly in the distribution of one or more divisions of cranial nerve V. The electric shock–like pains along with wincing during the stabs were severe enough that the appellation tic douloureux was given to the disorder (CASE 10-1).

Classical trigeminal neuralgia is predominantly a geriatric cranial neuralgia. Overall, the prevalence of trigeminal neuralgia in the population is 0.7 per 100,000.[3,4] Trigeminal neuralgia is more common in women, with prevalence

ranging from 0.03% to 0.3%.[5] The *ICHD-3* diagnostic criteria for classical trigeminal neuralgia are listed in TABLE 10-2.

A realization that not all classical trigeminal neuralgia pain is discrete and stabbing led to the subdivision of the disorder into two forms, a purely paroxysmal form, and a form with concomitant persistent interictal facial pain in a trigeminal distribution. The *ICHD-3* divides the classification between the purely paroxysmal form (numbered in the *ICHD-3* as 13.1.1.1.1) and the form with concomitant persistent interictal facial pain in a trigeminal distribution, the distinction made by what is described as persistent background facial pain (numbered as 13.1.1.1.2).[1]

The American Academy of Neurology (AAN)/European Federation of Neurological Societies (EFNS) guidelines on treatment of trigeminal neuralgia were published in 2008.[6,7] The guideline states:

> The presence of trigeminal sensory deficits, bilateral involvement, and abnormal trigeminal reflexes should be considered useful to disclose

CASE 10-1

A 75-year-old woman presented to the office for evaluation of pain. She described 3 months of terrible pain, which was the worst she had ever experienced and was worse than childbirth. The pain was not continuous, but rather paroxysmal, and she stated it was as if someone had put her cheek in an electric socket. She experienced seconds of pain on the cheek, radiating from in front of her ear to her upper lip and to just below her left nostril.

She could trigger the pain by talking, brushing her teeth, and chewing, and even a light wind on the cheek could precipitate these lightninglike pains. She reduced her eating and had lost weight. She avoided kissing her husband and grandchildren. She had volleys of the pains through the day, and she winced dramatically with each stab.

She went to her dentist, who diagnosed temporomandibular joint syndrome and prescribed a night guard, but this did not alleviate her symptoms. When she tried to put the night guard in, this elicited barrages of pains. The dentist said he would consider a left tooth extraction.

Her neurologic examination was normal. She had a normal corneal reflex on the left, both directly and consensually. Although she was reticent to allow the examination, primary sensory modalities on the left appeared normal in the V1 through V3 distributions.

COMMENT

This patient's history is consistent with classical trigeminal neuralgia, with brief lancinating pains strictly limited to a V2 distribution and no pain in between. The severity of the pain, which had caused the patient to stop eating because of the trigger, speaks to the gravity of the clinical situation, and the severity and the wincing explain the use of the term *tic douloureux*.

Workup should involve an MRI of the brain to include careful assessment of the trigeminal nerve and cerebellopontine angle with and without contrast and magnetic resonance angiogram (MRA) to look for a vascular loop, tumor, or other causes of the syndrome. Treatment should begin with oxcarbazepine.

symptomatic trigeminal neuralgia, whereas younger age of onset, involvement of the first division, unresponsiveness to treatment and abnormal trigeminal evoked potentials are not useful in distinguishing symptomatic from classic trigeminal neuralgia.[6,7]

Maarbjerg and colleagues[8] described 158 patients with trigeminal neuralgia prospectively collected at the Danish Headache Center in Copenhagen in a case series in 2014. Of patients screened for trigeminal neuralgia, 208 had classical trigeminal neuralgia, while 28 were classified as symptomatic. The average age of onset was around 53 years of age. They reported a female predominance (60%) and a slight right-sided predominance (56%) in the patients with classical trigeminal neuralgia. In this series, trigeminal neuralgia affected only V1 in just 4% of patients. Location was either V2, V3, or both in 69%. Location is thus a critical piece of information for the diagnosis. Almost all the cases were unilateral, but 3% did have bilateral pain; this is consistent with the literature, suggesting that 1% to 5% of patients experience bilateral pain, but unilateral pain almost always comes years before the pain becomes bilateral.[9] Most patients' syndrome began with paroxysmal pains (87%). The percentage who experienced concomitant persistent pain plus lancinating pain was 49%.

The overall clinical picture was periods of electriclike jabs of pain with periods of remission. The duration of each attack was 10 seconds to 2 minutes, and then a refractory period generally occurred.[8] Duration of attacks or cycles of pain was generally less than 60 minutes at a time, but 40% of patients had more than 10 cycles of paroxysmal pain per day. The number of attacks per day generally was from three to five in 22% of patients to 10 to 50 in 35% of patients,

***ICHD-3* Criteria for Trigeminal Neuralgia and Classical Trigeminal Neuralgia[a]** TABLE 10-2

Trigeminal Neuralgia

A **Recurrent paroxysms of unilateral facial pain in the distribution(s) of one or more divisions of the trigeminal nerve, with no radiation beyond, and fulfilling criteria B and C**

B **Pain has all of the following characteristics:**

1 Lasting from a fraction of a second to 2 minutes

2 Severe intensity

3 Electric shock–like, shooting, stabbing, or sharp in quality

C **Precipitated by innocuous stimuli within the affected trigeminal distribution**

D **Not better accounted for by another *ICHD-3* diagnosis**

Classical Trigeminal Neuralgia

A **Recurrent paroxysms of unilateral facial pain fulfilling criteria for trigeminal neuralgia**

B **Demonstration on MRI or during surgery of neurovascular compression (not simply contact), with morphological changes in the trigeminal nerve root**

ICHD-3 = International Classification of Headache Disorders, Third Edition; MRI = magnetic resonance imaging.

[a] Reprinted with permission from Headache Classification Committee of the International Headache Society, Cephalalgia.[1] © 2018 International Headache Society.

although some patients had fewer and more attacks than these bookends. Fortunately for the patients, 63% had longer times of remission, and 37% had months of no pain, while 63% had years of no pain, but the trigeminal neuralgia often returned.[8]

One of the considerations in distinguishing classical trigeminal neuralgia from secondary, painful trigeminal neuropathies is the presence of an abnormal neurologic examination, specifically sensory changes. The assumption has been that viral injury or a mass lesion would leave a footprint of sensory changes not seen with the classical form of trigeminal neuralgia. However, 29% of the Danish patients with classical trigeminal neuralgia had sensory abnormalities, usually hypoesthesia (17%), and these finding were in the painful area in 95% of patients, all on the symptomatic side. As a result, the *ICHD-3* no longer requires a normal neurologic examination for the diagnosis of classical trigeminal neuralgia.[1] An abnormal examination suggests a secondary cause, but this is not invariable.

Triggers are a common accompaniment in classical trigeminal neuralgia and occur in up to 60% of patients. Triggers are described as minimal, seemingly harmless touches to the critical areas. Among the commonly described triggers are chewing, talking, touching, cold or hot sensations, shaving, or wind, usually over the division of cranial nerve V affected. Some latency can occur between the trigger and the onset of pain.[10]

It can be difficult to distinguish classical trigeminal neuralgia from short-lasting unilateral neuralgiform headache attacks (SUNHA).[11,12] SUNHA is the term in the *ICHD-3* that includes two subsets of trigeminal autonomic cephalalgias: short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA). The usual ways to sort out the two disorders has been to look for the autonomic features and a V1 location for SUNHA and for the triggers in classical trigeminal neuralgia. However, in the Danish case series, 31% of patients with classical trigeminal neuralgia had autonomic features. Less surprising was that 91% of the patients with classical trigeminal neuralgia indeed had triggers, including mastication (73%), touch (69%), tooth brushing (66%), eating (59%), talking (58%), and cold wind on the face (50%).[8] Trigeminal neuralgia should be strictly localized to a trigeminal nerve distribution, while SUNHA can be out of the trigeminal distribution in 20% to 25% of cases.[13,14]

Lacrimation can accompany classical trigeminal neuralgia of any division, and rhinorrhea can occur as well.[15] Lacrimation occurs in up to 25% of patients with classical trigeminal neuralgia but is less regular than with SUNHA and is associated with severe pain.[16]

The overlap in treatment is discussed in the treatment section. Because of overlapping clinical features, some of the Danish patients could not be diagnosed definitively as having trigeminal neuralgia or SUNHA, and Benoliel and colleagues[11] speculated that some may be on a spectrum.

PATHOPHYSIOLOGY. The cause of classical trigeminal neuralgia for most patients was described by Maarbjerg and colleagues[17] as "demyelination of primary sensory trigeminal afferents in the root entry zone." Maarbjerg and colleagues[17] explain that, "most likely, demyelination paves the way for generation of ectopic

impulses and ephaptic crosstalk. In a significant proportion of the patients, the demyelination is caused by a neurovascular conflict with morphological changes such as compression of the trigeminal root."[17]

That is, in at least 50% of patients with classical trigeminal neuralgia, an abnormal vascular loop severely compresses the symptomatic trigeminal division around the dorsal root entry zone, also called neurovascular compression. Studies suggest that these vessels cause destructive demyelination and neurolysis, although some of the described changes can also occur in asymptomatic individuals, but not to the same degree as a symptomatic side (FIGURE 10-1[18]).[19,20] A summary on the controversy of the pathogenesis of classical trigeminal neuralgia and the separation of it from SUNHA can be found in a 2016 review by Burchiel and colleagues[21] and a 2017 review by Benoliel and colleagues.[11]

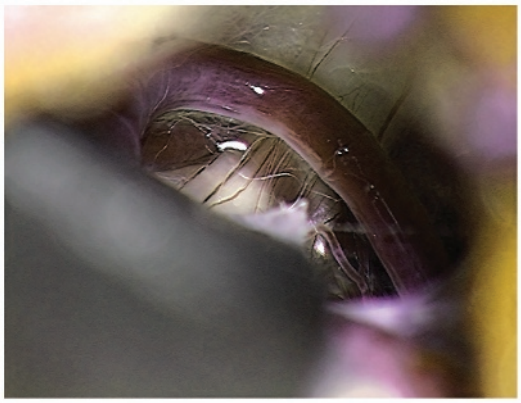

FIGURE 10-1

Aberrant vascular loop seen in classical trigeminal neuralgia.

Reprinted with permission from Rappaport ZH.[18]

Another group of patients has what appears to be classical trigeminal neuralgia but really has subclinical herpes simplex virus involvement. One piece of evidence for this is the reactivation of the virus after surgical procedures for the presumed classical trigeminal neuralgia. This observation suggests that some patients may have a different cause or two causes of symptoms or that in some patients the vascular loop may be unrelated to the presentation.[22]

TREATMENT. The AAN/EFNS trigeminal neuralgia treatment management guidelines state:

> ...carbamazepine (stronger evidence) or oxcarbazepine (better tolerability) should be offered as first-line treatment for pain control. For patients with trigeminal neuralgia refractory to medical therapy, early surgical therapy may be considered. Gasserian ganglion percutaneous techniques, gamma knife treatment, and microvascular decompression may be considered. Microvascular decompression may be considered over other surgical techniques to provide the longest duration of pain freedom.[6,7]

Pharmacologic treatment of classical trigeminal neuralgia, as noted, generally begins with an AED, usually carbamazepine or oxcarbazepine. Carbamazepine works in around 70% of patients, but tachyphylaxis can ensue. Adverse events are also an issue, with neutropenia or bone marrow suppression and syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and associated hyponatremia requiring discontinuation of dosing. These problems may occur with oxcarbazepine as well but, with the exception of hyponatremia, with lower frequency than with carbamazepine. As the guidelines point out, oxcarbazepine is better tolerated.

KEY POINTS

- **Classical trigeminal neuralgia can occur in two forms: a purely paroxysmal form and a form with concomitant persistent interictal facial pain in a trigeminal distribution.**
- **Most cases of trigeminal neuralgia involve the second or third division of cranial nerve V.**
- **An abnormal examination suggests a secondary cause of trigeminal or other neuralgias, but this is not invariable.**
- **Classical trigeminal neuralgia is almost never in a V1 distribution. Consider other diagnoses and ask about accompanying autonomic features to differentiate short-lasting unilateral neuralgiform headaches, which are usually in a V1 distribution.**
- **Most cases of classical trigeminal neuralgia are thought to be secondary to an abnormal vascular loop compressing the symptomatic trigeminal division around the dorsal root entry zone, also called neurovascular compression.**

Backup medications include baclofen, gabapentin, pregabalin, topiramate, lamotrigine, and valproate, and sometimes multiple medications must be combined.[23,24] These medications work better in the purely paroxysmal classical trigeminal neuralgia with shorter attacks than in the form with concomitant persistent facial pain and longer duration attacks.[25]

SUNHA generally responds to gabapentin or lamotrigine, while classical trigeminal neuralgia responds to carbamazepine or oxcarbazepine. However, either syndrome can respond to any of the AEDs, so response to medication is only partially helpful in a difficult differential diagnosis.[11]

Unfortunately, response to oral medications for classical trigeminal neuralgia becomes less marked with time. Combining medications often becomes necessary, and this is often a harbinger of the need for more aggressive treatment, usually surgery.[26] Use of onabotulinumtoxinA is an intermediate approach between oral medications and surgical or radiologic interventions. Four randomized controlled trials as well as many case series have confirmed its effectiveness. The dose range of onabotulinumtoxinA is 25 units to 75 units, and techniques vary from prespecified injection sites to a follow-the-pain approach.[27–31]

Following oral medications and onabotulinumtoxinA, interventions become more invasive. Radiologic treatment is generally gamma knife therapy. There were more than 165 available papers on PubMed on gamma knife therapy as a treatment for trigeminal neuralgia at the time of writing of this article, and almost all are case series. A representative 2016 case series followed 117 patients for a minimum of 2 years between 1993 and 2011.[32] The authors reported complete response following gamma knife therapy in 81% of patients, excellent response with no medication in 52% of patients, and a pain-free response off medications in 85% of patients at 3 years and 81% at 5 years. About one-third had new or worse numbness on the face, but no patients developed anesthesia dolorosa. The recurrence rate was 12%.[32]

The only randomized controlled trial on gamma knife treatment prospectively compared two doses but was not randomized versus sham or a comparator.[33] With regard to gamma knife treatment, the AAN/EFNS guidelines note about a 50% recurrence rate at 3 years posttreatment and state, "facial numbness is reported in 9% to 37% of patients (although it tends to improve with time) and troublesome sensory loss and/or paresthesia are reported in 6% to 13% (whereas anesthesia dolorosa is practically absent)."[6,7]

There are peripheral nerve alternatives, as noted by the AAN/EFNS guidelines:

> …block or destruction of portions of the trigeminal nerve distal to the gasserian ganglia,…cryotherapy, neurectomies, alcohol injection, phenol injection, peripheral acupuncture, [and] radiofrequency thermocoagulation have all been reported as case series with no independent outcome assessment.[6,7]

They estimated approximately a 50% pain recurrence rate at 1 year for these techniques. Some controversy surrounds the possibility of reactivation of the herpes simplex virus with any invasive surgical procedure.[22]

More invasive techniques are "percutaneous rhizotomies [which] involve penetration of the foramen ovale with a cannula and then controlled lesion of the trigeminal ganglion or root by various means: thermal (radiofrequency thermocoagulation),… chemical (injection of glycerol), or mechanical

(compression by a balloon inflated into Meckel' s cave)."[6,7] Again, only case series exist, and no randomized controlled trials on these techniques have been completed. The AAN/EFNS guidelines note about a 50% recurrence rate by 5 years and sensory loss in at least 50% of patients.[6,7]

Finally, most invasive, but possibly most effective, is microvascular decompression. Although this procedure can be done with endoscopic techniques, most neurosurgeons still perform an open craniotomy. The vascular loop compressing one or more trigeminal nerve roots or divisions is separated from the nerve, with, generally, a gelatin sponge pledget inserted between the vessel and the nerve. The AAN/EFNS guidelines state the following:

> Ninety percent of patients obtain pain relief. Over 80% will still be pain free at 1 year, 75% at 3 years, and 73% at 5 years. The average mortality associated with the operation is 0.2%, although it may raise to 0.5% in some reports. Postoperative morbidity is lowest in high-volume units. Up to 4% of patients incur major problems such as CSF leaks, infarcts, or hematomas. Aseptic meningitis is the [most common] complication (11%). Diplopia due to fourth or sixth nerve damage is often transient… Sensory loss occurs in 7% of patients. The major long-term complication is ipsilateral hearing loss, which can be as high as 10%.[6,7]

Recurrence is up to 50% at 5 years posttreatment, making the effectiveness of microvascular decompression about the same as percutaneous rhizotomies and lower than gamma knife treatment.[6,7] Benoliel and colleagues[10] rated the effectiveness, recurrence, side effects, and complications of trigeminal neuralgia surgery (FIGURE 10-2 and FIGURE 10-3).

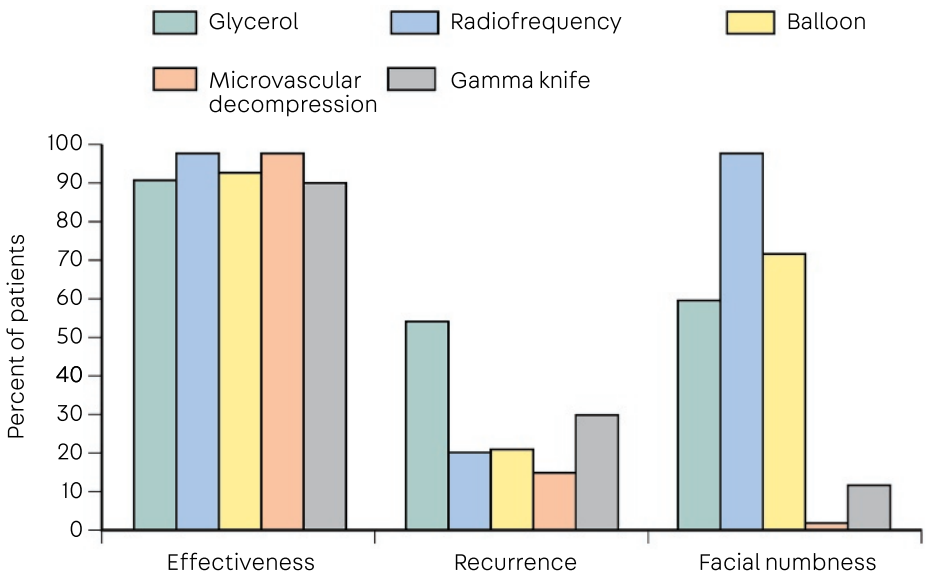

FIGURE 10-2

Effectiveness, recurrence, and side effects of surgical and radiofrequency interventions for trigeminal neuralgia.

Reprinted with permission from Benoliel R, et al.[10] © 2015 Quintessence Publishing Co, Inc.

KEY POINTS

- **Although most cases of classical trigeminal neuralgia respond initially to carbamazepine or oxcarbazepine, short-lasting unilateral neuralgiform headache attacks can also respond to these antiepileptic drugs, so that therapeutic response does not always yield a clear diagnosis.**
- **Numerous peripheral and central surgical and nonsurgical approaches can be tried for classical trigeminal neuralgias, including block or destruction of portions of the trigeminal nerve distal to the gasserian ganglia, percutaneous rhizotomies, gamma knife treatment, and microvascular**
- **The most common painful trigeminal neuropathy is herpetic.**
- **Pain related to any of the painful trigeminal neuropathies is best treated with antiepileptic drugs or tricyclic antidepressants. Early addition of gabapentin to the antiviral regimen in acute shingles may help prevent postherpetic trigeminal neuropathy.**

TREATMENT TRENDS. Because tachyphylaxis appears to occur frequently with the medications used to treat classical trigeminal neuralgia, and combining medications becomes the rule rather than the exception with time, use of gamma knife treatment or microvascular decompression is increasing. The time to consider these procedures has moved to earlier in the disease course, as well.

Painful Trigeminal Neuropathies

The painful trigeminal neuropathies listed by the *ICHD-3* include those due to acute herpes zoster infection, postherpetic, posttraumatic, multiple sclerosis (MS) plaque, and neoplasm. The terminology remains controversial, with some specialists lobbying for a return to the term *symptomatic trigeminal neuralgia*, which did not get adopted in the *ICHD-3* and is therefore archaic.

PAINFUL TRIGEMINAL NEUROPATHY ATTRIBUTED TO ACUTE HERPES ZOSTER. Diagnosis of acute herpetic trigeminal infection (shingles) is made by a confluence of a previous history of chicken pox and an anatomy of dermatologic lesions that respects a division of the trigeminal nerve. It is most common in V1, unlike classical trigeminal neuralgia, which is more common in V2 and V3 (FIGURE 10-4[34]). In the absence of rash or when clinically necessary, a positive assay for varicella-zoster antigen direct immunofluorescence or varicella-zoster viral polymerase chain reaction (PCR) will confirm the diagnosis. There is a female predominance. Acute herpetic infection should always raise the question of immunocompromise either by infection, such as human immunodeficiency virus (HIV), or by cancer.[1,34] Other illnesses or associations with the onset of shingles include trauma, malnutrition, diabetes mellitus, steroid use or dependence, chemotherapeutic or cytotoxic medications, stress, and the presence of chronic obstructive pulmonary disease.[35]

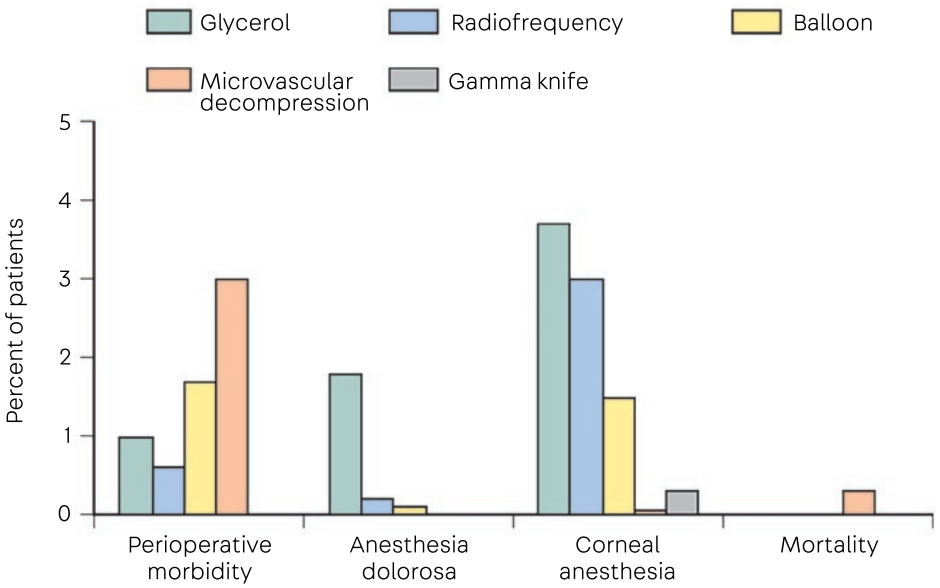

FIGURE 10-3

Complications and side effects of surgical and radiofrequency interventions for trigeminal neuralgia.

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Once a diagnosis of acute herpes zoster in a trigeminal root is established, the first step for treatment is antiviral medication; treatment can consist of acyclovir, famciclovir, valacyclovir, and, where available, brivudine. Doses are listed in TABLE 10-3.[36]

Neuralgic pain from any of the painful trigeminal neuropathies, including acute herpetic infection, is best treated with AEDs, specifically gabapentin and pregabalin or tricyclic antidepressants (TCAs), eg, amitriptyline and nortriptyline.[36,37] The pain of acute trigeminal herpes zoster infection may actually play a role in precipitating postherpetic neuropathy, and some case series suggest that the addition of gabapentin to the antiviral regimen from the beginning may reduce the rate of onset of the delayed syndrome.[38]

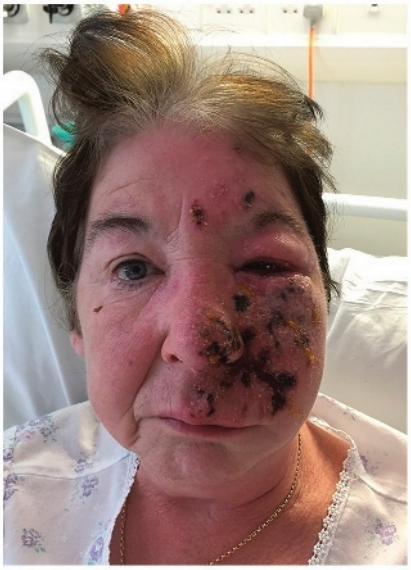

FIGURE 10-4
Painful trigeminal neuropathy attributed to acute herpes zoster.
Reprinted with permission from Lovell B, BMJ Case Rep.[34] © 2015 British Medical Journal Publishing Group.

POSTHERPETIC TRIGEMINAL NEUROPATHY. When the pain within a trigeminal division from a herpes infection persists beyond 3 months, the diagnosis of postherpetic neuropathy, also called postherpetic neuralgia, can be made. This problem is more frequent in older patients. Again, the usual location is V1 in at least 22% of patients. Most patients have continuous pain, generally described as burning, sometimes with paroxysms of pain superimposed.[10] The prevalence of postherpetic neuropathy has been reported to be as low as 0.09 and as high as 0.7 per 100,000.[3,4,39]

The cause of postherpetic neuropathy is localized trigeminal demyelination where the acute infection occurred. (Refer to the open access online version of the *ICHD-3* for a complete listing of the diagnostic criteria of postherpetic neuropathy.[1]) A wide range of estimates for the likelihood of developing the delayed syndrome have been promulgated, from 9% to 73%, but a predictor is

Antiviral Therapy for Acute Trigeminal Herpes Zoster Infection[a] TABLE 10-3

Medication	Dose
Acyclovir	800 mg orally 5 times daily for 7–10 days
Famciclovir	500 mg orally every 8 hours for 7 days
Valacyclovir	1 g orally every 8 hours for 7 days
Brivudine	125 mg/d orally for 7 days (not available in the United States)

[a] Data from Klasser GD, Ahmed AS, J Can Dent Assoc.[36]

when pain is present after the dermatologic eruption clears.[35,38] As noted, the addition of gabapentin during the acute phase may help prevent the later symptom development.[38]

Proven pain-reducing medications for postherpetic trigeminal neuropathy begin with the AEDs, the most effective of which are gabapentin, pregabalin, carbamazepine, and phenytoin. If these fail or are contraindicated, TCAs and serotonin norepinephrine reuptake inhibitors (SNRIs) can be useful, as can topical capsaicin (8%) and lidocaine. Again, when all else fails, there have been a handful of case reports on the use of onabotulinumtoxinA in treatment of the syndrome.[35] Finally, reports of performance of dorsal root entry zone lesioning procedures have described benefit in more than half of patients.[18]

PAINFUL POSTTRAUMATIC TRIGEMINAL NEUROPATHY. Painful posttraumatic trigeminal neuropathies come from a wide variety and severities of injuries, from dental surgery to fractures. One form of this disorder was previously called anesthesia dolorosa, now subsumed into this group of disorders when trigeminal in location. Benoliel and colleagues[37] summarized the pathophysiology:

> Following traumatic tissue damage, an inflammatory response is initiated, crucial to the onset of neuropathic pain… If as a consequence of trauma, neuronal tissue is severely injured (eg, transection), cell death may ensue. However, if the proximal stump survives, healing involves disorganized sprouting of nerve fibers that form a neuroma. Neuroma formation is often dependent on the degree of nerve damage and always occurs when the perineurium is cut. Milder injuries, such as nerve constriction or compression, may also cause regions of neuroma formation and focal demyelination. These regions are characterized by ectopic discharge… also seen in the cell bodies of injured nerves in the dorsal root or trigeminal ganglia. These phenomena partly explain spontaneous neuropathic pain.[37]

Medical, not surgical, management is recommended for painful posttraumatic trigeminal neuropathies; the standby medications remain AEDs and TCAs. Gabapentin and pregabalin work in both postherpetic and posttraumatic trigeminal painful neuropathies. SNRIs also work in posttraumatic painful trigeminal neuropathies.

Benoliel and colleagues[37] list the following algorithm:

> The choice between TCAs or SNRIs and the use of gabapentin or pregabalin is based on the medical profile and other patient-based variables (profession, comorbidities). TCAs are more effective than gabapentin/pregabalin but have significantly more side effects. SNRIs have not been as extensively tested as TCAs but seem less effective for neuropathic pain.[37]

PAINFUL TRIGEMINAL NEUROPATHY ATTRIBUTED TO MULTIPLE SCLEROSIS PLAQUE. MS lesions at the dorsal root entry zone can trigger neuropathic pain in a trigeminal division, and at times can be difficult to distinguish from classical trigeminal neuralgia. Cruccu and colleagues[40] studied 130 patients with MS who had trigeminal neuralgia or trigeminal disturbances; the patients were

imaged and usually demonstrated pontine demyelinating lesions (FIGURE 10-5[41]). Tenser and colleagues[42] described patients with MS with both a plaque and a vascular loop, so there may be a dual mechanism in some cases.

Prevalence of painful trigeminal neuropathy attributed to an MS plaque ranges from 1.5% to 7.9% of patients with MS, with onset of the syndrome occurring at a mean of 12 years into established MS. The pain of MS trigeminal neuralgia can be bilateral.[43,44]

Once a diagnosis of MS is established, treatment is empiric. No randomized controlled trials exist for MS plaque-induced trigeminal pain, and the level of evidence is quite low. The pain may be more refractory in MS than in classical trigeminal neuralgia.

Small case series and reports suggest possible benefit of AEDs including gabapentin, carbamazepine, topiramate, and lamotrigine. Two case series describe the effectiveness of misoprostol.[6]

Both percutaneous retrogasserian balloon compression and gamma knife treatment have been suggested for refractory MS trigeminal neuralgia pain. Again, prospective randomized controlled trials are lacking.

KEY POINTS

- Proven pain-reducing medications for postherpetic trigeminal neuropathy begin with antiepileptic drugs. If these fail or are contraindicated, tricyclic antidepressants or serotonin norepinephrine reuptake inhibitors can be useful, as can topical capsaicin and lidocaine.
- Medical, not surgical, management is recommended for treatment of painful trigeminal neuropathies.
- Prevalence of painful trigeminal neuropathy attributed to a multiple sclerosis plaque ranges from 1.5% to 7.9% of patients with multiple sclerosis.

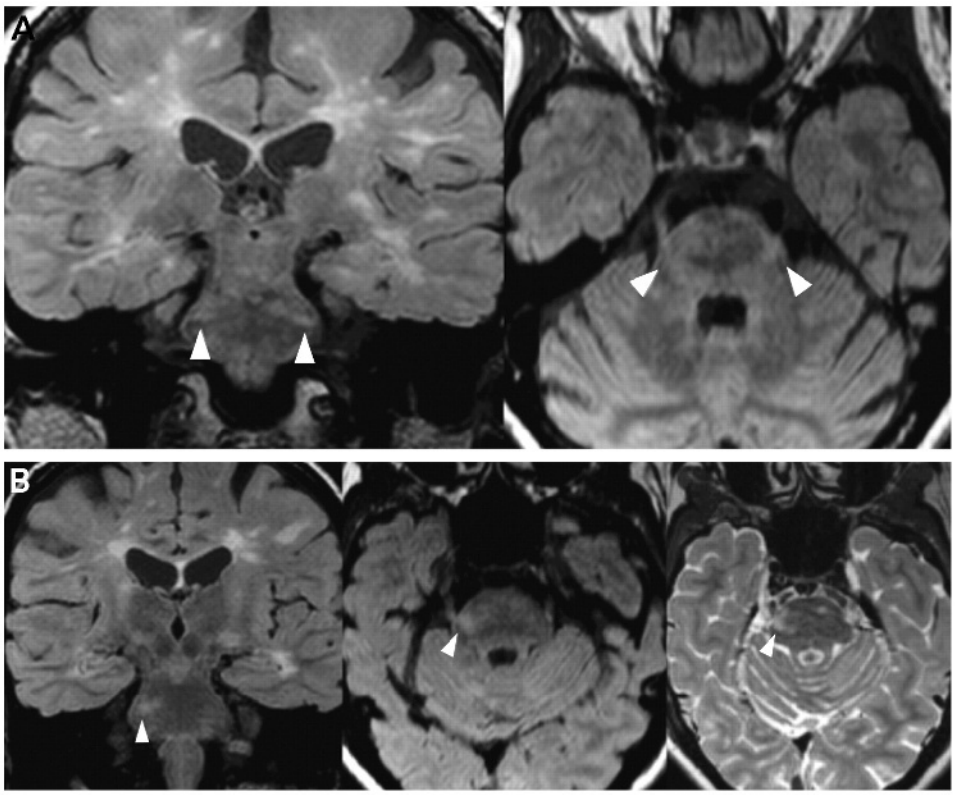

FIGURE 10-5

Multiple sclerosis demyelinating lesions causing painful trigeminal neuropathy. *A*, Coronal fluid-attenuated inversion recovery (FLAIR) (*left*) and axial reconstruction (*right*) showing bilateral hyperintense lesions in the trigeminal root entry zones and tracts (*arrowheads*), with increased signal in the transcisternal parts of the nerves. *B*, Coronal FLAIR (*left*), axial reconstruction (*middle*), and the corresponding axial T2 turbo spin echo axial reconstruction (*right*) showing a hyperintense lesion in the trigeminal root entry zone (*arrowheads*), with high signal seen in the transcisternal part of the trigeminal nerve.

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In 2014, Tuleasca and colleagues[45] described an uncontrolled but prospectively collected series of 43 patients with MS who had trigeminal neuralgia who were treated with gamma knife treatment and were followed for a mean of 53.8 months. More than 90% of patients experienced immediate pain relief, and the study showed a 12.8% relapse rate at 1 year, a 29.2% relapse rate at 3 years, and a 66.9% relapse rate at 5 years. Hypoesthesia occurred in 11.5% of patients for up to 2 years. This case series was suggestive of a very fast onset and long duration of effect.[45]

A large retrospective comparison of case series was reported in 2017. A quick response for pain relief was reported in 87% of patients treated with balloon compression and in 23% of patients treated with gamma knife, which often requires a longer period of time to show clinical effect. The 50% recurrence rate was at 1 year for the patients treated with balloon compression and at 18 months for the patients treated with gamma knife. The adverse events were higher with balloon compression at 21% versus only 3% for gamma knife.[46] This may confirm a number of features of gamma knife treatment observed in classical trigeminal neuralgia in that it is perhaps slower to show onset, perhaps has a lower ceiling of effect, and has a potential for longer effect duration.

GLOSSOPHARYNGEAL NEURALGIA

The *ICHD-3* description on glossopharyngeal neuralgia is very helpful in setting the stage for the clinician and is defined as the following:

> A disorder characterized by unilateral brief stabbing pain, abrupt in onset and termination, in the distributions not only of the glossopharyngeal nerve but also of the auricular and pharyngeal branches of the vagus nerve. Pain is experienced in the ear, base of the tongue, tonsillar fossa, and/or beneath the angle of the jaw. It is commonly provoked by swallowing, talking, or coughing and may remit and relapse in the fashion of trigeminal neuralgia.[1]

Anatomy

Recognition of the anatomy of the glossopharyngeal nerve is necessary for understanding the variety of presentations of glossopharyngeal neuralgia. The nerve has both efferent and afferent functions, including motor, parasympathetic, and sensory. The nerve connects with the sympathetic nervous system, the facial nerve, and the vagus nerve.

The afferent part of the nerve has two major branches: the auricular branch, also called the tympanic, and the pharyngeal branch. The auricular branch carries sensation from the auricle and external auditory meatus of the ear and from the mastoid. The pharyngeal branch conducts sensation from the mucosa of the pharynx. The connections between the vagal sensory nerves and the pharyngeal branches allow for sensory transmission from the posterior throat, soft palate, the tongue base, and the tonsils.

These afferents synapse in the trigeminal nucleus caudalis and spinal nucleus of V. Because there is a combination of nerves from the somatic, visceral, and autonomic pathways peripherally and centrally, the admixture activation can result in syncope and other vagal manifestations, described below.

Clinical Features and Epidemiology

The onset of glossopharyngeal neuralgia is often subacute, as patients begin to have unpleasant sensations in one side of the jaw, inside the mouth, and in the ear for weeks to months. The actual distribution of pain not only includes the glossopharyngeal nerve, but, by virtue of the anatomy described above, can extend into the pharyngeal and auricular vagal branches.

The location of pain can be in the ear, throat, tongue, larynx, and jaw or inferior to the angle of the jaw. The pain often radiates, most commonly from the mouth and pharynx to the ear. Patients can trigger attacks by chewing, swallowing cold liquids, talking, coughing, sneezing, touching the inside of the mouth, or yawning.

The pain is usually paroxysmal, from 2 seconds to 2 minutes (average duration is 8 to 50 seconds); however, many patients have lingering, burning, deep interictal pain. Sometimes patients experience globus or a foreign body sensation in the throat. The quality of the pain is lightninglike but can be described as clicking or scratching. The attacks can awaken patients at night, and stabbing pains can occur 30 to 40 times up to 200 times per day.[47] Diagnosis can be confirmed with administration of a local anesthetic to the pharynx and tonsils, which can stop the paroxysms transiently.

About 25% of glossopharyngeal neuralgia presents bilaterally. There is a geriatric predominance, with mean age of onset at 64 years of age.[48] Although prevalence numbers are lacking, the incidence of glossopharyngeal neuralgia in population-based studies has been reported from 0.2 to 0.8 per 100,000.[4] (Refer to the open access online version of the *ICHD-3* for a complete listing of the diagnostic criteria of glossopharyngeal neuralgia.[1])

The distribution of pain is glossopharyngeal but also vagal in the auricular and pharyngeal branches. When these vagal branches are more involved, vagal consequences can be seen clinically, which can include voice abnormalities such as hoarseness and cough, as well as neurocardiogenic bradycardia, sick sinus syndrome, asystole, and syncope.[49] When both the vagus and the glossopharyngeal cranial nerves are involved, some prefer the term vagoglossopharyngeal neuralgia, a term which is not included in the *ICHD-3*.

As with any neuralgia, the neuralgia can be primary or classical or secondary or symptomatic. The primary pathogenesis again is attributed to neurovascular compression (**FIGURE 10-6**[50]). The secondary causes, requiring a careful imaging workup, include tumor, trauma, infection, carotid aneurysm, demyelinating lesions, Chiari malformation, or elongation of the stylohyoid ligament or process lateral to the glossopharyngeal nerve (**CASE 10-2**).

As noted for diagnosis, topical anesthesia of the trigger areas stops both the trigger and the pain of glossopharyngeal neuralgia transiently. Further treatment for classical glossopharyngeal neuralgia starts with the same medications used for trigeminal neuralgia: carbamazepine, oxcarbazepine, baclofen, gabapentin, pregabalin, lamotrigine, or phenytoin. Invasive procedures suggested if medications fail include radiofrequency ablation, gamma knife treatment, glossopharyngeal and vagal rhizotomy, or microvascular decompression; the latter treatment is suggested if a vascular loop is identified on imaging. Recurrence rates may be lower with surgical

KEY POINTS

- **The pain of glossopharyngeal neuralgia not only includes the distribution of the glossopharyngeal nerve but can extend into the pharyngeal and auricular vagal branches.**

- **Glossopharyngeal neuralgia is generally felt in the posterior tongue, pharynx, tonsillar fossa, or below the lower jaw angle and the ear. Clinical manifestations such as hoarseness, cough, neurocardiogenic bradycardia, sick sinus syndrome, asystole, seizures, and syncope suggest vagal involvement.**

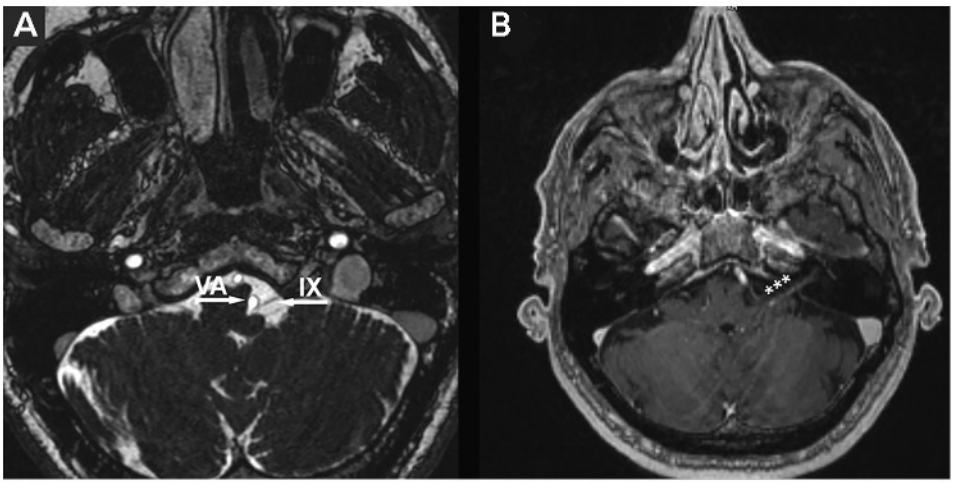

FIGURE 10-6

MRI findings in a patient with recent-onset glossopharyngeal neuralgia. Axial T2-weighted image (*A*) shows the neurovascular conflict between the left glossopharyngeal nerve (IX) and the vertebral artery (VA). The VA, lying on the medulla, compresses the proximal portion of the glossopharyngeal nerve. On postcontrast T1-weighted image (*B*), the nerve shows homogeneous enhancement (*asterisks*) after gadolinium.

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CASE 10-2

A 65-year-old woman was referred for a 6-month history of paroxysms of severe, shooting pains in the back left side of her mouth at the tongue base, radiating up to the angle of the jaw and bottom of the ear. Each stab lasted about 10 seconds, and she experienced about six shocks of pain per hour. She could trigger the pains by swallowing or yawning.

The pains were terrible, but even worse was that she had been fainting with some of the attacks, losing consciousness for 10 to 30 seconds. She did not experience tongue biting, incontinence, or postevent confusion. Sometimes she experienced severe coughing jags.

She had a normal brain MRI with and without contrast and a normal EEG. She underwent cardiac monitoring during a syncopal pain spell and had severe bradycardia and premature atrial contractions. A magnetic resonance angiogram (MRA) showed an abnormal loop of the posterior inferior cerebellar artery near the left cranial nerves IX and X.

COMMENT

This patient meets *International Classification of Headache Disorders, Third Edition* (*ICHD-3*) criteria for glossopharyngeal neuralgia, but the syncope and bradycardia point to vagal involvement as well, also suggested by the MRA findings. Her diagnosis would have been vagoglossopharyngeal neuralgia by the old *ICHD-3 beta* terminology, now just a subset of *ICHD-3* glossopharyngeal neuralgia. The cardiac manifestations are severe and potentially life-threatening. Surgical intervention, most likely with microvascular decompression, should be considered urgently rather than waiting to see if medications will suppress her vagal signs and symptoms.

glossopharyngeal neuralgia procedures than for classical trigeminal neuralgia, but, in the past, operative mortality has been reported as high as 5%. Adverse events from surgery include dysphagia and hoarseness.[51]

Treatment Trends

The presence of syncope, suggestive of vagal involvement, makes an imaging search for a surgically remediable vascular loop more urgent. Also, glossopharyngeal neuralgia with or without vagal involvement is so rare that a secondary cause should always be thought of and searched for first.

When glossopharyngeal neuralgia is poorly responsive to medication, a more invasive procedure, such as microvascular decompression or gamma knife treatment, is clearly indicated. Current thought is to consider proceeding to these interventions without first stepping through medications, as the consequences of untreated vagal discharge can be fatal.

NERVUS INTERMEDIUS (FACIAL NERVE) NEURALGIA

The nervus intermedius is a sensory branch of the facial nerve. It serves sensation around the ear, including the external auditory meatus and the skin behind the ear, as well as over the mastoid. The nerve travels centrally with the perikaryons in the geniculate ganglion. A former term for this neuralgia was geniculate neuralgia. In 1907, Hunt[52] originally described this neuralgia, which he called "prosopalgia," as involving both ear pain and a poorly characterized and deep facial pain.

Nervus intermedius neuralgia can present as either a set of brief, severe, stabbing, shooting, piercing, or sharp pains, or pains of longer duration, from 2 seconds to minutes in length. Continuous persistent pain is also described in this condition.

The location of pain is recognizable, as it is deep within the internal auditory canal. The patients usually have a trigger that occurs with touching the posterior wall of the external auditory canal or a zone around the ear.

Refer to the open access online version of the *ICHD-3* for a complete listing of the diagnostic criteria of nervus intermedius neuralgia.[1] Nervus intermedius neuralgia is rare enough that a very careful workup for secondary causes is required. Herpes zoster is the most frequently described attributable etiology.

Treatment recommendations are empiric, and the medications used are similar to those used with other neuralgias. A small noncontrolled series of refractory patients have successfully undergone surgical removal of the geniculate ganglion and the nervus intermedius.[53]

OCCIPITAL NEURALGIA

Occipital neuralgia is a neuralgia that is often overdiagnosed when patients with migraine have posterior pain and tenderness over the greater occipital notch or where the greater occipital nerve exits. The *ICHD-3* criteria for diagnosis of occipital neuralgia require that paroxysms of pain occur, variously described as brief (seconds to minutes) or sharp or stabbing strictly localized to one or more of the three occipital nerves, greater, lesser, or third, and either unilateral or bilateral.[1] Thus, persistent chronic, aching pain is not consistent with this diagnosis.

Furthermore, the criteria require tenderness, dysesthesia, or allodynia over the emerging symptomatic nerve or a trigger point there. A positive Tinel sign

KEY POINTS

- **Nervus intermedius neuralgia can present as either a set of brief, severe, stabbing, shooting, piercing, or sharp pains, or pains of longer duration, from 2 seconds to minutes in duration deep within the internal auditory canal. The patients usually have a trigger that occurs with touching the posterior wall of the external auditory canal or a zone around the ear.**
- **Occipital neuralgia is paroxysmal and generally occurs in the distribution of the greater occipital nerve. A different location or a continuous pain, especially with other associated symptoms, should call for a reconsideration of the diagnosis.**
- **Treatment of occipital neuralgia begins with a peripheral nerve block.**

can occur over the nerve. Finally, elimination of the pain with a nerve block over the affected nerve is mandatory for diagnosis. Location can be radiating up the posterior part of the head to the vertex. The affected nerve is the greater occipital nerve 90% of the time.[54]

Occasionally, the pain may reach to frontal and periorbital locations as trigeminocervical interneurons overlap in the spinal nucleus of V,[55] but generally the pain should respect the dermatome of the affected nerve from a diagnostic standpoint. Complicating the diagnosis are connections with cervical sympathetic pathways and cranial nerves VIII, IX, and X, which can result in descriptions by patients of alteration of vision, eye pain, nausea, dizziness, tinnitus, and nasal congestion.

The greater occipital nerve derives from the C2 dorsal ramus, travels below the inferior oblique, then pierces the semispinalis capitis, splenius capitis, and trapezius. The usual cause of greater occipital neuralgia is entrapment along the path from C2 to the trapezius aponeurosis (FIGURE 10-7).[54]

Again, differential diagnosis requires elimination of secondary causes, including neoplasm, infection, vascular malformations, giant cell arteritis, or Chiari malformations. Structural causes can include abnormalities in the atlantoaxial, atlantooccipital, or zygapophysial joints or cervical facet arthritis. No studies exist on the prevalence of occipital neuralgia in the general population (CASE 10-3). Refer to the open access online version of the *ICHD-3* for a complete listing of the diagnostic criteria of occipital neuralgia.[1]

Treatment begins with the nerve block. This is generally done over the occipital notch, but ultrasound can give greater accuracy.[56]

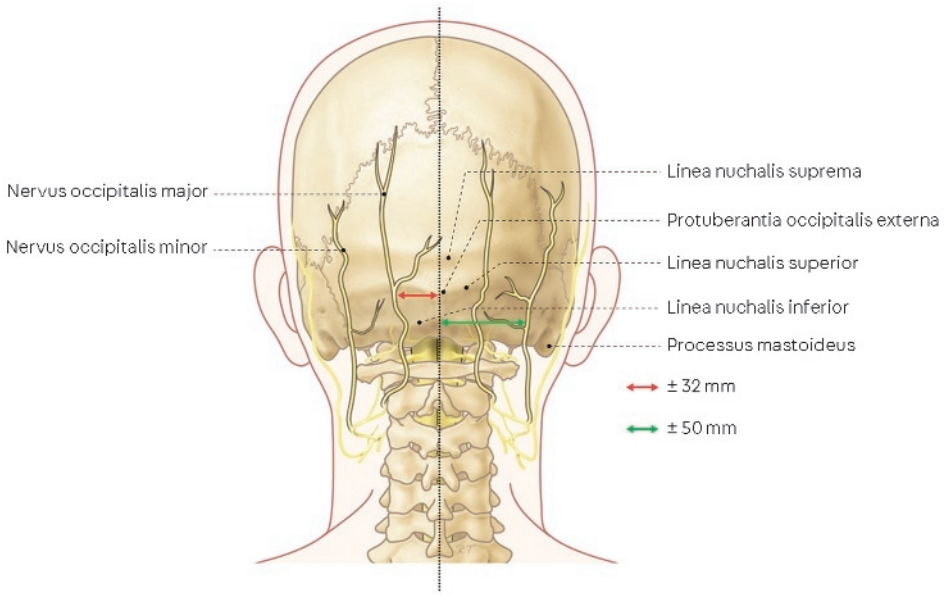

FIGURE 10-7
Anatomy of the occipital nerves.
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Controversy exists about whether this should be done simply with anesthetic or whether steroids should be included. The block should work rapidly, but if repeated blocks prove necessary, radiofrequency ablation can be considered.[54]

CONCLUSION

This article covered classical trigeminal neuralgia, painful trigeminal neuropathies, glossopharyngeal neuralgia, nervus intermedius neuralgia, and occipital neuralgia. These neuralgias are, for the most part, brief, lancinating pains in the distribution of the nerve in question but sometimes also have an achy or severe persistent interictal pain, depending on the nerve involved.

The *ICHD-3* is the referral document to standardize diagnosis so that concern for secondary causes can be weighed. However, classical trigeminal neuralgia and glossopharyngeal neuralgias are generally secondary to an anomalous vascular loop pathologically compressing the nerve, and so the terminology has moved on from primary and symptomatic to the current hierarchy.

Treatment for most of the neuralgias includes AEDs, baclofen, TCAs, and SNRIs. Following medication or combination medication failures, invasive

CASE 10-3

An 83-year-old woman presented to the emergency department for evaluation of new-onset severe pain exclusively in the right suboccipital region. She said that the pain occurred in stabs or bursts, lasted only a few seconds, and radiated up the back of her head to the right vertex. She had no pain between the paroxysms.

Palpation over the right greater occipital notch reproduced her pain and triggered attacks. No autonomic features were seen during the witnessed pain, which lasted about 2 seconds and spontaneously remitted.

The trigger zone was infiltrated with 2% lidocaine and a steroid, and the patient called the next day to say that the attacks had stopped.

COMMENT

This is a classic presentation of occipital neuralgia, and the response to injection is so definitive that further workup is probably not necessary. The paroxysmal presentation and its location and treatment response in this age group confirm the diagnosis.

Note that migraine pain is often posterior, in the occiput and neck, throbbing, bilateral in at least 40% of patients, occurs in attacks lasting 4 to 72 hours, is worse with activity, and is associated with nausea, photophobia, and phonophobia. Although both conditions can be associated with notch tenderness, the other features of migraine easily help to differentiate the two conditions. A migraine attack can be responsive to greater occipital nerve injections, but the treatment response does not diagnose occipital neuralgia by itself. Occipital neuralgia is paroxysmal and lancinating (and focal, as in this case) and is not generally associated with other migrainous features.

procedures can be considered, up to and including gamma knife treatment and microvascular decompression. Exceptions to this approach include glossopharyngeal neuralgia with neurocardiac events, when surgical approaches may be necessary early, and occipital neuralgia, which often remits with anesthetic and steroid injection over the nerve affected.

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DISCLOSURE

Continued from page 1157

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Secondary Headache Syndromes

By Denise E. Chou, MD

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

ABSTRACT

PURPOSE OF REVIEW: **This article is intended to assist clinicians in distinguishing benign primary headache syndromes from serious headache presentations that arise from exogenous causes.**

RECENT FINDINGS: **Although most cases of severe headache are benign, it is essential to recognize the signs and symptoms of potentially life-threatening conditions. Patients with primary headache disorders can also acquire secondary conditions that may present as a change in their baseline headache patterns and characteristics. Clinical clues in the history and examination can help guide the diagnosis and management of secondary headache disorders. Furthermore, advances in the understanding of basic mechanisms of headache may offer insight into the proposed pathophysiology of secondary headaches.**

SUMMARY: **Several structural, vascular, infectious, inflammatory, and traumatic causes of headache are highlighted. Careful history taking and examination can enable prompt identification and treatment of underlying serious medical disorders causing secondary headache syndromes.**

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UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Chou discusses the unlabeled/investigational use of glucocorticoids for the treatment of giant cell arteritis and Tolosa-Hunt syndrome, indomethacin for the treatment of hemicrania continua, and nonsteroidal anti-inflammatory drugs and oral or locally injected steroids for the treatment of primary trochlear headache (trochleitis).

INTRODUCTION

The differential diagnosis of a new-onset severe headache differs from that of a chronic recurrent headache. A potentially serious cause is more likely with a new severe headache than with a headache that has been recurrent over years. While a life-threatening headache is relatively rare, caution is required to identify and appropriately manage these cases. Headache disorders are divided into *primary headache syndromes* (in which the headache and associated features comprise the disorder itself) and *secondary headache syndromes* (in which the headache results from exogenous etiologies).

The first step in the diagnosis of a patient presenting with headache is to differentiate between a benign headache disorder (usually a primary headache syndrome) and a serious underlying condition (causing a secondary headache). A potentially life-threatening headache can be identified by eliciting red flags during the patient's history and examination.

Symptoms or signs that may suggest a serious underlying condition are summarized by the mnemonic, SNOOP (***s***ystemic symptoms/signs, ***n***eurologic symptoms/signs, ***o***nset sudden, ***o***lder age of onset, ***p***attern change) (TABLE 11-1).[1] Despite the useful applicability of SNOOP, the best indicator of structural

intracranial pathology remains the neurologic examination, as symptoms alone cannot adequately distinguish primary from secondary headache syndromes.

The *International Classification of Headache Disorders, Third Edition* (*ICHD-3*)[2] categorizes secondary headache disorders according to the following:

- **Headache attributed to trauma or injury to the head and/or neck**
- **Headache attributed to cranial and/or cervical vascular disorder**
- **Headache attributed to nonvascular intracranial disorder**
- **Headache attributed to a substance or its withdrawal**
- **Headache attributed to infection**
- **Headache attributed to disorder of homoeostasis**
- **Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cervical structure**
- **Headache attributed to psychiatric disorder**[2]

This article reviews several of the worrisome conditions listed above that may cause headache; however, the majority of patients presenting with severe headache have a benign condition.

HEADACHE SECONDARY TO NEOPLASM

In contrast to common belief, brain tumors constitute a rare cause of headache and even less frequently present with severe pain. Approximately 30% of patients diagnosed with a brain tumor report headache on presentation; however, only 1% to 2% report headache as the sole clinical symptom.[3] In addition to focal neurologic deficits on examination, potential signs of an intracranial lesion include headache exacerbation with exertion or change in position, a headache that awakens the patient from sleep, or an abrupt change

TABLE 11-1 **Red Flags for a Potentially Life-Threatening Headache Using the Mnemonic SNOOP4**[a]

Red Flags	Description/Examples
Systemic symptoms/signs/disease	Fever, chills, rash, myalgia, night sweats, weight loss, comorbid systemic disease (eg, human immunodeficiency virus [HIV], immunocompromised state, malignancy), pregnancy or postpartum
Neurologic symptoms/signs	Change in mental status or level of consciousness, diplopia, abnormal cranial nerve function, pulsatile tinnitus, loss of sensation, weakness, ataxia, history of seizure/collapse/loss of consciousness
Onset sudden	Onset sudden or first ever, severe or "worst" headache of life, thunderclap headache (pain reaches maximal intensity instantly after onset)
Older onset	Onset after 50 years of age
Pattern change	Progressive headache (eg, to daily, continuous pattern), precipitated by Valsalva maneuver, postural aggravation, papilledema

[a] Modified with permission from Dodick DW, Semin Neurol.[1] © 2010 Thieme Medical Publishers.

in the pattern of a prior headache disorder. It should be noted that these features can also occur with primary headache disorders such as migraine and cluster headache. The nature of headache caused by a brain tumor is typically nondescript—an intermittent dull, deep aching quality of moderate severity that may be associated with nausea and vomiting; however, depending on the location of the tumor, the phenotype may mimic a primary headache disorder (CASE 11-1). Vomiting over weeks prior to the onset of headache is highly suggestive of a posterior fossa mass, as is headache induced by Valsalva maneuvers such as bending, lifting, or coughing. Development of galactorrhea or amenorrhea should raise suspicion for a prolactin-secreting pituitary adenoma or polycystic ovary syndrome. A new headache presentation in a patient with a known malignancy may be indicative of intracranial metastases or carcinomatous meningitis. The pathophysiology of headache in the setting of a brain tumor is thought to involve traction on innervated vascular structures, compression of cranial or cervical nerves, as well as peripheral sensitization with neurogenic inflammation; central sensitization may also arise through trigeminovascular afferents on the meninges and cranial vessels.[6]

KEY POINTS

- A potentially serious cause is more likely with a new severe headache than with a headache that has been recurrent over years.
- In contrast to common belief, brain tumors constitute a rare cause of headache and even less frequently present with severe pain. Approximately 30% of patients diagnosed with a brain tumor report headache on presentation; however, only 1% to 2% report headache as the sole clinical symptom.
- Distinguishing headache features in cases of nontraumatic subarachnoid hemorrhage include occipital location, a "stabbing" quality, a rapid peak of intensity (within 1 second of onset), and associated meningismus.

HEADACHE SECONDARY TO VASCULAR DISORDERS

This section addresses headache arising from vascular conditions, including intracranial hemorrhage, arterial dissection, acute ischemic stroke, cerebral venous sinus thrombosis, reversible cerebral vasoconstriction syndrome (RCVS), severe arterial hypertension, and cardiac cephalalgia.

Subarachnoid Hemorrhage

Acute onset of severe headache, particularly the "worst headache of life" that is accompanied by neck stiffness and without fever may suggest subarachnoid hemorrhage. An estimated 25% of cases of thunderclap headache are secondary to subarachnoid hemorrhage.[7] However, up to 50% of patients with subarachnoid hemorrhage may present with transient or milder headache (sentinel bleed) and therefore are at risk for delayed diagnosis with subsequent morbidity.[8] A recent prospective, observational study found that distinguishing headache features in cases of nontraumatic subarachnoid hemorrhage included occipital location, a "stabbing" quality, a rapid peak of intensity (within 1 second of onset), and associated meningismus.[9] Headache alone can be the presenting symptom of a ruptured aneurysm, arteriovenous malformation, or intraparenchymal hemorrhage; focal neurologic signs may be present on examination depending on the location and the extent of the hemorrhage. A posterior communicating artery aneurysm may manifest with a third nerve palsy; an anterior communicating artery aneurysm may present with bilateral leg weakness or abulia; and a middle cerebral artery aneurysm may be associated with hemiparesis or neglect. In addition, increased intracranial pressure or mass effect within the posterior fossa may present with a sixth nerve palsy, nystagmus, or ataxia. If these symptoms are present, urgent noncontrast head CT imaging should be pursued, although it may be normal in some instances (eg, if hemorrhage is small, below the foramen magnum, or occurred in the immediate hours before the CT scan). If clinical suspicion remains for subarachnoid hemorrhage, lumbar puncture is warranted for further evaluation (looking for the presence of red blood cells or xanthochromia).[8,10] It should also be noted that normal CT and CSF findings can occur in patients with

subarachnoid hemorrhage presenting with headache for more than 2 weeks, prompting further workup with brain MRI and vessel imaging with magnetic resonance angiography (MRA), CT angiography, or conventional angiography.

Subdural Hematoma

Headache associated with subdural hematoma can have a more insidious onset than in subarachnoid hemorrhage. Characteristics of the headache may be similar to those of a brain tumor (as a result of mass effect). A recent large series of patients with chronic subdural hematoma identified the occurrence of midline shift to be the most influential factor for the development of headache, possibly as a result of stretching or compression of pain-sensitive meninges and meningeal blood vessels.[11] Mental status changes can also be present, particularly

CASE 11-1

A 39-year-old woman presented for a neurologic consultation for headache. Four months earlier, she had developed throbbing, left-sided neck, occipital, retroauricular, and temporal pain upon waking one morning, with no precipitating events. Her headache became constant and daily over the next 4 months, and she described a continuous pressure with superimposed sharp exacerbations in the left occipital and posterior temporal region. These exacerbations were accompanied by ipsilateral cranial autonomic symptoms, including left-sided nasal congestion and aural fullness. She also noted mild left-sided photophobia and phonophobia, but no nausea, with her baseline pain.

Neurologic examination was unrevealing. MRI of the brain revealed a left foramen magnum uniformly enhancing dural-based mass, consistent with a meningioma, causing crowding at the pontomedullary and medullary levels with minimal rightward displacement of the medulla (FIGURE 11-1).

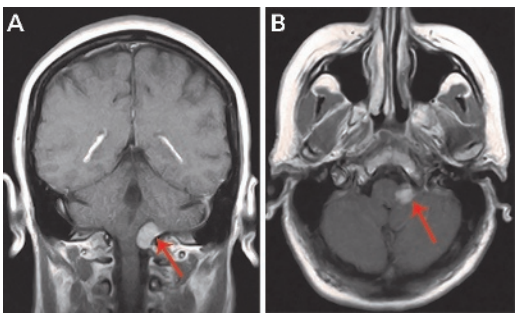

FIGURE 11-1
Brain MRI of the patient in CASE 11-1. Postcontrast T1-weighted coronal (*A*) and axial (*B*) images reveal a uniformly enhancing left foramen magnum dural-based mass consistent with a meningioma (*arrows*), causing crowding at the pontomedullary and medullary levels with minimal rightward displacement of the medulla.

She was referred for neurosurgical consultation and subsequently underwent gamma knife radiosurgery to the mass, with coadministration of dexamethasone. She experienced temporary pain relief for 1 week, but her headache intensity later worsened. After multiple failed medication and procedural trials, she was given a trial of indomethacin for a presumptive diagnosis of hemicrania continua. She reported 90% relief of her headache intensity at a maximum indomethacin dosage of 75 mg 3 times daily.

among elderly patients who are at higher risk for developing subdural hemorrhages (frequently from unwitnessed falls).

Arterial Dissection

Headache occurs in 60% to 95% of cases of carotid artery dissections, is usually unilateral with face/neck pain on the same side, and may be accompanied by ipsilateral Horner syndrome or amaurosis fugax (**CASE 11-2**).[12,13] It should be noted that Horner syndrome ipsilateral to the side of pain can also be a cranial autonomic feature seen in primary headache disorders, including migraine and cluster headache. In vertebral artery dissections, headache is a presenting symptom in about 70% of cases.[12] Lower cranial neuropathies, cerebellar signs, and visual field defects can also accompany the headache.

COMMENT

Although hemicrania continua more commonly manifests as a primary headache syndrome, its phenotype (as well as of other trigeminal autonomic cephalalgias) has been reported to occur in the context of structural lesions. (For more information, refer to the article "Cluster Headache and Other Trigeminal Autonomic Cephalalgias" by Mark Burish, MD, PhD,[4] in this issue of *Continuum*.) Positron emission tomography (PET) imaging in hemicrania continua has revealed brainstem involvement including the contralateral posterior hypothalamus, ipsilateral dorsal rostral pons, ipsilateral ventrolateral midbrain, and bilateral pontomedullary junction.[5] In this case, the location of the meningioma with extension and impingement on the left lateral medulla and pontomedullary junction suggests a plausible mechanism for her hemicrania continua–like headache syndrome. It is interesting to note that, in contrast to most cases of primary hemicrania continua, the patient's response to indomethacin (even at maximum dosage) was not complete. While some secondary hemicrania continua presentations may remit entirely with indomethacin, a partial response to indomethacin should raise suspicion for underlying structural causes of the headache.

Acute Ischemic Stroke

Headache has been reported to occur in 27% of cases of acute stroke, prior to the development of other symptoms. Factors that have been independently associated with headache at ictus include female sex, younger age, prior history of migraine, and cerebellar as well as right hemispheric location of stroke.[14] It should be noted that migraine with aura is also associated with an increased risk of stroke.

Cerebral Venous Sinus Thrombosis

Thrombosis of the cerebral venous sinuses is a relatively rare vascular condition with a 1:250,000 annual incidence; the outflow obstruction following venous thrombosis can result in hemorrhage from vascular congestion.[15] Headache is the most common but least specific feature of cerebral venous thrombosis, present in approximately 75% to 90% of cases; other signs include focal neurologic deficits,

CASE 11-2

A 41-year-old man presented for evaluation of right-sided neck pain that began 2 weeks prior while weight lifting. He reported a prior history of episodic migraine with visual aura since adolescence that had significantly improved over the last few years. Shortly before the onset of his neck pain, he experienced transient visual scintillations (which he attributed at the time to a visual aura), followed by a right posterior temporal headache. His headache and neck pain persisted, despite treatment with naproxen and sumatriptan, which he had used for his migraines.

On examination, he was noted to have mild right-sided ptosis and miosis. Urgent magnetic resonance angiography (MRA) of the head and neck was performed and revealed an acute dissection of the right internal carotid artery with an intramural hematoma (FIGURE 11-2). MRI of the brain was normal. He was started on antiplatelet therapy and fortunately avoided any further neurovascular sequelae.

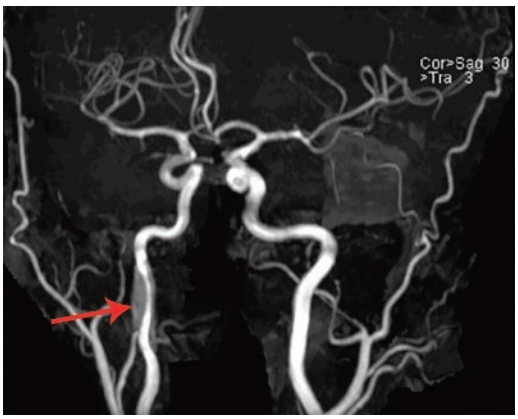

FIGURE 11-2
Magnetic resonance angiogram (MRA) of the head of the patient in CASE 11-2 showing an acute dissection of the right internal carotid artery with an intramural hematoma (*arrow*).

COMMENT

Patients with a history of a primary headache disorder can also develop secondary headache conditions with symptoms that may overlap with their primary syndrome. A detailed neurologic examination is essential even in patients with a known primary headache disorder, particularly when a change in headache pattern occurs.

altered mental status, seizure, and papilledema.[16] Risk factors for cerebral venous thrombosis include female sex (4:1 female-to-male ratio), pregnancy or postpartum state, and use of estrogen-containing hormonal contraceptives.

Reversible Cerebral Vasoconstriction Syndrome

RCVS, or Call-Fleming syndrome, is characterized by recurrent severe headache attacks in combination with the radiologic finding of diffuse segmental vasoconstriction of intracranial arteries that resolves over a 3-month period.[17] Several potential triggers have been identified, and alterations in cerebral vascular tone likely contribute to the syndrome, although the precise etiology of RCVS has not been definitively established. Reported triggers include exposure to certain substances or medications (such as marijuana, tacrolimus, cyclophosphamide, pseudoephedrine, selective serotonin reuptake inhibitors [SSRIs]), carcinoid tumor, and the puerperium period. RCVS headaches are often bilateral, brief in duration (1 to 3 hours), recurrent over a span of days to weeks, and are sudden in onset, rapidly reaching a maximal severe intensity (thunderclap). Patients may have associated nausea and vomiting, and focal neurologic deficits or seizures can occur in up to 43% of patients. It should be noted that the hallmark radiologic vasoconstriction can develop 2 to 3 weeks after the onset of symptoms. Serologic and CSF analysis is usually unremarkable. The syndrome is transient, with clinical symptomatology remitting within 1 month and vascular findings resolving within 3 months.[18]

Arterial Hypertension

Headache may arise as the result of severe arterial hypertension, defined as systolic blood pressure of 180 mm Hg or more and/or diastolic blood pressure of 120 mm Hg or more. There must be temporal evidence of causation, with development of the headache at the onset of hypertension, significant worsening of the headache in parallel with worsening hypertension, and/or significant improvement of the headache with resolution of hypertension. Headache that is precipitated by a hypertensive crisis, defined as a paroxysmal rise in systolic (to 180 mm Hg or more) and/or diastolic (to 120 mm Hg or more) blood pressure, may occur with or without symptoms of encephalopathy (eg, lethargy, confusion, visual disturbances, or seizure). The nature of such a headache is typically bilateral or diffuse, pulsating, and aggravated by physical activity.[2] Headache may also be caused by pheochromocytoma, diagnosed by the demonstration of increased excretion of catecholamines or catecholamine metabolites. Headache attributed to pheochromocytoma is often of short duration (less than 15 minutes in 50% of patients and less than 1 hour in 70% of patients), with attacks developing upon abrupt increases in blood pressure and resolving upon normalization of blood pressure. Pain is usually severe, frontal or occipital, and characterized as constant or throbbing pain; the headache may be accompanied by sweating, palpitations, facial pallor, and/or anxiety.[2,19]

Cardiac Cephalalgia

Cardiac cephalalgia refers to a headache that occurs in temporal relation to the onset of acute myocardial ischemia, is typically exacerbated by exercise/exertion, and is relieved by treatments for acute coronary syndrome such as nitroglycerin or surgical interventions including angioplasty or coronary artery bypass grafting.[20] Headache features can vary in location (bifrontal, bitemporal, or

KEY POINTS

- **Headache occurs in 60% to 95% of cases of carotid artery dissections, is usually unilateral with face/neck pain on the same side, and may be accompanied by ipsilateral Horner syndrome or amaurosis fugax.**
- **Reversible cerebral vasoconstriction syndrome headaches are often bilateral, brief in duration (1 to 3 hours), recurrent over a span of days to weeks, and are sudden in onset, rapidly reaching a maximal severe intensity (thunderclap).**

occipital), intensity (mild to severe), and duration (minutes to hours); nausea may also accompany the headache, which may sometimes resemble migraine. Cardiovascular risk factors including diabetes mellitus, hypertension, hyperlipidemia, smoking, and family history of cardiac disease are frequently present, although cardiac cephalalgia has also been reported to occur in patients at low risk of cardiovascular disease.[21] Ischemic changes can be seen on ECG or cardiac stress testing when the patient is symptomatic; however, coronary angiography may be required for confirmation. Distinguishing cardiac cephalalgia from migraine, which may also be aggravated by exertion, is essential to avoid the inappropriate administration of triptan or ergot medications, which are contraindicated in coronary syndromes because of their vasoconstrictive effects.

HEADACHE SECONDARY TO INFLAMMATORY DISORDERS

This section addresses headache arising from inflammatory conditions, such as giant cell arteritis (temporal arteritis) and Tolosa-Hunt syndrome.

Giant Cell Arteritis (Temporal Arteritis)

Onset of headache at or past the age of 50, with associated tenderness of the temporal artery or shallow temporal artery pulsations, should raise concern for giant cell arteritis (temporal arteritis). Giant cell or temporal arteritis is an inflammatory disorder of arteries that commonly affects the extracranial carotid circulation. It is most frequently seen in the elderly population, with an average age of onset of 70 years (annual incidence is 77 per 100,000 individuals age 50 and older), with a female predominance. Blindness can be a complication of untreated temporal arteritis in approximately half of patients due to involvement of the ophthalmic artery and its branches; however, visual loss can be prevented with prompt glucocorticoid treatment. Headache is the most common presenting symptom, which can be unilateral or bilateral and is often temporally located but can occur in any cranial region. The quality of the headache is generally dull and aching, although patients may experience intermittent stabbing pains superimposed on the background headache and report scalp tenderness. The headache is usually worse at night and can be aggravated by exposure to cold. As giant cell arteritis is a systemic condition, other associated symptoms include jaw claudication, myalgia, unexplained weight loss, and malaise. In suspected cases, an erythrocyte sedimentation rate or C-reactive protein should be checked, and a temporal artery biopsy should be completed for diagnostic confirmation.[22] However, it should be noted that false-negative results can also occur with the latter if the length of the artery is not sufficient and the specimen is taken from a "skip area."[23] Headache generally resolves or significantly improves within 3 days of treatment initiation with high-dose glucocorticoids.

Tolosa-Hunt Syndrome

Tolosa-Hunt syndrome is a disorder characterized by severe, unilateral, periorbital headache associated with painful ophthalmoplegia; the course is typically relapsing and remitting, with attacks recurring every few months to years. The annual incidence is estimated to be 1 per million per year, with an average age of onset of 41 years and no male-female predisposition. The syndrome is thought to arise from nonspecific inflammation in the cavernous sinus or superior orbital fissure. In addition to the classic periorbital location, the

headache may extend to the retro-orbital, frontal, or temporal regions. Ophthalmoplegia results from involvement of the oculomotor, trochlear, and/or abducens nerves. Pupillary abnormalities can also occur if sympathetic and parasympathetic pathways are affected. Contrast-enhanced MRI may demonstrate granulomatous inflammation of the cavernous sinus, superior orbital fissure, or orbit. Treatment with high-dose glucocorticoids can significantly reduce pain within a few days and also improves ophthalmoplegia as well as MRI abnormalities.[24]

HEADACHE SECONDARY TO INFECTION

Patients presenting with headache associated with fever, nuchal stiffness, and Kernig and Brudzinski signs (low sensitivity but high specificity) warrant further evaluation with head imaging (CT/MRI) followed by lumbar puncture (if not contraindicated) to rule out an infectious or inflammatory meningitis. Immunosuppressed, pediatric, and elderly populations are at particular risk, and treatment should be initiated as soon as possible. If meningitis is suspected, empiric antibiotics should be administered while awaiting CSF results.[25] Meningitis can be mistaken for migraine given the common symptoms of throbbing headache, photophobia, nausea, and vomiting, perhaps reflecting the underlying physiology in some cases.

Systemic bacterial and viral infections may also cause headache, typically of moderate to severe intensity and diffuse/holocranial in location, which develops in temporal relation to the onset of the infection and improves in parallel with its resolution.[2] It should also be noted that a systemic infection can worsen underlying migraine headache in predisposed patients.

HEADACHE SECONDARY TO TRAUMATIC CAUSES

This section addresses headache arising from trauma, as in posttraumatic headache and postcraniotomy headache.

Posttraumatic Headache

Posttraumatic headache has gained increasing recognition as a global health concern. Longitudinal studies report a cumulative incidence of 71% after moderate or severe traumatic brain injury and 91% after mild traumatic brain injury at 1 year following the event. However, the precise incidence and prevalence of posttraumatic headache is unclear, as many patients do not seek care following mild injury. Risk factors for the development of posttraumatic headache include a prior history of headache, milder degree of head trauma, and age younger than 60 years.[26] To be classified as posttraumatic headache, the onset must occur within 7 days of injury to the head or within 7 days of regaining consciousness following the event or of cessation of any medications that could potentially interfere with the patient's perception of the headache. Headache during the first 3 months after onset is considered to be acute and is classified as persistent if lasting beyond that period.[2] The phenotype of posttraumatic headache can vary, although most often is migrainous; tension-type headache is also commonly reported. Other accompanying symptoms can include dizziness, fatigue, cognitive difficulties, anxiety, insomnia, and personality changes. The treatment of posttraumatic headache is empiric, usually directed toward the presenting phenotype of the headache, as robust evidence from clinical trials is lacking at this time.

KEY POINTS

- Distinguishing cardiac cephalalgia from migraine, which may also be aggravated by exertion, is essential to avoid the inappropriate administration of triptan or ergot medications, which are contraindicated in coronary syndromes because of their vasoconstrictive effects.
- Blindness can be a complication of untreated temporal arteritis in approximately half of patients because of involvement of the ophthalmic artery and its branches; however, visual loss can be prevented with prompt glucocorticoid treatment.
- Contrast-enhanced MRI may demonstrate granulomatous inflammation of the cavernous sinus, superior orbital fissure, or orbit in Tolosa-Hunt syndrome.
- Risk factors for the development of posttraumatic headache include a prior history of headache, milder degree of head trauma, and age younger than 60 years.

Postcraniotomy Headache

Like posttraumatic headache, headache following craniotomy is common and may have similar underlying pathophysiology. Approximately two-thirds of patients experience acute postcraniotomy headache, defined by the *ICHD-3* as headache of variable intensity, maximal in the area of the craniotomy, which develops within 7 days after craniotomy and either (1) resolves within 3 months after craniotomy or (2) persists, but 3 months have not yet passed since craniotomy. About one-fourth of patients who develop acute postcraniotomy headache later develop the chronic form, which persists for more than 3 months after craniotomy.[2] Risk factors include a prior history of headache and suboccipital surgery.[27] The precise mechanism of postcraniotomy headache is unclear at the current time; however, it is believed that headache following craniotomy may occur through activation of the trigeminovascular system.

HEADACHE SECONDARY TO DISORDERS OF THE EYES, EARS, NOSE, SINUSES, OR OTHER CRANIOFACIAL STRUCTURES

This section addresses headache occurring in the context of acute angle-closure glaucoma, primary trochlear headache (trochleitis), rhinosinusitis, headache attributed to mucosal contact points, and headache due to temporomandibular disorders.

Acute Angle-Closure Glaucoma

Severe headache and eye pain can result from intermittent angle-closure glaucoma, whereby acute obstruction of aqueous humor at the drainage angle of the eye leads to a significant rise in intraocular pressure. Intermittent angle-closure glaucoma may be mistaken for migraine, as both conditions can present with unilateral eye pain, nausea/vomiting, light sensitivity, and visual disturbances including blurred vision as well as rainbow-colored halos around lights. The latter visual changes typically occur at the ictus of pain in acute angle-closure glaucoma. On examination, the eye is often injected with a fixed, moderately dilated pupil. However, between attacks, eye appearance and intraocular pressures are usually normal. Triggers for angle closure include sudden contrast in lighting conditions, prolonged reading, and use of specific medications (including some cold/allergy drugs with adrenergic agonist effects, certain anticholinergic medications such as tricyclic antidepressants, and some sulfa-based agents such as topiramate and acetazolamide). Patients with suspected acute angle-closure glaucoma should be referred urgently to ophthalmology for slit-lamp and gonioscopic examination. Laser iridotomy can help prevent future angle-closure attacks.[28,29]

Primary Trochlear Headache (Trochleitis)

Trochleitis signifies inflammation of the trochlea, which is a cartilaginous apparatus along the superomedial orbital rim that permits movement of the superior oblique. Patients present with localized superonasal pain of dull to severe intensity that worsens with eye movement, along with tenderness around the orbit. The pain may spread to involve the ipsilateral side of the head, but cranial autonomic features are not seen (as may occur in the trigeminal autonomic cephalalgias).[28] Some patients may experience diplopia, and palpation of the trochlear region can reproduce the pain. Treatment with oral

nonsteroidal anti-inflammatory drugs often alleviates pain; other treatments include oral or locally injected steroids.[30]

Rhinosinusitis

Rhinitis and sinusitis can cause a de novo headache or facial pain but may also exacerbate a primary headache disorder. Many patients who present with facial or frontal headache and are referred for sinus evaluation in fact have underlying migraine with no evidence of rhinosinusitis on CT imaging or endoscopic evaluation.[31] The occurrence of cranial autonomic symptoms in migraine (such as lacrimation, nasal congestion, and rhinorrhea) may contribute to the misdiagnosis of "sinus headache." *ICHD-3* diagnostic criteria for headache or facial pain attributed to acute rhinosinusitis necessitates clinical, nasal endoscopic, and/or imaging evidence of acute rhinosinusitis, as well as at least two of the following: (1) establishment of a temporal relation of pain to the onset of rhinosinusitis, (2) either reduction or exacerbation of pain symptoms paralleling improvement or worsening of rhinosinusitis symptoms, (3) increase of pain upon application of pressure over the paranasal sinuses, and (4) ipsilateral pain in the case of unilateral rhinosinusitis. The diagnosis of headache or facial pain attributed to chronic rhinosinusitis is based on evidence of current or past infection and evidence of causation, as listed above.[2]

Symptoms of acute rhinosinusitis include purulent rhinorrhea, fever, halitosis, and hyposmia. Headache can arise from activation of the trigeminal system via inflammatory mediators that are released in response to infectious or allergic triggers. The first and second divisions of the trigeminal nerve innervate the nasal and sinus mucosa: the first division innervates the frontal and anterior ethmoid sinuses, while the second division relays nociceptive inputs from the posterior ethmoid, maxillary, and sphenoid sinuses. The pain of acute sinusitis is often characterized as deep pressure, fullness or congestion in the face, and is frequently worsened with lying down.[32] Frontal sinusitis pain is commonly retro-orbital or directed toward the center of the forehead, with frontal tenderness to percussion. Pain can also be retro-orbital in ethmoid sinusitis and may involve the temples, with orbital sensitivity to pressure. With maxillary sinusitis, pain tends to be localized over the cheek area but can spread to the teeth or ears; patients may experience dental sensitivity to percussion. Although relatively infrequent, sphenoid sinusitis is a serious condition because of the potential complication of cavernous sinus thrombophlebitis. Patients frequently present with refractory nonlocalizing headache (without tenderness on examination), visual abnormalities, and cranial nerve palsies; the diagnosis is confirmed via CT, MRI, or endoscopic evaluation.

Headache Attributed to Mucosal Contact Points

Mucosal contact points, which are structures in the nasal cavity that remain in contact following decongestion therapy, have also been implicated as a cause for headache or facial pain. While surgical outcome series report relief of headache and facial pain after endoscopic endonasal surgery, a large study of a cohort of patients in a rhinology clinic found equal prevalence of nasal mucosal contact points in patients with and without facial pain.[33] In another study, nasal mucosal contact points were identified on CT imaging in 55% of patients without correlation to facial or head pain.[34] Thus, the causal relationship between mucosal contact points and facial pain or headache remains unclear.

KEY POINTS

- Intermittent angle-closure glaucoma may be mistaken for migraine, as both conditions can present with unilateral eye pain, nausea/vomiting, light sensitivity, and visual disturbances.
- The occurrence of cranial autonomic symptoms in migraine (such as lacrimation, nasal congestion, and rhinorrhea) may contribute to the misdiagnosis of "sinus headache."
- Although relatively infrequent, sphenoid sinusitis is a serious condition because of the potential complication of cavernous sinus thrombophlebitis.
- Headache attributed to temporomandibular disorders is usually unilateral and should be ipsilateral to the pathology when the temporomandibular complex is the source of pain, but can be bilateral when muscular involvement is present.

Headache Due to Temporomandibular Disorders

Temporomandibular disorders involve pathology to the temporomandibular joint or muscles. The temporomandibular joint is comprised of an upper and lower compartment separated by a fibrocartilaginous disk that permits translational and rotary motion of the mandible. Causes of dysfunction include trauma, joint asymmetry, changes in occlusion, disk displacements, joint osteoarthritis, and joint hypermobility. Headache attributed to temporomandibular disorders is usually unilateral and should be ipsilateral to the pathology when the temporomandibular complex is the source of pain, but can be bilateral when muscular involvement is present. Pain is most pronounced in the preauricular regions of the face, masseter muscles, or temporal areas; the headache is commonly described as tightening, aching, throbbing, or sharp and occurs at rest or is triggered by movements in the ramus of the mandible and the temporal, preauricular, and postauricular areas. Myofascial pain is characterized as achy or dull, and patients may note trigger points involving the masseters or temporalis muscles directly or with referred pain to the temporal/preauricular areas, ear, or other regions of the head.[35] Temporomandibular disorder–associated pain is mediated via the sensitive joint capsule and posterior disk attachment, with transmission of nociceptive signals via the trigeminal nerve (mandibular branch). The etiology of muscular pain (myalgia and myofascial pain with referral) in temporomandibular disorders is not clearly known. The diagnosis of facial pain or headache secondary to a temporomandibular disorder requires clinical and/or radiologic evidence of a pathologic process involving the temporomandibular joint, masticatory muscles, or associated structures; evidence of causation including the temporal relationship of pain to a temporomandibular disorder; and the same laterality and triggering or worsening of pain by provocative maneuvers such as movement or pressure on the temporomandibular joint or muscles of mastication.[2]

CONCLUSION

Secondary causes of headache are diverse and include various structural pathologies, vascular disorders, and infectious and inflammatory conditions. Despite the multitude of etiologies that can precipitate headache, the majority of severe headache cases are benign. A thorough medical and headache history, combined with a careful neurologic examination, can help to determine when further laboratory or imaging studies are warranted to rule out potentially life-threatening conditions.

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Unusual Headache Disorders

By Amaal Jilani Starling, MD, FAHS

ABSTRACT

PURPOSE OF REVIEW: Unusual headache disorders are less commonly discussed and may be misdiagnosed. These headache disorders frequently have a benign natural history; however, without reassurance, therapeutic education, and treatment, they can negatively affect the health and function of patients.

RECENT FINDINGS: This article reviews the clinical features, diagnosis, workup, and proposed treatments for several unusual headache disorders including primary cough headache, primary headache associated with sexual activity, primary exercise headache, cold-stimulus headache, primary stabbing headache, nummular headache, hypnic headache, and headache attributed to travel in space. Exploding head syndrome is also discussed, which is a sleep disorder commonly confused with a headache disorder.

SUMMARY: Unusual headache disorders are usually benign, yet without the correct diagnosis can be very worrisome for many patients. Through greater awareness of these headache disorders, neurologists can evaluate and effectively manage unusual headache disorders, which offers significant benefits to patients and practice satisfaction to neurologists.

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RELATIONSHIP DISCLOSURE:
Dr Starling has received personal compensation for serving on the medical advisory boards of Alder BioPharmaceuticals, Inc; Amgen Inc; Eli Lilly and Company; and eNeura Inc and as a consultant for Amgen Inc and Eli Lilly and Company. Dr Starling receives research/grant support from the Mayo Clinic and the Migraine Research Foundation.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Starling discusses the unlabeled/investigational use of acetazolamide, beta-blockers including nadolol and propranolol, caffeine, celecoxib, clomipramine, clonazepam, cyclobenzaprine, ergotamine, flunarizine, gabapentin, indomethacin, lithium, melatonin, nifedipine, nonsteroidal anti-inflammatory drugs, onabotulinumtoxinA, topiramate, and tricyclic antidepressants including amitriptyline for the treatment of unusual headache disorders.

INTRODUCTION

Although most patients with headache disorders have migraine or tension-type headache (because of the high lifetime prevalence of these disorders), more unusual headache disorders also present to the general neurologist. Fortunately, the natural history of most unusual headache disorders is benign. However, any type of new-onset head pain or sensation can be alarming for patients. In addition, every new-onset headache should be considered a secondary headache until proven otherwise. Knowledge of these unusual headache disorders will guide the neurologist's ability to identify, evaluate, and treat these disorders. Oftentimes, treatment may include education and reassurance of a benign course, although, at times, pharmacologic measures are essential to meet the needs of the patient. The purpose of this article is to discuss the clinical features, diagnosis, recommended workup, and treatment for primary cough headache, primary headache associated with sexual activity, primary exercise headache, cold-stimulus headache, primary stabbing headache, nummular headache, hypnic headache, headache attributed to travel in space, and exploding head syndrome.

PRIMARY COUGH HEADACHE

Primary cough headache is a benign headache precipitated by coughing or straining that is not attributed to a secondary cause, such as an intracranial lesion.

Clinical Features and Diagnostic Criteria

Primary cough headache is rare, with an estimated prevalence of about 1%.[1,2] Given that primary cough headache is rare, when a patient presents with a headache triggered by cough or some other Valsalva maneuver that may raise intracranial pressure, the most essential first step is to rule out a secondary cause based on red flags identified on history and examination. In some studies, more than 50% of cases of headache triggered by cough or Valsalva maneuvers are secondary headache disorders, most commonly a headache attributed to an Arnold-Chiari malformation type I.[2]

To meet *International Classification of Headache Disorders, Third Edition* (*ICHD-3*) diagnostic criteria for primary cough headache, at least two sudden-onset headache attacks must occur that are brought on by coughing, straining, and/or other Valsalva maneuvers and last from 1 second to 2 hours, and it must not be better accounted for by another *ICHD-3* diagnosis.[3] (Refer to the open access online version of the *ICHD-3* for a complete listing of the diagnostic criteria discussed in this article.[3]) Primary cough headache is more common in women (64%) compared to men, with an average age of onset of 60 years of age (range of 22 to 80 years of age).[2] Clinically, it can be bilateral or unilateral, most commonly with a mixed quality of pain (electrical, explosive, or pressing), lasting for only seconds in 78% of cases.[2]

Differential Diagnosis and Recommended Workup

The differential diagnosis includes posterior fossa structural lesions, Arnold-Chiari malformation type I, etiologies of thunderclap headache including reversible cerebral vasoconstriction syndrome (RCVS), cervical artery dissection, and perturbations in CSF pressure. Typically, patients with a secondary cause will have symptoms in addition to headache (eg, dizziness, unsteadiness, facial or upper limb numbness, vertigo, or syncope).[2]

Workup to assess for causes of secondary headache should include diagnostic neuroimaging with a brain MRI with and without contrast and a magnetic resonance angiogram (MRA) of the head and neck. If increased CSF pressure is suspected, a magnetic resonance venogram (MRV) of the head and lumbar puncture (if no contraindications) are indicated.

Proposed Mechanism

The mechanism for primary cough headache is unknown; however, it is suspected to be related to a sudden increase in intracranial venous pressure, hypersensitivity of mechanoreceptors located in venous structures, or crowding of the posterior fossa.[4–6]

Treatment

Since primary cough headaches are benign attacks of short duration, often reassurance is the only treatment needed. However, if symptoms are bothersome and affect daily function, treatments known to reduce CSF pressure appear to be effective, including indomethacin, high-volume lumbar puncture, and acetazolamide.[2,4,7,8] Primary cough headache is an indomethacin-responsive

KEY POINTS

- Given that primary cough headache is rare, when a patient presents with a headache triggered by cough or some other Valsalva maneuver that may raise intracranial pressure, the most essential first step is to rule out a secondary cause based on red flags identified on history and examination.
- Since primary cough headaches are benign attacks of short duration, often reassurance is the only treatment needed.

headache. Indomethacin titrated up to 50 mg/d to 100 mg/d is an effective treatment.[2] In cases where indomethacin is ineffective or not tolerated, acetazolamide is an option. Based on previous observations, Raskin[7] demonstrated that a large-volume lumbar puncture (removal of 40 mL of CSF) may have a therapeutic long-lasting benefit in primary cough headache.[9] In this author's practice, a therapeutic high-volume lumbar puncture, if effective, can often allow patients to avoid medications including indomethacin, which has gastrointestinal complications, and acetazolamide, which is typically poorly tolerated.

PRIMARY HEADACHE ASSOCIATED WITH SEXUAL ACTIVITY

Primary headache associated with sexual activity was previously called benign sex headache, coital headache, preorgasmic headache, or orgasmic headache. However, clinical studies were unable to differentiate between preorgasmic and orgasmic headaches; therefore, all subtypes now fall into the more inclusive single diagnosis of primary headache associated with sexual activity.

Clinical Features and Diagnostic Criteria

Primary headache associated with sexual activity is rare, with an estimated lifetime prevalence of about 1%.[1] To meet *ICHD-3* diagnostic criteria, there must be at least two attacks brought on by and occurring only during sexual activity that last anywhere from 1 minute to 24 hours with severe intensity and/or up to 72 hours with mild intensity.[3] These attacks can increase in intensity with increasing sexual arousal or can occur suddenly with explosive intensity just before or with orgasm.[3] Clinically, the headache location can vary, although it is commonly bilateral.[10] The pain is typically pulsating or throbbing and lasts for minutes to hours.[11]

This headache disorder has been described in adults[12,13] but can occur in adolescents as soon as the capacity to have an orgasm is achieved.[14] There is a male predominance.[10,15] For many patients, remission may occur after several months; however, some may have a more chronic course or experience recurrence.[11–13,15] Primary headache associated with sexual activity is comorbid with primary exertional headache (about 30% to 40%) and migraine (about 30%).[3]

Differential Diagnosis and Recommended Workup

It is essential to remember that a new-onset headache associated with sexual activity is a secondary headache until proven otherwise. An explosive attack just before or with orgasm is a thunderclap headache, which is a headache red flag and a neurologic emergency. A thunderclap headache, which is a severe sudden-onset headache that reaches peak intensity within 60 seconds, is concerning for intracranial bleeding, most commonly a subarachnoid hemorrhage from an aneurysmal rupture and other vascular entities. Because of the high rate of morbidity and mortality, a subarachnoid hemorrhage must be ruled out as soon as possible. However, if intracranial bleeding is not present, other causes of a thunderclap headache should be investigated as well. Other causes of thunderclap headache include RCVS, cerebral venous sinus thrombosis, or cervical artery dissection.[16] All patients with a thunderclap headache must undergo a noncontrast head CT. If the head CT does not reveal the cause of the thunderclap headache, a lumbar puncture is indicated. A lumbar puncture helps to evaluate for a possible subarachnoid hemorrhage or other causes of a

thunderclap headache. If both the head CT and lumbar puncture are unrevealing, additional neurovascular head and neck imaging (MRA/MRV or CT angiography/CT venography) is recommended to rule out other causes of a thunderclap headache.[16] Once more alarming causes of headache have been ruled out, a diagnosis of primary headache associated with sexual activity can be considered. Thus, it is a diagnosis of exclusion.

Proposed Mechanism

The pathophysiology of primary headache associated with sexual activity is largely unknown; however, it is suspected to be related to sudden changes in hemodynamics and abnormal cerebrovascular autoregulation.[17,18] In one study, 12 out of 19 patients were found to have venous stenosis via MRV of the head, suggesting that venous blood flow abnormalities may contribute to the mechanism or at least be a risk factor for the disorder.[19]

Treatment

Treatment starts with education and reassurance of the benign, self-limiting natural history of this headache disorder. Anticipatory treatment 30 minutes prior to sexual activity with indomethacin can be an effective treatment plan for most patients.[10,12,13,15] However, if longer term prevention is needed, beta-blockers have also been used successfully.[2,10,12,15]

PRIMARY EXERCISE HEADACHE

Primary exercise headache is a benign primary headache disorder that was previously termed primary exertional headache.

Clinical Features and Diagnostic Criteria

Although clinically similar to primary cough headache and primary headache associated with sexual activity, primary exercise headache is unique in that it is precipitated by sustained physically strenuous activity rather than short-duration precipitating factors such as cough, Valsalva maneuver, or orgasm.[3] Primary exercise headache typically lasts less than 48 hours, has a pulsating quality, occurs particularly in hot weather or high altitudes, and is self-limited, requiring treatment for 2 to 6 months.[2] To meet *ICHD-3* diagnostic criteria for primary exercise headache, there must be at least two headache episodes brought on by and occurring only during or after strenuous physical exercise that last for less than 48 hours and are not better accounted for by another *ICHD-3* diagnosis.[3]

Prevalence

Primary exercise headache is thought to be a relatively uncommon primary headache disorder, although prevalence has varied in studies from 1% to 26%.[1,2] A prospective series performed in a headache clinic found that 11 out of 6412 patients with headache met the criteria for primary exercise headache.[2] Low prevalence, high comorbidity with migraine, and self-limited prognosis was confirmed in this prospective study.[2] However, in a study performed in highly athletic cyclists, the prevalence was much higher (26%), which may be a result of exposure to hot weather, extreme exertion, or dehydration.[20] Given the high prevalence in athletes, this entity should be considered when evaluating an athlete with headache.

KEY POINTS

- An explosive attack just before or with orgasm is a thunderclap headache, which is a headache red flag and a neurologic emergency.
- A diagnosis of primary headache associated with sexual activity can be considered once more alarming causes of headache have been ruled out; thus, it is a diagnosis of exclusion.
- Anticipatory treatment 30 minutes prior to sexual activity with indomethacin can be an effective treatment plan for most patients with primary headache associated with sexual activity. However, if longer term prevention is needed, beta-blockers have also been used successfully.
- Primary exercise headache is unique in that it is precipitated by sustained physically strenuous activity rather than short-duration precipitating factors such as cough, Valsalva maneuver, or orgasm.
- Given the high prevalence in athletes, primary exercise headache should be considered when evaluating an athlete with headache.

Proposed Mechanism

The pathophysiology of primary exercise headache is unclear, although internal jugular vein valve incompetence has been proposed based on a study demonstrating that 70% of subjects with primary exercise headache had retrograde venous flow in the jugular vein compared to 20% of healthy controls.[21] It has been suggested that pain-sensitive venous sinus dilatation secondary to incompetent valves and retrograde flow may have a nociceptive and causative role in primary exercise headache.[21] However, this does not explain why primary exercise headache is typically a self-limited disorder, since internal jugular vein valve incompetence does not resolve spontaneously.

CASE 12-1

A 54-year-old man with obesity, untreated hypertension, hyperlipidemia, and a family history of coronary artery disease at a young age had been instructed by his primary care physician to begin an exercise regimen to better control his vascular risk factors. After 4 weeks, he reported that he was unable to exercise because of severe headaches that developed toward the end of a 40-minute aerobic workout. The headaches lasted about 1 to 2 days. He also noted neck pain since he started exercising, but he denied any other associated features. He denied a sudden thunderclap headache.

He was referred for a neurologic evaluation. Examination showed an elevated blood pressure of 151/85 mm Hg; neurologic examination was normal. Because the patient's headaches were precipitated by exercise, and considering the patient's vascular risk factors, additional investigations were performed. MRI of the brain, magnetic resonance angiography (MRA) of the head and neck, and stress echocardiogram were all within normal limits.

After ruling out a secondary headache, primary exercise headache was diagnosed. He had a history of gastritis, and therefore indomethacin was avoided. Although the headache disorder was felt to be benign, prevention was discussed to enable him to exercise, lose weight, and reduce his vascular risk factors. Propranolol was titrated to 60 mg twice a day, which was effective for headache prevention and reduced his blood pressure to an acceptable range.

COMMENT

Headache precipitated by exercise is a secondary headache until proven otherwise, especially in a patient with vascular risk factors. Cardiac cephalalgia is caused by myocardial ischemia, and headache may be the sole manifestation. A stress test is diagnostic, and revascularization is curative. In this case, cardiac cephalalgia and other causes of secondary exercise-induced headaches were appropriately considered and excluded. Primary exercise headache can be effectively treated with indomethacin, if tolerated, or beta-blockers for those who cannot use nonsteroidal anti-inflammatory drugs because of gastrointestinal or other contraindications.

However, one proposed hypothesis is that incompetent internal jugular vein valves are a risk factor for primary exercise headache, and that the self-limited course of primary exercise headache may be a result of transient circulating metabolic substrates triggering symptoms in the setting of the incompetent valves.[18,21]

Differential Diagnosis and Recommended Workup

A secondary headache must be ruled out in all patients with new-onset headache by evaluating red flags in the history and on examination. Precipitation of headache by exercise or exertion is a headache red flag and should raise concern for a secondary cause of headache. Thus, a detailed headache history and comprehensive neurologic examination with appropriate neurovascular imaging and other tests may be required prior to the diagnosis of primary exercise headache. Secondary headache disorders that should be considered include intracranial hemorrhage (subarachnoid hemorrhage), RCVS, cervical artery dissection, cerebral venous sinus thrombosis, intracranial hypertension or hypotension, Arnold-Chiari malformation type I, cardiac cephalalgia, or pheochromocytoma.

A noncontrast head CT will help assess for intracranial hemorrhage in the acute setting with consideration for a lumbar puncture depending on the clinical scenario. In addition, neurovascular imaging using a CT angiogram or MRA should be completed to rule out other vascular causes of secondary headache when precipitated by exertion or exercise.

Cardiac cephalalgia should be considered in older adults with vascular risk factors, as demonstrated in **CASE 12-1**. The headache in cardiac cephalalgia is a result of myocardial ischemia and can be the sole manifestation of cardiac ischemia.[22] A cardiac stress test is diagnostic, and revascularization of coronary vessels is curative.[23] Pheochromocytoma is a rare, non-neurologic cause of exertional headache that can be investigated with blood and urinary work, which is especially sensitive during the headache episode.

Although the clinician must look for secondary causes of exercise or exertion-triggered headache onset, the majority of these headaches are concluded to be primary and benign.[24]

Treatment

Given that primary exercise headache is a self-limited benign disorder, once a workup has been completed, treatment is often as simple as trigger avoidance.[25] However, exercise is essential for healthy living, and if primary exercise headache is a barrier to exercise, then pharmacotherapy is available and typically effective. Primary exercise headache is an indomethacin-responsive headache. Indomethacin can be taken on a scheduled basis or prior to exercise.[25] For patients who do not respond to or are unable to tolerate indomethacin, beta-blockers such as nadolol or propranolol have been effective.[10]

HEADACHE ATTRIBUTED TO INGESTION OR INHALATION OF A COLD STIMULUS

An "ice cream headache" or "brain freeze," as is commonly referred to, is classified by the *ICHD-3* as a headache attributed to ingestion or inhalation of a cold stimulus.[3]

KEY POINTS

- **Precipitation of headache by exercise or exertion is a headache red flag and should raise concern for a secondary cause of headache.**
- **Cardiac cephalalgia should be considered in older adults with vascular risk factors who present with a headache precipitated by exercise. The headache is a result of myocardial ischemia and can be the sole manifestation of ischemia. A stress test is diagnostic, and revascularization of coronary vessels is curative.**
- **Given that primary exercise headache is a self-limited, benign disorder, once a workup has been completed, treatment is often as simple as trigger avoidance. However, exercise is essential for healthy living, and if primary exercise headache is a barrier to exercise, then pharmacotherapy is available and typically effective.**

Clinical Features and Diagnostic Criteria

To meet *ICHD-3* diagnostic criteria for headache attributed to ingestion or inhalation of a cold stimulus, there must be at least two episodes of acute frontal or temporal headache brought on by and occurring immediately after a cold stimulus to the palate and/or posterior pharyngeal wall that resolve within 10 minutes after removal of the cold stimulus and which are not better accounted for by another *ICHD-3* diagnosis.[3] Although this type of headache typically occurs in the setting of eating or drinking something very cold, it has also been reported during surfing in the winter and during ice-skating; thus, the inhalation of cold air was added to the criterion.[26,27] Typically, intense pain begins within a few seconds of the rapid ingestion or inhalation of cold material and is short lasting, persisting only seconds. Two large survey studies have demonstrated that the majority of cold-stimulus headache episodes last less than 30 seconds.[28,29] Rapid passage is important. In a study that compared placing an ice cube on the palate compared to the ingestion of 200 mL of ice water as fast as possible, rapid ice water ingestion more consistently provoked a cold-stimulus headache in 51% versus 12% of subjects.[30] The speed at which waters cooled down the entire oral cavity was thought to be a differentiating factor. In addition, a randomized trial of accelerated (consumption of 100 mL of ice cream in less than 5 seconds) versus cautious (consumption of 100 mL of ice cream in greater than 30 seconds) ice cream eating demonstrated that eating ice cream quickly was about 2 times more likely to trigger a cold-stimulus headache.[31] The reported prevalence of cold-stimulus headache varies, largely based on study population demographics, ranging from 7.6% to 93%.[28,31–34] It is more common in people with migraine.[32–34]

Proposed Mechanism

The underlying mechanism of cold-stimulus headache is thought to be vascular and is similar to when a person runs his or her icy cold hands under hot water, resulting in hand pain. Cold-induced pain of the hand is correlated with reduced arterial pulses in the hand[35] followed by erythema of the hands, which is correlated with vasodilation. The exposure of the palate or the posterior pharyngeal wall to a very cold substance may trigger rapid constriction and dilation of vessels, thus activating the nociceptors in the vessel wall. In addition, cold-stimulus headache is an example of referred pain where cold stimulation of the palate or posterior pharyngeal wall results in frontal or temporal head pain.[35]

Treatment

Aside from trigger avoidance, no specific treatment is required. Patients should ingest cold substances slowly and avoid rapid exposure of cold substances to the posterior aspect of the palate if possible. Most importantly, these headaches are benign and short lasting, thus the abstinence of ingesting cold substances, such as ice cream, is not necessary or recommended by this author; just savor it slowly.

PRIMARY STABBING HEADACHE

Primary stabbing headache, commonly referred to as ice pick headache, is characterized by ultrashort localized jabs, jolts, or stabs of pain usually lasting 1 to 2 seconds.[36]

Clinical Features and Diagnostic Criteria

Primary stabbing headache is likely very common. Some studies have estimated up to 35% of the general population has experienced at least one episode of primary stabbing headache.[37] The true estimate may be even higher given that individuals with one or two episodes may have forgotten about these benign symptoms. Interestingly, in patients with migraine, the prevalence of primary stabbing headache is high at about 40%.[38] Primary stabbing headache is more common in females, and onset is typically in adulthood.[37]

To meet *ICHD-3* diagnostic criteria for primary stabbing headache, each stab must last for up to a few seconds and occur at an irregular frequency, from a single stab to a series of stabs and from one to many episodes per day.[3] No cranial autonomic features are present.[3] Clinically, primary stabbing headaches are headaches with the shortest duration, with studies demonstrating that 80% of stabbing pains last 3 seconds or less.[36] These episodes are not triggered by mechanical stimuli such as touch, eating, or talking. No migrainelike features or sensory sensitivities are associated with the stabbing pains. Based on the trigeminal distribution of pain, trigeminal nerve hyperexcitability is hypothesized, but the mechanism of primary stabbing headache remains unknown.[24]

Differential Diagnosis and Recommended Workup

The differential diagnosis for primary stabbing headache includes trigeminal neuralgia and trigeminal autonomic cephalalgias, specifically short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA). Trigeminal neuralgia is typically localized to one trigeminal branch distribution (usually V3 or V2), is easily triggered by mechanical stimuli, and is responsive to treatment with carbamazepine. SUNCT is typically localized to one trigeminal branch distribution (usually V1), is often triggerable, and is associated with unilateral cranial autonomic features.[39] These distinguishing features should narrow the differential diagnosis. However, new-onset primary stabbing headache, especially in a patient without a history of migraine, should first prompt a workup for a secondary cause. Short stabs of pain have been described with trauma, glaucoma, increased intracranial pressure secondary to mass lesions, pituitary lesions, and herpes zoster.[24,36,40,41] In addition to a thorough history and examination, neuroimaging may be indicated depending on headache red flags.

Treatment

Idiopathic primary stabbing headache is benign and typically does not require any specific treatment aside from reassurance. However, if the stabbing pains are more frequent, indomethacin is the medication of choice.[36,42] Melatonin, celecoxib, and gabapentin have also been used when indomethacin is ineffective, not well tolerated, or contraindicated.[24]

NUMMULAR HEADACHE

Nummular headache is an unusual primary headache disorder characterized by head pain that occurs in a small, fixed, very well-circumscribed coin, oval, or elliptical shape.

KEY POINTS

- In headache attributed to ingestion or inhalation of a cold stimulus, intense pain typically begins within a few seconds of the rapid ingestion or inhalation of cold material and is short lasting, persisting only for seconds.
- In headache attributed to ingestion or inhalation of a cold stimulus, the exposure of the palate or the posterior pharyngeal wall to a very cold substance may trigger rapid constriction and dilation of vessels, thus activating the nociceptors in the vessel wall, resulting in referred pain to the head.
- Aside from trigger avoidance, no specific treatment is required for headache attributed to ingestion or inhalation of a cold stimulus. Cold substances should be ingested slowly while avoiding rapid exposure of cold substances to the posterior aspect of the palate if possible.
- Clinically, primary stabbing headaches are headaches with the shortest duration, with studies demonstrating that 80% of stabbing pains last 3 seconds or less.
- The differential diagnosis for primary stabbing headache includes trigeminal neuralgia and trigeminal autonomic cephalalgias, specifically short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms.

Clinical Features and Diagnostic Criteria

Because of its rarity, its true prevalence is unknown, although one hospital series estimated 6.4 out of 100,000 patients per year experience nummular headache.[43] Nummular headaches are more common in females, about 1.8:1, with a mean age of onset at 45.4 years of age (range of 4 to 82 years of age). About 13% of patients report prior head trauma. Interestingly, limited correlation typically exists between the site of trauma and the location of the focal, well-circumscribed head pain. Others have not identified any potential precipitating factors. Almost 50% of patients have a preexisting headache diagnosis, most commonly migraine.[44]

To meet *ICHD-3* diagnostic criteria for nummular headache, the head pain should be felt in one area of the scalp and be sharply contoured, fixed in size and shape, round or elliptical, and 1 cm to 6 cm in diameter. The pain can either be continuous or episodic.[3] Clinically, the pain quality is described as pressurelike, sharp, or stabbing. The pain remains focal and well circumscribed and never radiates. Exacerbation of pain can be triggered by mechanical stimuli and can occur spontaneously. The pain will rarely awaken a patient from sleep.[43] About 50% of patients endorse not only pain but also sensory dysfunction (paresthesia, allodynia, hypoesthesia, or hyperesthesia) in the coin-shaped area of pain.[44] Although the diagnostic criteria allow for pain of variable duration, two-thirds of patients have chronic, continuous head pain. Typically, associated features including photophobia, nausea, vomiting, or unilateral cranial autonomic features are not present.

Differential Diagnosis and Recommended Workup

Given the focal nature of nummular headache, it is essential to rule out a secondary headache disorder with a detailed history and neurologic examination, laboratory studies, and neuroimaging. The examination must include careful inspection of the epicranial tissues. Laboratory studies should include a complete blood cell count, basic metabolic panel, liver function tests, thyroid function tests, erythrocyte sedimentation rate, antinuclear antibodies, and rheumatoid factor.[43] In the setting of well-circumscribed pain, an underlying structural lesion must be ruled out with imaging studies. A skull x-ray, CT head, or MRI brain without contrast can be performed to rule out a structural lesion.[43] Once a secondary headache or underlying structural lesion has been ruled out, other entities to consider in the differential diagnosis include primary stabbing headache, although this is typically multifocal and not unifocal as in nummular headache; epicrania fugax,[45] although this head pain is in motion rather than a single focal, coin-shaped area as occurs in nummular headache; and other cranial neuralgias, although a cranial neuralgia would follow the relevant nerve distribution and respond to anesthetic blocks, both of which do not occur in nummular headache.

Proposed Mechanism

It is unclear if the mechanism underlying nummular headache is peripheral or central. The evidence for a more peripheral process includes a small, fixed area of pain and associated sensory dysfunction in the same location.[46] However, nummular headache has not responded consistently to peripheral nerve blocks and does not follow a particular nerve distribution. In addition, centrally acting treatment options have been effective.[44] It has been hypothesized that nummular headache may be a focal form of complex regional pain syndrome, particularly when onset is temporally correlated with injury or surgery to

the head.[43] In addition, trophic changes have been reported, such as focal skin depression, hair loss, reddish color, or increased temperature as seen in complex regional pain syndrome.[47,48]

Treatment

Unfortunately, because of the rarity of nummular headache, little evidence exists upon which to base clinical treatment recommendations. About 60% of patients respond to simple analgesics and nonsteroidal anti-inflammatory drugs, but preventive options are considered for patients with more severe refractory pain.[44] In this author's practice, patients with severe, refractory, continuous pain can be difficult to treat effectively. Gabapentin, tricyclic antidepressants, and onabotulinumtoxinA injections have at least been partially effective in 45% to 92% of patients.[44] Surprisingly, anesthetic blocks of the symptomatic area have been largely ineffective.[44] Other treatment options have been reported to be helpful in case reports including cyclobenzaprine,[49] indomethacin,[50,51] and even transcutaneous electrical nerve stimulation.[52]

HYPNIC HEADACHE

Hypnic headache is a recurrent primary headache disorder of short duration that typically occurs in older persons, typically after the age of 50.

Clinical Features and Diagnostic Criteria

Hypnic headache occurs only during sleep and will cause the person to awaken. It is commonly referred to as an "alarm clock headache" because of its untimely occurrence at the same time every night. Its epidemiology is unknown but is likely rare.[24] Hypnic headache is more prevalent in females (65%) than males.[24] To meet *ICHD-3* diagnostic criteria for hypnic headache, symptoms must include recurrent headaches lasting 15 minutes to 4 hours that develop only during sleep, cause awakening, and occur on 10 or more days per month for more than 3 months.[3] These headache attacks are not associated with unilateral cranial autonomic features, restlessness, or sensory sensitivities. The pain is constant, of mild to moderate intensity, and can be bilateral or unilateral.[53] The mechanism is unknown, although age-related dysfunction of the suprachiasmatic nucleus of the hypothalamus is hypothesized.[54,55]

Differential Diagnosis and Recommended Workup

Given that a new-onset headache in older patients is a headache red flag, secondary causes of headache must be ruled out before the diagnosis of hypnic headache can be made, as demonstrated in **CASE 12-2**. The differential diagnosis for nocturnal headaches includes nocturnal hypertension, increased intracranial pressure (mass lesion or idiopathic intracranial hypertension), trigeminal autonomic cephalalgias (specifically cluster headache), caffeine withdrawal headache, medication-overuse (rebound) headache, and sleep apnea headache. Cluster headache attacks occur at nightly intervals; however, the presence of autonomic features should guide the diagnosis. Caffeine withdrawal or medication-overuse headaches frequently occur at night or in the early morning; however, these headaches are typically present upon awakening rather than the headache attack itself waking the patient. In addition to a careful history and examination, neuroimaging, laboratory studies (including an erythrocyte sedimentation rate), lumbar puncture, ambulatory blood pressure

KEY POINTS

- Idiopathic primary stabbing headache is benign and typically does not require any specific treatment aside from reassurance. However, if the stabbing pains are more frequent, indomethacin is the medication of choice.
- Nummular headache is an unusual primary headache disorder characterized by head pain that occurs in a small, fixed, very well-circumscribed coin, oval, or elliptical shape.
- Entities to consider in the differential diagnosis for nummular headache include primary stabbing headache, although this is typically multifocal and not unifocal as in nummular headache; epicrania fugax, although this head pain is in motion and not a focal, coin-shaped area as occurs in nummular headache; and other cranial neuralgias, although these would follow the relevant nerve distribution and respond to anesthetic blocks, both of which do not occur in nummular headache.
- Hypnic headache is a recurrent primary headache disorder of short duration that typically occurs in older persons, typically after the age of 50. These headaches occur only during sleep and will cause the person to awaken.

monitoring, or a sleep study, depending on the red flags present, may be needed to further narrow the differential diagnosis.

Treatment

Treatment options for hypnic headache include caffeine (100 mg to 200 mg), melatonin (3 mg to 12 mg), or lithium (200 mg to 600 mg); these medications should be given prior to bedtime.[56] Although effective, lithium may be problematic especially for older patients because of the possibility for lithium toxicity, narrow therapeutic window, altered pharmacokinetics, reduced renal function, drug-drug interactions, and adverse effects that can affect mental status or balance. Fortunately, caffeine and/or melatonin are typically effective, thus avoiding use of lithium altogether.[56,57]

CASE 12-2

A 68-year-old woman presented to the neurology clinic for evaluation of new-onset headaches. The headaches had occurred almost every night for the past 4 months at about 4:00 AM and had been waking her up. The headache was a bilateral, moderate intensity, pressurelike pain that lasted for about 20 minutes. She usually woke up, went to the bathroom, and got a drink of water; by that time, the headache would be gone; and she would try to go back to sleep. This affected her sleep, and she felt that it was impairing her ability to function during the day because of fatigue. She had no significant past medical history.

She denied daytime headache, scalp tenderness, jaw claudication, visual symptoms, body aches and pains out of the ordinary, or any other systemic symptoms. She denied any autonomic features or restlessness. She endorsed fatigue, and she snored quite heavily, although her bed partner denied any obvious apneic spells. She had no prior history of headaches.

Her general and neurologic examination was essentially normal, except for obesity and some reduced range of active motion of her neck with extension, lateral flexion, and horizontal rotation. Pertinent negative findings included normal blood pressure, intact temporal artery pulsations, no temporal artery or scalp tenderness or scalp allodynia, and normal cranial nerves, including funduscopic examination. Complete blood cell count, erythrocyte sedimentation rate, C-reactive protein, ambulatory blood pressure monitor, sleep study, and noncontrast head CT were all within normal limits.

She was diagnosed with hypnic headache and was advised to drink a strong cup of coffee prior to bedtime. This treatment regimen immediately stopped her nightly headaches, and she was able to sleep despite the caffeine prior to bedtime.

COMMENT

Older patients with a new-onset headache should be investigated for a secondary cause of headache. However, once secondary causes are ruled out, a nocturnal headache that wakens the patient is likely hypnic headache. Caffeine prior to bedtime can be both diagnostic and therapeutic.

HEADACHE ATTRIBUTED TO TRAVEL IN SPACE

Headache attributed to travel in space, or space headache, was previously attributed to space motion sickness syndrome.[58] More recently, it has been identified as a separate entity from space motion sickness syndrome and is included in the appendix of the *ICHD-3.* With more scientific evidence, this diagnosis may move into the main body of the classification on the next revision.[3]

Clinical Features and Diagnostic Criteria

Headache attributed to travel in space is a secondary headache classified as a *headache attributed to disorder of homeostasis* based on the presumed pathophysiology.[3] The *ICHD-3* diagnostic criteria do not provide characteristics of the headache itself or associated clinical features but simply describe a temporal relationship to travel in space. It is a headache that occurs exclusively during space travel and remits spontaneously on return to earth.[3]

A 2009 study demonstrated that 12 out of 17 (71%) astronauts reported headache episodes during a space mission.[58] Among this small sample size, headache was reported as occurring in all phases of space flight (launch, docking, extravehicular activity, and landing). It typically has a moderate to severe intensity with an exploding or heavy quality of pain requiring analgesics.[58] None of the astronauts had a history of recurrent headache on earth. Studies using head-down-tilted bed rest, which simulates space microgravity on earth, have demonstrated headache episodes in the absence of symptoms associated with space motion sickness syndrome.[59]

Proposed Mechanism and Treatment

In a study of head-down-tilted bed rest, counter measures, including 30 minutes of upright aerobic exercise and enhanced artificial gravity, reduced the severity of space headache.[59] This may serve as a model for space headache on earth to further elucidate the pathophysiology and treatment. It is well-known that significant fluid shifts occur in microgravity, resulting in elevated intracranial pressure.[60] Another pathophysiologic consideration for space headache is hypoxia in microgravity. Microgravity reduces the hypoxic drive but not the hypercapnic drive to ventilate.[61] With further prospective studies, both in space and simulated microgravity, a better understanding of the underlying disorder of homeostasis will hopefully guide effective treatment for this common but debilitating headache during space flight.

EXPLODING HEAD SYNDROME

Exploding head syndrome is a sleep disorder commonly confused for a headache disorder by both patients and clinicians.

Clinical Features and Diagnostic Criteria

During an acute attack of exploding head syndrome, the patient has a perception of a loud, explosive noise in the absence of objective acoustic stimulation that usually occurs during sleep transitions when going to sleep or awakening. It is sudden, causes fear, but is not associated with head pain, as is demonstrated in CASE 12-3. The actual attack is very brief, lasting less than 1 second; however, the frequency is highly variable, ranging from one attack every few days to several attacks per night. Exploding head syndrome is classified as a sensory parasomnia; however, because of its sudden onset and other clinical characteristics, both

KEY POINTS

- The differential diagnosis for nocturnal headaches includes nocturnal hypertension, increased intracranial pressure (mass lesion or idiopathic intracranial hypertension), trigeminal autonomic cephalalgias (specifically cluster headache), caffeine withdrawal headache and medication-overuse (rebound) headache, or sleep apnea headache.
- Treatment options for hypnic headache include caffeine, melatonin, and lithium. Although effective, lithium may be problematic especially for older patients because of the possibility for lithium toxicity. Fortunately, caffeine and/or melatonin are typically effective, thus avoiding use of lithium altogether.
- Space headache has been reported in all phases of space flight. It typically has a moderate to severe intensity with an exploding or heavy quality of pain requiring analgesics.
- During an acute attack of exploding head syndrome, the patient has a perception of a loud, explosive noise in the absence of objective acoustic stimulation that usually occurs during sleep transitions when going to sleep or awakening. It is sudden, causes fear, but is not associated with head pain.

primary and secondary headache disorders should be included in the differential diagnosis. The *ICHD-3* diagnostic criteria include three components: (1) a complaint of a sudden loud noise or sense of explosion in the head at the wake-sleep transition or upon awakening during the night, (2) abrupt arousal following the event, often with a sense of fright, and (3) not associated with significant pain.[62] In addition to the perception of a loud noise or explosion and fear, patients have also reported flashes of light or other visual phenomena, tachycardia, sweating, and, rarely, myoclonic jerks.[63,64]

Because of misdiagnosis, lack of adequate assessment tools, and patient reluctance to report symptoms to medical providers, the true prevalence of exploding head syndrome is unknown. Based on recent studies, rough prevalence estimates suggest 10% to 14%.[63] Females are more affected than males.[63,65] Exploding headache syndrome occurs predominately in older people with a median age of onset of 54 years.[63] Although the natural history of the syndrome is variable, more recent case series and review of the literature support a more chronic course with a variable attack frequency.[63]

Proposed Mechanism

The pathophysiology of exploding head syndrome is unknown, but possibilities include middle ear dysfunction, brief focal seizures, drug withdrawal, calcium channel dysfunction, or abnormal function of the brainstem reticular formation.[64] Cortical EEG recordings have not demonstrated epileptiform

CASE 12-3

A 50-year-old woman presented to the emergency department in a panic. She had been falling asleep when she suddenly heard a loud "pop" or "explosion" in her head. She worked as a nurse, and she requested a head CT as she was concerned that a blood vessel had exploded. She denied any head pain. She had experienced two or three similar events over the prior week. She was very worried these were warning signs of impending aneurysmal rupture and a subarachnoid hemorrhage. She had no significant past medical history.

She was tachycardic at 108 beats/min and her blood pressure was 141/85 mm Hg, but her general and neurologic examinations were otherwise normal.

A noncontrast head CT was performed and was negative for any acute abnormalities including intracranial bleeding. The patient was discharged from the emergency department without a diagnosis with a neurology referral.

At her outpatient neurology visit, she was diagnosed with exploding head syndrome. With her background as a health care professional, reading the diagnostic criteria for the syndrome provided her with the necessary education and reassurance. Other treatment options were deferred because of the benign condition and side effects of medications.

COMMENT

Attacks of exploding head syndrome can be very alarming for patients. Appropriate diagnosis and patient education are the mainstays for treatment in this benign self-limited syndrome.

activity.[66] However, depth electrode recordings have not been done, and thus subcortical seizures have not been definitively ruled out. Acute attacks have occurred in the setting of rapid withdrawal from benzodiazepines and antidepressant medications.[67] Similar to familial hemiplegic migraine and episodic ataxia, mutations in the *CACNA1A* gene on chromosome 19 have been identified, which could result in calcium channel dysfunction.[66,68,69] Although EEGs and polysomnograms have not provided definitive etiologies, they have demonstrated that just prior to the acute attack, there is a short alerting effect consisting of alpha blocking and beta activity on the EEG and an increase in EMG activity.[68] This may be related to the most commonly accepted hypothesis of delayed inhibition of the brainstem reticular formation during sleep transitions.[70]

Recommended Workup

Because of the sudden onset of the attack, associated fear, and occurrence during sleep transitions that can be associated with poor recall of historical details, a secondary headache disorder may need to be ruled out. Neuroimaging studies, EEG, or a sleep study can be completed depending on the clinical scenario. These studies should be normal in patients with exploding head syndrome.[63,68,71] Of note, in the setting of a clear-cut history and normal neurologic examination, no additional testing may be needed for the diagnosis.

Treatment

Exploding head syndrome is benign, and reassurance is the cornerstone of treatment. Treatment with clomipramine,[68,72] topiramate,[69] clonazepam,[73] amitriptyline,[63] and nifedipine[74] have been reported. However, since it is a benign condition that remits over time in most patients, the risks and side effects of medications should be weighed against the potential benefits of a medication.

KEY POINT

- **Exploding head syndrome is benign, and reassurance is the cornerstone of treatment.**

CONCLUSION

Although the unusual headache disorders discussed in this article commonly have a benign, self-limiting course, headache red flags should prompt a thorough workup looking for a secondary cause of the headache. Once a symptomatic lesion has been ruled out, the accurate identification of clinical features, diagnosis, and treatment can provide patients with reassurance and relief. Understanding the potential pathophysiology and various treatment options allows for therapeutic education and an individualized treatment regimen for the patient. Not only does this meet the needs of the patient, but it also improves the practice satisfaction of the treating neurologist.

USEFUL WEBSITE

INTERNATIONAL CLASSIFICATION OF HEADACHE DISORDERS, THIRD EDITION (ICHD-3)
The online version of the *ICHD-3* is a useful resource for accessing a complete listing of the unusual headache disorder diagnostic criteria discussed in this article.
ichd-3.org/wp-content/uploads/2018/01/The-International-Classification-of-Headache-Disorders-3rd-Edition-2018.pdf

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Common Legal Considerations When Moving to a New Medical Practice

By Joseph S. Kass, MD, JD, FAAN; Rachel V. Rose, JD, MBA

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

ABSTRACT

This article presents a hypothetical case of the legal issues a physician must consider when moving to a new medical practice, such as the enforceability of a noncompete clause, malpractice insurance, communicating this change in practice to existing patients, and custody of medical records.

CASE

Note: The following scenario is hypothetical and is not a substitute for legal advice.

A neurologist's practice was devoted almost exclusively to the diagnosis and management of patients with headache, and for the past 10 years, she had been the primary headache specialist in a neurology practice composed of 10 neurologists, all partners in the practice. Her headache practice had been highly remunerative for the practice as a whole. However, she was considering leaving this practice and was being courted by a large multispecialty practice in the same city in which she was practicing as well as by an academic practice in a neighboring state that was still part of the metropolitan area in which she practiced. While searching the Internet for information about what she faced if she chose to move practices, the neurologist came upon guidance from the American Academy of Ophthalmology, which offered useful advice on various third parties that must be notified in the event of change in practice affiliation. That document stated the following:

> **Dependent upon the provisions of contracts and state law, both the departing physician and the practice may need to notify various third parties:**
>
> - **The underwriting department of the relevant professional liability carrier needs to know of any changes in order to ensure coverage of the care rendered in both the prior and future practice settings. Physicians who are retiring and have a "claims made" policy should inquire about "extended reporting period endorsements" or "tail" coverage.**
> - **Managed care companies with whom you have contracts.**
> - **The medical staff committee of hospitals where the departing physician has privileges. If he or she is on-call at the hospital, notify the emergency department as well.**

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- The state board of medicine (if required by state law).
- Legal counsel for assistance as needed in contract provisions and employment law.[1]

Therefore, the neurologist consulted an attorney to help her understand the legal implications of a move to a new practice. She informed her attorney that she would like to "take her patients" with her to her new practice. The neurologist had not reviewed her partnership agreement since she signed it, but she recalled something about a noncompete clause. She asked the attorney to review her partnership agreement, advise her on the enforceability of the noncompete clause, and review with her other contentious legal issues she would likely face when separating from her current practice that would likely need to be addressed in a formally executed separation agreement. The attorney informed her of the need to ensure that she had tail malpractice insurance to cover her for work done at the practice she was leaving.

In addition, the most critical legal issues she had to consider were the enforceability of the noncompete clause, the responsibility of communicating her departure to existing patients, the custody of her patients' medical records, and the propriety of creating and taking a list of her active patients with her.[2]

DISCUSSION

Enforceability of a Noncompete Clause in a Physician Employment or Partnership Agreement

A noncompete clause is a type of restrictive covenant found in both employment and partnership agreements that limits a physician's ability to practice medicine within a defined distance of the current practice for a specified period of time. A noncompete clause may not only limit the physical distance between two practice locations but may also have implications for the hospitals where a physician acquires or maintains privileges.[2] Many factors determine if a court will enforce such contractual language, and these standards may vary from state to state.[3] Despite some jurisdictional variations, the enforceability of noncompete clauses does rest on a common principle: the noncompete clause must be reasonable in both time and scope (eg, geography).[4] Courts will judge the reasonableness of the time and scope differently depending on the medical landscape of the community. Thus, a rural location will be viewed differently than a large city with a high concentration of physicians. Although one may think that a rural location may permit the noncompete clause to restrict practice over greater distances, courts have found that limiting a physician's presence in a medically underserved location is against the public interest and have therefore rendered such noncompete clauses unenforceable.[2] In a densely populated city, the geographic restrictions may need to be considerably more narrowly drawn to allow a physician to continue practicing in the greater metropolitan area even if he or she is restricted from the center of the city.[4] Therefore, when negotiating either an employment or partnership agreement, neurologists should pay close attention to the terms of any noncompete clauses and carefully consider the negative professional and personal impact of such restrictive covenants should the need arise to move practices. Therefore, the noncompete clause must be a source of careful negotiation with the goal of removing the restrictive covenant from the contract altogether. However, if

removal is not an option, it should be negotiated to be as geographically and temporally narrow as possible.[5]

Malpractice Insurance

A variety of practical sources, some written by state medical societies[6] or articles such as one published in 2016 in *Medical Economics,* provide physicians with practical information about malpractice coverage issues that arise when changing medical practices.[7] Some physicians have *occurrence* medical malpractice policies. Even after physicians stop paying insurance premiums on occurrence policies, as would typically happen when physicians move practices, they still maintain insurance coverage for lawsuits arising from activities taking place while they were paying their occurrence malpractice insurance premiums. Therefore, physicians with occurrence policies do not need to purchase supplementary insurance to cover their past activities. However, the majority of physicians carry *claims-made* malpractice insurance. This type of policy only covers physicians for claims filed during the time the claims-made policy was in force. However, when a physician leaves one practice for another, the malpractice insurance carrier may change, and the previous claims-made policy is terminated. The terminated claims-made policy will not cover claims filed after the policy was terminated, even for medical care provided while the claims-made policy was in effect. Tail insurance fills this critical coverage gap.[7] More information about tail coverage, including advice on how to obtain such coverage and how to negotiate tail coverage payment, is beyond the scope of this article, but understanding the nuances of tail coverage is important for all physicians, whether they are negotiating their initial employment contract or hammering out their practice separation agreement.

Communicating a Physician's Departure to Existing Patients

Ideally, the physician's initial employment or partnership agreement anticipated each party's responsibilities in the event of a separation from the practice, and the terms of separation were agreed to ahead of time. A formal separation agreement executed at a physician's departure must include provisions concerning these critical issues. Rules of medical ethics as well as state and federal laws govern the relationship among the departing physician, the current practice, and the physician's patients.[8]

State laws prohibiting physicians from abandoning their patients form the fundamental legal basis for requiring physicians to inform their patients about their departure from a practice. Notice must typically be made in writing to each active patient (definition varies by state, but the American Medical Association Code of Medical Ethics considers active patients to be those seen within the last 2 years or who have chronic conditions)[9] with sufficiently advanced notice (time frame varies by state statute) to allow patients time to find alternative care. Although some states follow the American Medical Association Code of Medical Ethics, others, such as Oregon, define active patients as those whom the physician saw within the past 3 years.[10] States may have additional requirements in addition to written notice to patients. For example, both Illinois and Texas mandate public notification of the practice change in the form of a notice published in a local newspaper.[6,11–13] These two states also require the posting of a notice at the practice location itself.[6,11–13]

Although employment or partnership agreements may spell out who is responsible for dissemination of the departure information to patients (the

departing physician or the current practice), state abandonment laws will typically impose ultimate responsibility for following the law on the departing physician. Thus, even if the practice that the physician is leaving has agreed to inform the relevant patients, the departing physician may still be found liable for malpractice because of patient abandonment should the practice discharge its obligation negligently.[14] However, the practice would still have an incentive to communicate properly because the departing physician would be able to sue the practice he or she is leaving for compensation for damages collected against the physician. Communication requirements do not end merely with a notice that the physician is leaving the practice. In fact, patients have a right to know how to contact their physician at the new practice, especially if the physician remains in the practice area. Patients have a relationship with their specific physician and cannot be prevented from maintaining that relationship even if the physician moves practices.

Custody of Medical Records

The Health Insurance Portability and Accountability Act (HIPAA)[15] of 1996 and the Health Information Technology for Economic and Clinical Health (HITECH)[16] Act together establish requirements to maintain the confidentiality, integrity, and availability of patient data. Federal regulations developed to implement HIPAA and HITECH require that "a covered entity must retain the documentation required by paragraph (j)(1) of this section for 6 years from the date of its creation or the date when it last was in effect, whichever is later."[17] State laws and the age of the patient (typically dictated by the statute of limitations of a malpractice action, which differs for adults and minors) as well as legal holds due to pending litigation may require that the records be maintained for longer periods of time than stipulated by federal law.

The departing physician, however, cannot just take medical records with him or her and transfer them to a new practice. Patients who elect to move to the new practice with their physician must sign a HIPAA release form to effectuate transfer and may be charged a reasonable fee for this service from the physician's original practice.

Creating a Patient List To Take to the New Practice

While creating a patient list is not, per se, impermissible, the employment or partnership contract must be consulted to see how patient lists are treated. However, even if the contract does not bar the departing physician from creating such a list, the physician only has a right to his or her active patients, as defined by state law. Furthermore, other physicians' patients in a group practice are protected as trade secrets by numerous laws and cannot be included in such a list.

A recent action affecting the University of Rochester Medical Center (URMC) concerning patient lists and a HIPAA violation is highly instructive on this issue.[18] The settlement arose from events that occurred in the spring of 2015. In March 2015, a neurology nurse practitioner was preparing to leave URMC for a position at Greater Rochester Neurology. Before leaving, she asked for a list of patients she treated while employed at URMC, and URMC provided her with a spreadsheet containing the protected health information of 3403 patients. Although HIPAA prohibits the unauthorized disclosure of protected health information, the nurse practitioner disclosed the protected health information to her new employer, Greater Rochester Neurology, without the patients' authorization.

In April 2015, Greater Rochester Neurology sent letters to the patients whose names were on the spreadsheet announcing that the nurse practitioner had joined the practice and advising them of how to switch to Greater Rochester Neurology. URMC began receiving calls from patients who were upset that their confidential medical information had been disclosed without their permission.[19] The potential ramifications of such violations for physicians are significant. URMC paid fines and was mandated to undertake additional action under the terms of a settlement with prosecutors. Additionally, since 2015, regulators have increasingly focused their attention on issues of cybersecurity, and patients whose data have been breached have filed class action lawsuits.[20]

CONCLUSION

The neurologist in this case took the first important step in transitioning her practice: consulting an attorney who specializes in this area of the law. A multitude of steps need to be taken to uphold both fiduciary duties to patients and contractual obligations to the practice the physician is leaving. The obligations of all parties to the separation should be memorialized in a separation agreement, and this agreement must account for a complex web of state and federal laws.

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1	A	B	C	D	E					21	A	B	C	D	E						
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By D. Joanne Lynn, MD, FAAN; Allison L. Weathers, MD, FAAN

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ARTICLE 1: THE MIGRAINE PREMONITORY PHASE

1 Which of the following is the most common premonitory symptom experienced at the start of a migraine episode?

A changes in concentration
B fatigue
C mood changes
D sweet cravings
E yawning

2 Which of the following medications has evidence in the literature supporting an ability to prevent headaches when administered during the premonitory phase?

A calcitonin gene-related peptide receptor antagonist
B filorexant
C naratriptan
D somatostatin
E vasopressin

3 A 25-year-old man presents for evaluation of frequent migraines and states that the attacks are often preceded by a day of significant anorexia. Abnormal activity in what part of the brain is thought to mediate this part of the premonitory migraine syndrome?

A A11 nucleus
B pineal gland
C superior salivatory nucleus
D suprachiasmatic nucleus of the hypothalamus
E ventromedial nucleus of the hypothalamus

ARTICLE 2: THE MIGRAINE AURA

4 A 28-year-old woman develops episodes of expanding jagged lines in her vision, dizziness, and mental confusion. The episodes are followed by headache in most cases, but are distressing even when they are not. Which of the following is an acute treatment approved by the US Food and Drug Administration (FDA) for the patient's condition?

A ketamine
B onabotulinumtoxinA
C sublingual nifedipine
D sumatriptan
E transcranial magnetic stimulation

5 **Migraine with aura has been reported to be associated with which of the following psychiatric comorbidities?**

A anorexia
B autism
C bipolar disorder
D narcissistic personality disorder
E schizophrenia

6 **Which of the following is one of the criteria for a diagnosis of migraine with aura based on the *International Classification of Headache Disorders, Third Edition*?**

A aura is followed by headache within 4 hours
B each symptom lasts 5 to 60 minutes
C one 5-minute attack of gradually spreading paresthesia
D sudden onset of sensory symptoms
E visual aura symptoms of 30-second duration

ARTICLE 3: THE MIGRAINE POSTDROME

7 **A 26-year-old man presents with concerns about his neurologic status. He has occasional throbbing unilateral headache associated with nausea and photophobia. However, even after the throbbing headache resolves, he feels partially impaired by symptoms of 1 to 2 days of scalp tenderness, fatigue, and cognitive cloudiness. Which of the following best describes this phase of symptoms?**

A aura
B headache phase
C interictal phase
D postdrome
E premonitory phase

8 **Which of the following is a commonly reported feature of the migraine postdrome?**

A auditory hallucinations
B excessive sweating
C flushing
D metamorphopsia
E yawning

ARTICLE 4: ACUTE TREATMENT OF MIGRAINE

9 Triptans may be used for migraine management in patients with which of the following comorbidities?

A coronary artery disease
B hemiplegic migraine
C history of stroke
D peptic ulcer disease
E peripheral vascular disease

10 A 35-year-old man presents to the emergency department for evaluation of a severe throbbing headache that has not responded to ibuprofen 400 mg and oral sumatriptan 100 mg. He has developed severe nausea and vomiting, and it is uncertain how much of these oral medications have been absorbed. For which of the following parental medications is there Level B evidence for acute treatment efficacy per the American Headache Society?

A chlorpromazine
B dexamethasone
C octreotide
D sodium valproate
E tramadol

ARTICLE 5: PREVENTIVE THERAPY OF MIGRAINE

11 Which of the following clinical scenarios would be the most appropriate for consideration of migraine preventive therapy?

A 2 headache days per month with moderate response to treatment
B 3 headache days per month with good response to acute treatment and mild postdrome
C 2 moderate headache days per month accompanied by visual aura that lasts 15 minutes
D 4 moderate headache days per month with brisk response to acute treatment
E 4 severe headache days per month causing severe functional impairment with poor response to acute treatment

12 **Which of the following migraine preventive therapies has been given a Level A rating for evidence of efficacy by the American Headache Society and a high evidence level by the Canadian Headache Society?**

A amitriptyline
B lisinopril
C propranolol
D venlafaxine
E verapamil

13 **Which of the following treatments is recommended for the prevention of chronic but not episodic migraine?**

A candesartan
B divalproex sodium
C flunarizine
D onabotulinumtoxinA
E topiramate

ARTICLE 6: HEADACHES DUE TO LOW AND HIGH INTRACRANIAL PRESSURE

14 **A 32-year-old woman develops new-onset daily headaches that she describes as generalized pressure. Fundoscopic examination shows bilateral papilledema. The rest of her neurologic examination is unremarkable except for a partial left abducens palsy. Brain MRI with contrast is normal. Her medications include naproxen, levothyroxine, simvastatin, isotretinoin, and supplemental vitamin D_3. Which of her medications is most likely to be related to her headache syndrome?**

A isotretinoin
B levothyroxine
C naproxen
D simvastatin
E vitamin D_3

15 **Which of the following is a predisposing factor for spontaneous intracranial hypotension?**

A adrenal insufficiency
B Ehlers-Danlos syndrome
C Gilbert syndrome
D pulmonary hypertension
E systemic lupus erythematosus

16 **A 35-year-old man who is a professional golfer develops headaches 1 month into the tournament circuit. Initially intermittent, the headaches are now daily and bitemporal with radiation down the back of the head and neck. The headache tends to worsen as the day goes on and is made worse by each golf swing to the point that he has pulled out of recent competitions. The headache always improves when he lies down and, during examination, resolves after 10 minutes spent in the Trendelenburg position. His headaches are less severe when traveling to tournaments located at higher altitudes. Which of the following is the most likely diagnosis?**

A cluster headache
B exertional headache
C migraine
D pseudotumor cerebri
E spontaneous intracranial hypotension

17 **A 29-year-old woman has had daily headaches for several months. Recently, she has experienced transient episodes of bilateral visual loss lasting approximately 30 seconds. Her body mass index is 35 kg/m^2, and her neurologic examination is notable for bilateral papilledema. A previous head CT showed no mass lesion. Which of the following cranial MRI abnormalities is typically associated with her headache syndrome?**

A empty sella
B flattening of anterior pons
C pachymeningeal enhancement
D pituitary enlargement and hyperemia
E subdural fluid collections

ARTICLE 7: HEADACHE IN PREGNANCY

18 **Prolonged maternal IV magnesium sulfate exposure during pregnancy has been associated with which of the following adverse effects on the fetus?**

A bone demineralization
B heart defects
C hypospadias
D intrauterine growth restriction
E no known risks at dosing under 400 mg/d

19 **Which of the following triptans is likely the most compatible with breast-feeding?**

A eletriptan
B naratriptan
C rizatriptan
D sumatriptan
E zolmitriptan

20 **Migraine is a risk factor for which of the following pregnancy-associated conditions?**

A oligohydramnios
B pituitary apoplexy
C placenta accreta
D preeclampsia
E premature rupture of membranes

ARTICLE 8: PEDIATRIC AND ADOLESCENT HEADACHE

21 **A 4-year-old girl is referred by her pediatrician as her parents have noticed her grabbing her head and crying several times over the past 2 months. She is accompanied to the visit by her father. Which of the following techniques would most likely be effective to obtain a history of the patient's chief complaint?**

A ask the father to create a video journal of the patient's headaches and return after 1 month
B ask the patient to draw a picture of how she feels when her head hurts
C play a word association game with the patient
D provide the patient with a tablet in the examination room as a distractor so that the full history can be obtained from her father
E use the numeric pain rating scale

22 **A 9-year-old girl with no significant past medical history presents for evaluation of bilateral, pounding headaches that last for 2 hours on average and are associated with photophobia, phonophobia, and nasal congestion. These symptoms have occurred weekly over the past year, generally on Mondays after she has difficulty falling asleep on Sunday nights. Her mother and aunt both have migraine. Her pediatrician has tried lifestyle modifications including a more regular sleep schedule on the weekends, hydration, and exercise. She has also tried nonsteroidal anti-inflammatory drugs and acetaminophen with no significant relief. The patient is beginning to miss at least two Mondays of school a month. The patient's neurologic examination and vital signs are normal. Treatment with which of the following triptans would be most appropriate at this time?**

A almotriptan
B eletriptan
C naratriptan
D rizatriptan
E zolmitriptan

23 **A 5-year-old boy with no significant past medical history presents for evaluation of brief, severe, stabbing head pains that have occurred several times a day for the past 4 months. These attacks last seconds but are extremely painful. He will grab his head when they occur, burst into tears, and often drop to his knees. The pain is variable in location and is not associated with any other symptoms, specifically no lacrimation, rhinorrhea, or vision changes. General and neurologic examination are normal. What is the most appropriate next step?**

A brain MRI
B diclofenac 12.5 mg suppository nightly
C EEG
D magnetic resonance angiogram (MRA) of the brain
E melatonin 2.5 mg (melt or gummy) nightly

24 **A 15-year-old girl presents to the emergency room with her parents for evaluation of 2 days of severe nausea and frequent emesis associated with diffuse abdominal pain and anorexia. She has had numerous episodes like this in the last several months. Her parents note that she has been taking frequent hot showers during these episodes. Which of the following tests is most likely to be positive?**

A urine amphetamine screen
B urine human chorionic gonadotropin
C urine ketones
D urine porphyrins
E urine tetrahydrocannabinol screen

25 **A 54-year-old man presents for evaluation of 2 months of severe, episodic, unilateral pain with associated unilateral nasal stuffiness, lacrimation, and conjunctival injection. He is having three to four attacks per day that last approximately 60 minutes. Two of his attacks occur at night, specifically at 2:00 AM and 4:00 AM. He had a similar period of headaches 2 years ago that suddenly resolved after 6 months. He recently saw a primary care physician after not having seen a physician for some time. He was found to have numerous medical issues and was started on several new medications. Which of the following medications could be triggering some of his pain attacks?**

A aspirin
B lisinopril
C metformin
D nitroglycerin
E rosuvastatin

26 **For which of the following patient populations with cluster headache is a brain MRI with dedicated views of the pituitary indicated?**

A all patients with cluster headache
B patients who fail to respond to high-flow oxygen
C patients who fail to respond to verapamil
D patients with abnormal pituitary laboratory studies
E patients with galactorrhea

27 **A 58-year-old man presents for evaluation of 3 weeks of stabbing headaches. The headaches are unilateral, last about 90 seconds, occur approximately 100 times a day, and are associated with ipsilateral lacrimation. He has no interictal pain. Treatment with which of the following agents is most appropriate as first-line therapy?**

A carbamazepine
B duloxetine
C lamotrigine
D oxcarbazepine
E phenytoin

ARTICLE 10: CRANIAL NEURALGIAS

28 **What is the most common tumor associated with trigeminal neuropathic pain?**

A chordoma
B epidermoid
C medulloblastoma
D meningioma
E vestibular schwannoma

29 **A 35-year-old man presents for a second opinion of 1 year of paroxysmal, electric shock–like pains in the V1 distribution bilaterally. Wind blowing over the V1 region or touching this area triggers his pain, and he has associated lacrimation. He has been tried on multiple antiepileptic drugs and tricyclic antidepressants with minimal relief. Which of the following characteristics of his presentation is more consistent with a secondary, painful trigeminal neuropathy than classical trigeminal neuralgia?**

A bilateral distribution of pain
B patient's age and sex
C presence of lacrimation
D unresponsiveness to treatment
E V1 distribution of the patient's pain

30 **Which of the following is the most common complication of microvascular decompression performed for the treatment of classical trigeminal neuralgia?**

A aseptic meningitis
B CSF leak
C hematoma
D ipsilateral hearing loss
E trochlear nerve damage

31 **Neuroma formation is most likely to occur when which of the following structures is cut?**

A endoneurium
B epineurium
C myelin
D perineurium
E vasa nervorum

32 **A 70-year-old woman presents for evaluation of 5 months of severe, shooting, paroxysmal pain at the base of her tongue on the left side that radiates up her jaw and to the bottom of her left ear. The pain lasts 30 seconds, occurs 100 times a day, and is triggered by swallowing and yawning. Several of her attacks have been associated with syncopal events in which she would lose consciousness for approximately 20 seconds. MRI brain is normal, and magnetic resonance angiography (MRA) reveals an abnormal loop of the posterior inferior cerebellar artery near the left cranial nerves IX and X. Cardiac monitoring reveals profound bradycardia (35 to 40 beats/min) during her events and very brief periods of asystole. When a local anesthetic was applied to her throat, her pain subsided for several hours. Which of the following interventions would be most appropriate to offer to this patient?**

A initiation of high-dose gabapentin
B lidocaine patches applied to the throat for 20 hours a day for 2 weeks
C microvascular decompression
D same-day administration of onabotulinumtoxinA
E titration to therapeutic dose of lamotrigine

ARTICLE 11: SECONDARY HEADACHE SYNDROMES

33 **A 59-year-old man presents to the emergency department for evaluation of a worsening headache that began 2 months ago. He works as a football coach, and the headache is present only when walking up and down the football field during practices and games. He has a past medical history notable for tobacco use, type 2 diabetes mellitus, hypertension, hyperlipidemia, and a family history notable for coronary artery disease in his father and grandfather. His neurologic examination is normal. Which of the following studies is most likely to reveal the etiology of his headache?**

A cardiac stress test
B CT angiography head
C CT head
D magnetic resonance angiography (MRA) brain
E MRI brain

34 **A 35-year-old woman with a 12-year history of migraine presents for follow-up evaluation 3 months after a head injury that occurred when she ran full force into her garage door as it was opening to stop her toddler from running into the street. Three days following her accident, she noted the onset of a throbbing, unilateral headache with associated photophobia, phonophobia, nausea, and vomiting. This headache has persisted and is now occurring daily. She also reports dizziness, daytime fatigue, difficulty sleeping at night, moodiness, and feeling mentally "fuzzy." Prior to her accident, she had not had a migraine attack in the 3 years since the birth of her son. Head CT was obtained on the day of her accident and was normal. She tried acetaminophen and ibuprofen for several weeks after her headaches began but had no relief, so she stopped taking them. Treatment should be initiated with which of the following?**

A amitriptyline
B hydrocodone/acetaminophen
C indomethacin
D melatonin
E naproxen

35 **A 28-year-old woman presents to the emergency department for evaluation of a severe headache. She has had episodic migraines for 3 years that she describes as severe, unilateral, frontal, and periorbital throbbing headaches associated with photophobia and nausea and are preceded by an aura of a shimmering crescent in her vision. She has tried several preventive medications over the years with each one providing only modest relief. She was started on topiramate 2 weeks ago and is now on 25 mg twice daily. She reports that over the past 2 days she has had a severe right periorbital headache with light sensitivity and that her vision in the right eye is slightly blurred with rainbow halos around lights. On examination, she has a fixed dilated pupil on the right. Which of the following is the most appropriate next step?**

A administer IV dihydroergotamine with metoclopramide and diphenhydramine
B increase her topiramate dose to 50 mg twice daily
C obtain urgent ophthalmology consultation for slit-lamp examination and gonioscopy
D perform lumbar puncture with opening pressure
E perform MRI of the orbits

36 **A 63-year-old woman presents for evaluation of a new-onset headache that started 4 months ago. Her pain is unilateral, described as both a pressure and shooting pain, lasts 20 to 30 minutes, occurs frequently throughout the day, and is triggered by cough. She was started on lisinopril and atorvastatin 5 months ago. Neurologic examination is normal, but she is noted to have a dry cough throughout the visit, which she says is of relatively recent onset. Brain MRI, magnetic resonance angiography (MRA) of the head and neck, and magnetic resonance venography (MRV) are normal. Which of the following is the most appropriate next step in management?**

A initiate treatment with acetazolamide
B initiate treatment with indomethacin
C perform high-volume lumbar puncture
D recommend discontinuation of atorvastatin
E recommend discontinuation of lisinopril

37 **A 12-year-old girl presents for evaluation of a new-onset bifrontal pain that occurs only during ice-skating lessons. She reports that the pain feels like the occasional headaches she gets with eating ice cream or drinking a frozen drink, but this pain is happening much more frequently, to the point where it is disrupting her lessons. The pain resolves rapidly after she leaves the ice. Neurologic examination is normal. Which of the following mechanisms of action is presumed to account for her pain?**

A cortical spreading depression
B hyperexcitability of the V3 branch of the trigeminal nerve
C increased intracranial pressure
D internal jugular vein valve incompetence
E vasoconstriction followed by vasodilation of blood vessels within the pharyngeal wall

38 **Examination of a patient's epicranial tissues is critical during the workup for which of the following primary headache disorders?**

A epicrania fugax
B nummular headache
C occipital neuralgia
D primary stabbing headache
E short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA)

39 **Caffeine is the first-line of treatment for which of the following primary headache disorders?**

A headache attributed to travel in space
B hypnic headache
C primary exercise headache
D primary headache associated with sexual activity
E primary stabbing headache

40 **A 63-year-old woman without a significant past medical history describes a 6-month history of being awakened by a sound "like a gunshot." She denies any actual head pain or focal neurologic symptoms. Neurologic examination is normal. Mutations in which of the following genes have been associated with this presentation?**

A *CACNA1A*
B *CHRNA2*
C *CLCN1*
D *GABRG2*
E *SCN4A*

Postreading Self-Assessment and CME Test—Preferred Responses

By D. Joanne Lynn, MD, FAAN; Allison L. Weathers, MD, FAAN

HEADACHE

Following are the preferred responses to the questions in the Postreading Self-Assessment and CME Test in this *Continuum* issue. The preferred response is followed by an explanation and a reference with which you may seek more specific information. You are encouraged to review the responses and explanations carefully to evaluate your general understanding of the article topic. The comments and references included with each question are intended to encourage independent study.

US PARTICIPANTS: Upon completion of the Postreading Self-Assessment and CME Test and issue evaluation online at *continpub.com/CME*, participants may earn up to 20 *AMA PRA Category 1 Credits™* toward SA-CME. US participants have up to 3 years from the date of publication to earn SA-CME credits. No SA-CME will be awarded for this issue after August 31, 2021.

CANADIAN PARTICIPANTS: This program is an Accredited Self-Assessment Program (Section 3) as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada and approved by the Office of Continuing Medical Education and Professional Development, University of Calgary, on April 1, 2017. Refer to the CME tab on *ContinuumJournal.com* for dates of accreditation. Canadian participants should visit MAINPORT (*mainport.org*) to record learning and outcomes. Canadian participants can claim a maximum of 20 hours (credits are automatically calculated).

ARTICLE 1: THE MIGRAINE PREMONITORY PHASE

1 The preferred response is **B (fatigue).** Fatigue or tiredness has been reported to be the most common premonitory symptom of migraine, followed by mood and cognitive changes and yawning. For more information, refer to **page 1000** of the *Continuum* article "The Migraine Premonitory Phase."

2 The preferred response is **C (naratriptan).** Naratriptan has been shown to prevent 60% of migraine headaches when taken during the premonitory phase in a small open-label study. Further investigation of this promising result is needed. Trials of the orexin receptor antagonist filorexant and of somatostatin analogues have failed to demonstrate efficacy in migraine. For more information, refer to **page 1005** of the *Continuum* article "The Migraine Premonitory Phase."

3 The preferred response is **E (ventromedial nucleus of the hypothalamus)**. Cholecystokinin expression is increased in the ventromedial nucleus of the hypothalamus after noxious trigeminal stimulation. This nucleus is involved in feeding regulation, and abnormal activation could mediate feeding and appetite changes associated with the migraine prodrome. For more information, refer to **page 1002** and **Table 1-2** of the *Continuum* article "The Migraine Premonitory Phase."

ARTICLE 2: THE MIGRAINE AURA

4 The preferred response is **E (transcranial magnetic stimulation)**. Transcranial magnetic stimulation is currently the only treatment approved by the US Food and Drug Administration (FDA) for the specific indication of acute treatment for migraine with aura. Transcranial magnetic stimulation is also FDA approved for migraine prevention. For more information, refer to **page 1018** of the *Continuum* article "The Migraine Aura."

5 The preferred response is **C (bipolar disorder).** Migraine with aura has been reported to be associated with several different psychiatric comorbidities including depression, bipolar disorder, and a variety of anxiety disorders including generalized anxiety, panic disorder, posttraumatic stress disorder, and obsessive-compulsive disorder. The mechanisms underlying these associations are unclear. For more information, refer to **page 1018** of the *Continuum* article "The Migraine Aura."

6 The preferred response is **B (each symptom lasts 5 to 60 minutes).** The criteria for migraine with aura according to the *International Classification of Headache Disorders, Third Edition* require that the individual have two or more attacks of fully reversible visual, sensory, speech and/or language, motor, brainstem, or retinal symptoms and at least two of the following other characteristics: at least one aura symptom spread over 5 or more minutes and/or two or more symptoms occuring in succession, with each individual symptom lasting 5 to 60 minutes; at least one symptom is unilateral, and the aura symptom is accompanied with or followed by headache within 60 minutes. The key characteristic of migraine aura

is gradual onset and progression, which helps to differentiate it from ischemic symptoms. For more information, refer to **pages 1009–1010** and **Table 2-1** of the *Continuum* article "The Migraine Aura."

ARTICLE 3: THE MIGRAINE POSTDROME

7 The preferred response is **D (postdrome).** The migraine postdrome consists of the period between resolution of the throbbing headache and return to the normal baseline state. Common postdromal symptoms include fatigue, neck stiffness, and various cognitive symptoms including difficulty with concentration, irritability, and heightened sensitivity to light and sound. For more information, refer to **pages 1023–1024** of the *Continuum* article "The Migraine Postdrome."

8 The preferred response is **E (yawning).** Frequent yawning has been reported as a common feature of the migraine postdrome period as well as the premonitory phase. Auditory hallucinations and metamorphopsia (visual distortions of the shape, size, or color of objects) have been reported as features of migraine aura but are not common postdrome features. Excessive sweating is also not a common feature of the postdrome. For more information, refer to **page 1024, Table 3-1,** and **Table 3-2** of the *Continuum* article "The Migraine Postdrome."

ARTICLE 4: ACUTE TREATMENT OF MIGRAINE

9 The preferred response is **D (peptic ulcer disease).** Triptans are contraindicated in patients with a history of stroke, heart attack, coronary artery disease, peripheral vascular disease, hemiplegic migraine, ischemic bowel disease, coronary artery vasospasm, and uncontrolled hypertension. For more information, refer to **page 1035** of the *Continuum* article "Acute Treatment of Migraine."

10 The preferred response is **A (chlorpromazine).** The American Headache Society has not identified any parenteral medications as having Level A evidence to support use in treatment of acute migraine attacks. However, several parenteral medications are supported by Level B evidence, including chlorpromazine, droperidol, metoclopramide, prochlorperazine, dihydroergotamine, and ketorolac. Valproate, tramadol, and dexamethasone have Level C evidence for parenteral treatment of acute migraine attacks. For more information, refer to **pages 1039–1040** of the *Continuum* article "Acute Treatment of Migraine."

ARTICLE 5: PREVENTIVE THERAPY OF MIGRAINE

11 The preferred response is **E (4 severe headache days per month causing severe functional impairment with poor response to acute treatment).** Migraine preventive therapy is indicated for patients with 3 or more moderate or severe headaches days per month causing functional impairment that are not consistently responsive to treatment or for those with 6 to 8 or more headache days per month, even if acute treatments are effective. Other indications include poor tolerance or contraindications to acute therapies, severe complicated migraines such as hemiplegic varieties, risk of developing medication-overuse headache, and other significant impacts on life. For more information, refer to **page 1056** of the *Continuum* article "Preventive Therapy of Migraine."

12 The preferred response is **C (propranolol).** Propranolol 80 mg/d to 240 mg/d is rated at the highest efficacy evidence levels as a preventive migraine therapy by the American Headache Society and the Canadian Headache Society. Amitriptyline is rated Level B by the American Headache Society and high by the Canadian Headache Society. The other choices are all rated below the highest levels of evidence by the American Headache Society and Canadian Headache Society. For more information, refer to **page 1056** and **Table 5-1** of the *Continuum* article "Preventive Therapy of Migraine."

13 The preferred response is **D (onabotulinumtoxinA).** OnabotulinumtoxinA is recommended for prevention of chronic but not episodic migraine. The other choices are all recommended for the prevention of episodic migraine by the guidelines of at least one of the following organizations: the American Headache Society, the American Academy of Neurology, or the Canadian Headache Society. For more information, refer to **page 1058, Table 5-1,** and **Table 5-2** of the *Continuum* article "Preventive Therapy of Migraine."

ARTICLE 6: HEADACHES DUE TO LOW AND HIGH INTRACRANIAL PRESSURE

14 The preferred response is **A (isotretinoin).** Secondary pseudotumor cerebri can be associated with various medications including vitamin A and retinoids, levothyroxine (in children), leuprorelin acetate, fluoroquinolones and lithium. For more information, refer to **Table 6-7** of the *Continuum* article "Headaches Due to Low and High Intracranial Pressure."

15 The preferred response is **B (Ehlers-Danlos syndrome).** Numerous predisposing factors exist for spontaneous intracranial hypotension including various hypermobility disorders such as Ehlers-Danlos syndrome, degenerative disk disease, and various types of trauma affecting spinal structures. For more information, refer to **page 1070** and **Table 6-4** of the *Continuum* article "Headaches Due to Low and High Intracranial Pressure."

16 The preferred response is **E (spontaneous intracranial hypotension).** Spontaneous intracranial hypotension is a secondary cause of daily headaches that are classically but not invariably orthostatic with improvement in recumbence and in the Trendelenburg position. The headache is often absent upon awakening and then worsens throughout the day. Various physical activities such as golf can cause this condition by traction-induced spinal dural tears. For more information, refer to **pages 1067–1070** and **Table 6-3** of the *Continuum* article "Headaches Due to Low and High Intracranial Pressure."

17 The preferred response is **A (empty sella).** Brain MRI may demonstrate an expanded/empty sella or tonsillar descent in pseudotumor cerebri syndrome. Other possible abnormal findings may include flattening of the posterior sclerae, distension of the optic nerve sheath, papilledema, and widening of the foramen ovale. Flattening of the anterior pons, pituitary enlargement and hyperemia, pachymeningeal enhancement, and subdural fluid collections are more typically seen in spontaneous intracranial hypotension. For more information, refer to **page 1085** of the *Continuum* article "Headaches Due to Low and High Intracranial Pressure."

ARTICLE 7: HEADACHE IN PREGNANCY

18 The preferred response is **A (bone demineralization).** Prolonged maternal IV magnesium sulfate exposure has been associated with fetal bone demineralization. This has led to concerns about the safety of daily use of magnesium oxide in pregnant women. For more information, refer to **page 1100** of the *Continuum* article "Headache in Pregnancy."

19 The preferred response is **A (eletriptan).** Based on its low milk to plasma ratio, eletriptan is likely the triptan most compatible with breast-feeding. For more information, refer to **pages 1103–1104** and **Table 7-4** of the *Continuum* article "Headache in Pregnancy."

20 The preferred response is **D (preeclampsia).** Migraine is a risk factor for preeclampsia. In various studies, in addition to preeclampsia, it has also been associated with higher rates of preterm delivery, low birth weight, and other cardiovascular and cerebrovascular complications, including gestational hypertension, ischemic stroke, heart disease, and venous thromboembolism. For more information, refer to **pages 1104–1105** of the *Continuum* article "Headache in Pregnancy."

ARTICLE 8: PEDIATRIC AND ADOLESCENT HEADACHE

21 The preferred response is **B (ask the patient to draw a picture of how she feels when her head hurts).** Although parents and guardians of young children will likely provide most of the history, including specific details, the child should remain the focus of the visit. Having children draw a picture of how they feel during a headache may be helpful. It is also important to have the child sit in the seat closest to the provider and to set expectations with the child and his or her parents regarding the child's role in the interview. Young patients should not be given something that is so distracting that it removes them completely from the interview. The numeric pain rating scale is widely used in adults but may not be understood by a 4-year-old child. Asking the father to record a video and return would just delay obtaining a history and is not indicated in this case. For more information, refer to **page 1110** of the *Continuum* article "Pediatric and Adolescent Headache."

22 The preferred response is **D (rizatriptan).** Triptans are indicated in this patient at this point as her headaches are consistent with migraine; she has not responded to lifestyle modifications, nonsteroidal anti-inflammatory drugs, or acetaminophen; and she has no contraindications to triptan use. Out of the options provided, only rizatriptan is labeled by the US Food and Drug Administration (FDA) for use in patients ages 6 to 11 years. Sumatriptan, while not FDA labeled for patients ages 6 to 11 years, is often tried first as it is covered by most insurance plans. For more information, refer to **page 1123** and **Table 8-3** of the *Continuum* article "Pediatric and Adolescent Headache."

23 The preferred response is **E (melatonin 2.5 mg [melt or gummy] nightly).** The patient's presentation is consistent with primary stabbing headache, a not uncommon primary headache type in young children who present to clinic for headache. No abnormal features or other red flags are present in this patient that would raise concern for another diagnosis, and therefore further workup with MRI or magnetic resonance angiography (MRA) is not indicated, especially as anesthesia would be required in a patient of this age. The patient has no symptoms worrisome for seizures, and therefore EEG is also not indicated.

While reassurance about the benign nature of the patient's headaches is often sufficient for the patient and his or her parents/guardians, if attacks are frequent and particularly severe, as they are in this case, then a low dose of melatonin nightly can be tried. Diclofenac suppositories are not indicated in primary stabbing headache. Indomethacin could be tried; however, some patients with indomethacin-responsive disorders will also improve with melatonin treatment. Given that indomethacin can be difficult to tolerate, melatonin may be a gentler treatment to try first. For more information, refer to **pages 1129–1130** and **Case 8-3** of the *Continuum* article "Pediatric and Adolescent Headache."

24 The preferred response is **E (urine tetrahydrocannabinol screen).** The patient's presentation of severe paroxysmal nausea and emesis associated with diffuse abdominal pain and frequent hot water bathing is consistent with cannabinoid hyperemesis syndrome, and therefore her urine tetrahydrocannabinol screen would likely be positive. Cannabinoid hyperemesis syndrome is most often misdiagnosed as the migraine associated cyclic vomiting syndrome. Suspicions should be raised in adolescents who present with severe episodic vomiting, especially those who report frequent hot water bathing. This behavior is often the only intervention that alleviates the patient's symptoms and therefore quickly becomes a compulsion. If the patient or his or her parent/guardian do not volunteer a history of hot water bathing, then this should be specifically asked about. For more information, refer to **page 1116** of the *Continuum* article "Pediatric and Adolescent Headache."

ARTICLE 9: CLUSTER HEADACHE AND OTHER TRIGEMINAL AUTONOMIC CEPHALALGIAS

25 The preferred response is **D (nitroglycerin).** This patient's presentation is consistent with episodic cluster headache. Cluster attacks can be triggered by nitroglycerin but only during a headache period. Other triggers include alcohol, heat/exercise, high altitude, and strong smells. For more information, refer to **pages 1141–1142** and **Table 9-1** of the *Continuum* article "Cluster Headache and Other Trigeminal Autonomic Cephalalgias."

26 The preferred response is **A (all patients with cluster headache).** Given the extensive differential diagnosis for cluster headache, including the relatively high incidence of cluster headache secondary to pituitary tumors, MRI brain with dedicated views of the pituitary and the cavernous sinus is recommended for all patients with cluster headache, per consensus of the European Headache Federation, not just those with abnormal pituitary laboratory

studies or signs or symptoms of a pituitary lesion. For more information, refer to **page 1143** of the *Continuum* article "Cluster Headache and Other Trigeminal Autonomic Cephalalgias."

27 The preferred response is **C (lamotrigine).** The patient's headaches are consistent with a diagnosis of short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA). First-line treatment for this disorder is lamotrigine. Second-line treatments include topiramate or gabapentin, with carbamazepine, oxcarbazepine, or duloxetine also possibly being effective. For more information, refer to **pages 1150–1151** of the *Continuum* article "Cluster Headache and Other Trigeminal Autonomic Cephalalgias."

ARTICLE 10: CRANIAL NEURALGIAS

28 The preferred response is **B (epidermoid).** Epidermoid tumors are the most common tumor associated with trigeminal neuropathic pain. Vestibular schwannomas can also result in a painful trigeminal neuropathy. For more information, refer to **page 1158** of the *Continuum* article "Cranial Neuralgias."

29 The preferred response is **A (bilateral distribution of pain).** According to the American Academy of Neurology/European Federation of Neurological Societies guidelines on the treatment of trigeminal neuralgia, "bilateral involvement should be considered useful to disclose symptomatic trigeminal neuralgia."[1,2] The guideline also states that sensory deficits and abnormal trigeminal reflexes should be considered useful. According to this guideline, younger age of onset, involvement of the first division, and unresponsiveness to treatment are not useful in distinguishing symptomatic from classical trigeminal neuralgia. While there is a female predominance in trigeminal neuralgia, male sex is not a useful distinguishing characteristic. In one large case series, 31% of patients with classical trigeminal neuralgia had autonomic features, and lacrimation can occur with classical trigeminal neuralgia regardless of what division is involved.[3] Therefore, the presence of autonomic features is also not useful to distinguish between classical and secondary trigeminal neuralgia. For more information, refer to **pages 1160–1161** of the *Continuum* article "Cranial Neuralgias."

1 Cruccu G, Gronseth G, Alksne J, et al. AAN-EFNS guidelines on trigeminal neuralgia management. Eur J Neurol 2008;15(10):1013–1028. doi:10.1111/j.1468-1331.2008.02185.x.

2 Gronseth G, Cruccu G, Alksne J, et al. Practice parameter: the diagnostic evaluation and treatment of trigeminal neuralgia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the European Federation of Neurological Societies. Neurology 2008;71(15):1183–1190. doi:10.1212/01.wnl.0000326598.83183.04.

3 Maarbjerg S, Gozalov A, Olesen J, Bendtsen L. Trigeminal neuralgia—a prospective systematic study of clinical characteristics in 158 patients. Headache 2014;54(10):1574–1582. doi:10.1111/head.12441.

30 The preferred response is **A (aseptic meningitis).** While all the options are possible complications of microvascular decompression performed to treat classical trigeminal neuralgia, aseptic meningitis is the most common, occurring in 11% of patients. For more information, refer to **page 1165** of the *Continuum* article "Cranial Neuralgias."

31 The preferred response is **D (perineurium).** Neuroma formation occurs when the perineurium is cut, but milder injuries such as nerve constriction or compression may also result in neuroma formation and focal demyelination. Neuroma formation is characterized by ectopic discharges that are felt to contribute to the development of neuropathic pain and painful posttraumatic trigeminal neuropathy. For more information, refer to **page 1168** of the *Continuum* article "Cranial Neuralgias."

32 The preferred response is **C (microvascular decompression).** The patient's presentation is consistent with vagoglossopharyngeal neuralgia, a form of glossopharyngeal neuralgia. As she is having severe and potentially fatal cardiac manifestations, it is reasonable to consider microvascular decompression for her identified vascular abnormality without a preceding medication trial. For more information, refer to **page 1173** of the *Continuum* article "Cranial Neuralgias."

ARTICLE 11: SECONDARY HEADACHE SYNDROMES

33 The preferred response is **A (cardiac stress test).** In a patient of this age with extensive cardiovascular risk factors and a family history of cardiac disease, a headache that is present on exertion may represent cardiac cephalalgia. ECG or cardiac stress testing performed when the patient is symptomatic may show ischemic changes, while neuroimaging studies will be nondiagnostic. If ECG or stress testing is negative or if not able to be obtained during a symptomatic period of a patient with probable cardiac cephalalgia, coronary angiography should be obtained. Nitroglycerin and surgical interventions will relieve the pain of cardiac cephalalgia. The pain of cardiac cephalalgia may mimic that of migraine, and it is critical to distinguish between the two diagnoses as certain

acute migraine medications, such as triptans, are contraindicated in coronary syndromes. For more information, refer to **pages 1185–1186** of the *Continuum* article "Secondary Headache Syndromes."

34 The preferred response is **A (amitriptyline).** The patient's headaches are consistent with posttraumatic headaches, which are variable in characteristic but often resemble migraine. In the absence of evidence-based recommendations, treatment is empiric and targeted toward the type of headache that the posttraumatic headache most closely resembles. In this case, as the patient's headaches resemble migraine, amitriptyline is the most appropriate treatment choice. She has failed treatment with nonsteroidal anti-inflammatory drugs and therefore, these are unlikely to be successful and could cause medication-overuse headache. Melatonin may help with her insomnia but is unlikely to treat her headache. Opioids should be avoided because of the high risk of medication-overuse headache and abuse. This patient had a number of risk factors for developing posttraumatic headache including her prior history of headache, young age (younger than 60 years of age), and milder degree of head trauma. For more information, refer to **page 1187** of the *Continuum* article "Secondary Headache Syndromes."

35 The preferred response is **C (obtain urgent ophthalmology consultation for slit-lamp examination and gonioscopy).** Severe unilateral eye pain with light sensitivity and visual changes occurring at the ictus of pain and a dilated fixed pupil on examination in a patient recently started on topiramate should raise immediate concern for acute angle-closure glaucoma. This patient requires an urgent ophthalmology evaluation with slit-lamp examination and gonioscopy. Topiramate should not be increased or even continued in a patient who develops new visual symptoms while on it (even if the patient is not found to have glaucoma, other visual adverse effects have been described). MRI of the orbits and lumbar puncture are not indicated in this patient and would only delay the necessary ophthalmologic evaluation. Intermittent angle-closure glaucoma can resemble migraine, and therefore a careful history and examination is critical. For more information, refer to **page 1188** of the *Continuum* article "Secondary Headache Syndromes."

ARTICLE 12: UNUSUAL HEADACHE DISORDERS

36 The preferred response is **E (recommend discontinuation of lisinopril).** In the absence of a secondary etiology for her headaches, this patient's new-onset headaches in the setting of a new cough are consistent with primary cough headache. The most common side effect of angiotensin converting enzyme inhibitors is a dry cough, and therefore the most appropriate next step in her management is to discontinue lisinopril to see if this resolves her cough and, in

turn, her headaches. Statins are not associated with cough, and therefore discontinuing the atorvastatin would not be expected to have any effect on her headaches. For patients in whom an obvious cause of cough cannot be identified and addressed, reassurance may be sufficient. However, if the headaches are impacting daily function and quality of life, indomethacin, acetazolamide, and high-volume lumbar puncture are all considered effective treatments. For more information, refer to **pages 1193–1194** of the *Continuum* article "Unusual Headache Disorders."

37 The preferred response is **E (vasoconstriction followed by vasodilation of blood vessels within the pharyngeal wall).** The patient's pain is consistent with that seen in headache attributed to ingestion or inhalation of a cold stimulus. Although more commonly triggered by eating or drinking something cold, it can also occur with inhalation of cold air such as during ice skating. It is felt to be vascular in etiology, with the cold stimulus causing rapid vasoconstriction and dilation of the vessels of the posterior pharyngeal wall or palate, in turn activating nociceptors in the vessel wall, which causes referred frontal or temporal head pain. For more information, refer to **pages 1197–1198** of the *Continuum* article "Unusual Headache Disorders."

38 The preferred response is **B (nummular headache).** Examination of the epicranial tissues is necessary in the workup of a patient with nummular headache. The pain in this rare primary headache disorder occurs in a small, fixed, very well-circumscribed coin, oval, or elliptical shape. The pain may be continuous and is associated with sensory dysfunction such as allodynia or hypoesthesia. It is associated with prior head trauma, but often only a limited correlation exists between the site of the trauma and the site of the focal pain. As this pain is so focal, it is especially essential to evaluate for and rule out a focal epicranial tissue process such as a perifolliculitis capitis. The pain either radiates or is migratory in the other headache disorders listed or, in the case of short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA), is associated with autonomic features, making a focal scalp process much less likely as the underlying etiology. For more information, refer to **pages 1199–1201** of the *Continuum* article "Unusual Headache Disorders."

39 The preferred response is **B (hypnic headache).** Caffeine (100 mg to 200 mg dosed prior to bedtime) and melatonin are both first-line agents for the treatment of hypnic headache, a primary headache disorder that typically occurs in older adults. The headache in hypnic headache occurs only during sleep, causing the patient to awaken at about the same time every night (leading to it being referred to as "alarm clock headache"). This is a recurrent headache, occurring 10 or more days per month for longer than 3 months and lasting 15 minutes to 4 hours. Lithium is also effective in the treatment of

hypnic headache, but because of its adverse effect profile, it is not considered a first-line agent. For more information, refer to **pages 1201–1202** of the *Continuum* article "Unusual Headache Disorders."

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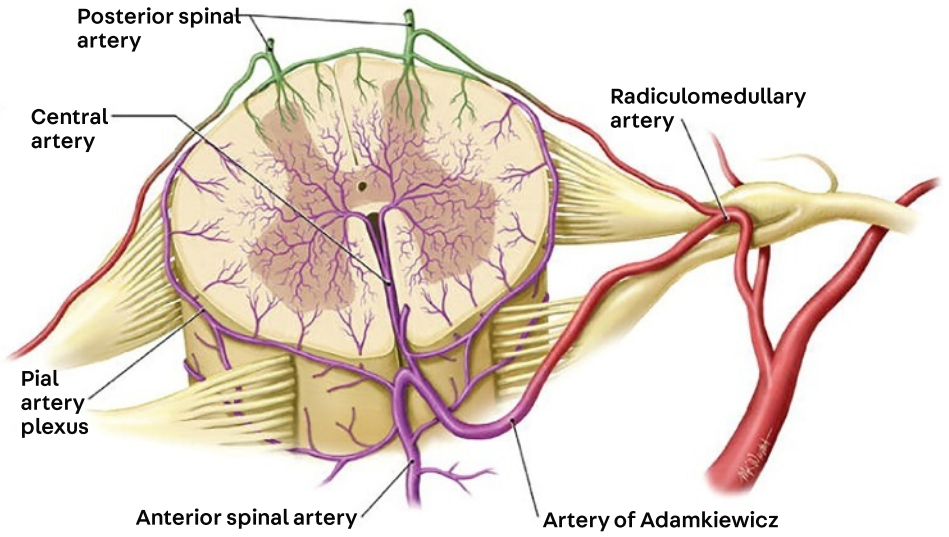
40 The preferred response is **A (*CACNA1A*).** The patient's presentation is consistent with exploding head syndrome, a sensory parasomnia that is manifested by the brief perception of a loud, explosive noise (in the absence of an actual noise) that occurs during sleep transition. It is not associated with pain and is associated with abrupt arousal following the event in which patients are often fearful. The exact pathophysiology is unknown; however, the syndrome may be due to calcium channel dysfunction, as mutations in the *CACNA1A* gene on chromosome 19 have been identified in some patients. For more information, refer to **pages 1203–1205** of the *Continuum* article "Unusual Headache Disorders."

ERRATUM

In the April 2018 issue of *Continuum* (Spinal Cord Disorders, Vol. 24, No. 2), the following error occurred:

In FIGURE 1-3 of "Approach to Myelopathy" by Tracey A. Cho, MD, FAAN, and Shamik Bhattacharyya, MD, MS (*Continuum: Lifelong Learning in Neurology 2018;24:390*), the posterior spinal artery (colored green) was incorrectly labeled as the anterior spinal artery.

The corrected FIGURE 1-3 is below.



Cho TA, Bhattacharyya S. Approach to myelopathy. Continuum (Minneap Minn) 2018;24(2, Spinal Cord Disorders):386–406. doi:10.1212/CON.0000000000000583.

The editors regret this error.

LEARNING OBJECTIVES AND CORE COMPETENCIES

Learning Objectives

Upon completion of this *Continuum: Lifelong Learning in Neurology* Headache issue, participants will be able to:

- Review the phenotype and possible neurobiological basis for premonitory symptoms of migraine, and recognize the importance of asking patients about these symptoms
- Apply current knowledge regarding migraine aura to clinical practice
- Recognize the key symptoms and salient features of the migraine postdrome
- Formulate an evidence-based, individualized, acute treatment plan for patients with migraine
- Discuss the indications and options for preventive therapy of migraine
- Recognize typical and atypical clinical features of spontaneous intracranial hypotension and the pseudotumor cerebri syndrome
- Discuss the symptoms, signs, risks, and management of headache disorders that present in pregnant and postpartum women
- Differentiate secondary from primary headache disorders in children and adolescents, diagnose the common primary headache disorders that present clinically in this age group, and apply evidence-based treatment strategies for headache in children and adolescents
- Diagnose and treat the trigeminal autonomic cephalalgias
- Discuss the clinical features, diagnostic criteria, pathophysiology, and treatment strategies of cranial neuralgias
- Recognize the clinical features of secondary headache syndromes and evaluate their underlying causes
- Discuss the epidemiology, clinical features, differential diagnosis, recommended workup, and treatment for less commonly discussed unusual headache disorders
- Review the legal issues a physician must consider when moving to a new medical practice

Core Competencies

This *Continuum: Lifelong Learning in Neurology* Headache issue covers the following core competencies:

- Patient Care
- Medical Knowledge
- Practice-Based Learning and Improvement
- Interpersonal and Communication Skills
- Professionalism
- Systems-Based Practice

LIST OF ABBREVIATIONS

Headache

5-HT$_{1F}$	5-Hydroxytryptamine 1F
AAN	American Academy of Neurology
AED	Antiepileptic drug
AHS	American Headache Society
ATP	Adenosine triphosphate
ATPase	Adenosine triphosphatase
CGRP	Calcitonin gene-related peptide
CHS	Canadian Headache Society
CPAP	Continuous positive airway pressure
CSF	Cerebrospinal fluid
CT	Computed tomography
ECG	Electrocardiography
EEG	Electroencephalogram
EFNS	European Federation of Neurological Societies
EMG	Electromyography
FDA	US Food and Drug Administration
FLAIR	Fluid-attenuated inversion recovery
fMRI	Functional magnetic resonance imaging
HIPAA	Health Insurance Portability and Accountability Act
HIT-6	Headache Impact Test
HITECH	Health Information Technology for Economic and Clinical Health
HIV	Human immunodeficiency virus
ICHD-3	*International Classification of Headache Disorders, Third Edition*
IIH	Idiopathic intracranial hypertension
IIHTT	Idiopathic Intracranial Hypertension Treatment Trial
IM	Intramuscular
IV	Intravenous
MRA	Magnetic resonance angiography/angiogram
MRI	Magnetic resonance imaging
MRV	Magnetic resonance venography/venogram
MS	Multiple sclerosis
mTOQ-4	Migraine Treatment Optimization Questionnaire-4
NIH	National Institutes of Health
NMDA	*N*-methyl-D-aspartate
NSAID	Nonsteroidal anti-inflammatory drug
PCR	Polymerase chain reaction
PedMIDAS	Pediatric Migraine Disability Assessment
PET	Positron emission tomography
PRES	Posterior reversible encephalopathy syndrome
RCVS	Reversible cerebral vasoconstriction syndrome
SIADH	Syndrome of inapporpriate secretion of antidiuretic hormone
SNRI	Serotonin norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
SUNA	Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms
SUNCT	Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing
SUNHA	Short-lasting unilateral neuralgiform headache attack
TAC	Trigeminal autonomic cephalalgia
TCA	Tricyclic antidepressant

Continuum
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Headache

Article 1: The Migraine Premonitory Phase

Nazia Karsan, MBBS, MRCP; Pyari Bose, MD, MRCP; Peter J. Goadsby, MD, PhD.
Continuum (Minneap Minn). August 2018; 24 (4 Headache):996–1008.

ABSTRACT

PURPOSE OF REVIEW:

The premonitory phase of migraine is defined as the presence of nonpainful symptomatology occurring hours to days before the onset of headache. Symptoms can include neck stiffness, yawning, thirst, and increased frequency of micturition. Clinical recognition of these symptoms is important to ensure early and effective attack management. Further understanding of the clinical phenotype and neurobiological mediation of these symptoms is important in the advancement of therapeutics research in both acute and preventive treatments of migraine.

RECENT FINDINGS:

Since 2014, functional imaging studies have been conducted during the premonitory stage of migraine and have provided novel insights into the early neurobiology and anatomy of the earliest stage of the migraine attack. These studies have shown early involvement of subcortical brain areas including the hypothalamus, substantia nigra, dorsal pons, and various limbic cortical areas, including the anterior cingulate cortex during the premonitory phase. More recent work has revealed altered hypothalamic-brainstem functional connectivity during migraine, which starts before the onset of pain. These exciting findings have provided functional correlation of the symptoms experienced by patients and changes seen on functional brain imaging.

SUMMARY:

This article focuses on the prevalence, phenotype, and proposed neurobiology of premonitory symptomatology in migraineurs as well as the scope of future research.

KEY POINTS

- **Prospective studies have shown that the presence of symptoms prior to the onset of headache can occur reliably and can predict pain onset in some individuals.**
- **The premonitory phase of migraine is likely more common than is currently reported in the literature.**
- **Premonitory symptoms can be experienced in the lead-up to headache or during headache itself, and similar symptoms can present in the postdrome after headache resolution.**
- **Physicians should ask about the presence of premonitory symptoms as a standard part of the migraine history.**
- **Premonitory symptoms of migraine can be experienced by adults, adolescents, and children as young as 18 months old.**
- **Common premonitory symptoms of migraine are fatigue, yawning, neck discomfort, and concentration difficulty.**

- Pharmacologic triggering models in human experimental research and functional neuroimaging have enabled the neurobiology of the premonitory phase of migraine to be studied and have provided functional correlation between the clinical phenotype and areas of brain seen to be activated on imaging.
- The engagement of limbic and subcortical brain areas prior to the onset of headache in migraine is, to date, unique to this as an acute pain condition and provides interesting insights into how the migraine attack starts and progresses to pain.
- Increasing evidence exists for the role of the hypothalamus and its connections in mediating the premonitory symptoms of migraine, as well as the role of these connections in trigeminal nociceptive signaling.
- Understanding of the brain areas and pathways involved in the premonitory phase of migraine, including the dopaminergic pathway, provide novel insights into targeted neurochemical therapeutic targets.
- Understanding the mechanisms behind the mediation of premonitory symptoms within the brain may lead to therapeutic advances for effective abortive migraine agents, as well as for agents that may treat disabling nonpainful symptomatology as well as headache.

Article 2: The Migraine Aura

Andrew Charles, MD. Continuum (Minneap Minn). August 2018; 24 (4 Headache): 1009–1022.

ABSTRACT

PURPOSE OF REVIEW:

This article discusses the basic mechanisms of migraine aura and its clinical significance based upon evidence from human studies and animal models.

RECENT FINDINGS:

Prospective clinical studies have reinforced the understanding that migraine aura is highly variable from one individual to the next as well as from attack to attack in an individual. While migraine with aura clearly has a higher heritability than migraine without aura, population studies have not identified specific genes that underlie this heritability for typical migraine with aura. Imaging studies reveal hypoperfusion associated with migraine aura, although the timing and distribution of this hypoperfusion is not strictly correlated with migraine symptoms. Mapping of migraine visual aura symptoms onto the visual cortex suggests that the mechanisms underlying the aura propagate in a linear fashion along gyri or sulci rather than as a concentric wave and also suggests that aura may propagate in the absence of clinical symptoms. Cortical spreading depression in animal models continues to be a translational model for migraine, and the study of spreading depolarizations in the injured human brain has provided new insight into potential mechanisms of cortical spreading depression in migraine. Migraine with aura has multiple comorbidities including patent foramen ovale, stroke, and psychiatric disorders; the shared mechanisms underlying these comorbidities remains a topic of active investigation.

SUMMARY:

Although it occurs in the minority of patients with migraine, aura may have much to teach us about basic mechanisms of migraine. In addition, its occurrence may influence clinical management regarding comorbid conditions and acute and preventive therapy.

KEY POINTS

- Migraine aura symptoms include visual, sensory, language, motor, or brainstem symptoms that begin and progress gradually, which reflect a slowly propagating physiologic phenomenon in the brain.

- The symptoms of migraine aura are highly variable from person to person and may vary significantly from attack to attack in a given individual.
- Characteristics of the visual percept of the migraine aura indicate that the brain activity underlying aura can begin in different parts of the visual cortex in the same individual and that the activity spreads in a linear fashion along a sulcus or gyrus rather than as a concentric wave.
- The diagnosis of migraine with brainstem aura has replaced the diagnosis of basilar migraine in the most recent version of the *International Classification of Headache Disorders, Third Edition*, reflecting an understanding that the symptoms included in this diagnosis are not necessarily produced by changes in perfusion through the basilar artery.
- Migraine with aura has greater heritability than migraine without aura, but thus far the only genes that have been identified in association with migraine are those responsible for monogenic familial hemiplegic migraine disorders.
- Although migrainous infarction is rare, migraine aura mechanisms occurring in response to ischemia may worsen stroke when it does occur.
- Cortical spreading depression has long been assumed to be the physiologic phenomenon underlying the migraine aura, and cortical spreading depression in animal models appears to be a valid translational model for migraine, but it has never been definitively demonstrated with migraine aura in humans.
- Cortical spreading depression can activate trigeminal pain pathways in animal models, but the variable relationship between migraine aura and headache does not support aura as a mechanism that triggers headache.
- Migraine with aura is associated with patent foramen ovale and increased risk of stroke; patent foramen ovale could play a significant role in the increased stroke risk associated with migraine with aura.
- No evidence supports a contraindication to triptans as acute therapies in attacks of migraine that include aura.

Article 3: The Migraine Postdrome

Pyari Bose, MD, MRCP; Nazia Karsan, MBBS, MRCP; Peter J. Goadsby, MD, PhD.
Continuum (Minneap Minn). August 2018; 24 (4 Headache):1023–1031.

ABSTRACT

PURPOSE OF REVIEW:

The migraine postdrome is the least studied and least understood phase of migraine. This article covers the salient features of the migraine postdrome and provides insight into the history, clinical symptoms, and future implications of this phase of migraine.

RECENT FINDINGS:

Prospective electronic diary studies have shown that patients are left disabled with various nonheadache symptoms in the migraine postdrome, and 81% of patients report at least one nonheadache symptom in the postdrome. Hence, it is important to understand this phase better and ensure that more effective treatments become available in the future to lessen the morbidity associated with this phase. Functional imaging shows widespread reduction in brain-blood flow in the postdrome, which explains the multitudes of symptoms experienced by patients.

SUMMARY:

The disability related to migraine is not exclusive to the headache phase but extends into the postdrome phase and is associated with several nonheadache symptoms that prolong the symptoms experienced by patients with migraine. Further research into the postdrome is crucial

to improve our overall understanding of migraine mechanisms. This knowledge may also help to treat the concurrent nonheadache symptoms better in the future. Novel neuroimaging techniques provide a valuable noninvasive tool to push the frontiers in the understanding of migraine pathophysiology. These methods may help shed further light onto the possible links between key brain structures and networks that could be implicated in the pathophysiology of the various migraine phases.

KEY POINTS

- Tiredness, concentration difficulty, and neck stiffness are the most typically reported postdrome symptoms of migraine.
- Postdrome symptoms appear to be common, with 81% to 94% of patients with migraine reporting these symptoms.
- Treatment with triptans does not appear to alter the underlying diencephalic and brainstem mechanisms involved in migraine pathophysiology, and persistent activation of these networks may explain some of the symptoms in the migraine postdrome.
- Comorbidities such as anxiety and depression do not appear to influence the presence or absence of the migraine postdrome.
- Assigning postdrome symptoms into four main groups (neuropsychiatric, sensory, gastrointestinal, and general symptoms) gives clarity in classifying and assessing the symptoms.
- Based on the similarity of symptoms, one can hypothesize that a shared neural network may be active in the postdrome and premonitory phases of migraine.
- Not recognizing the typical postdrome symptoms may lead to patients undergoing unnecessary investigations and hospital visits, and recognition and reassurance regarding postdrome symptoms may alleviate the patient's concerns.
- The role of brainstem noradrenergic mechanisms and cortical spreading depression in the postdrome pathophysiology needs to be explored further. Functional neuroimaging may hold the key.
- The lack of literature surrounding the postdrome phase of migraine and its significant burden for patients in terms of returning to normal function indicate a vital need to understand it better.

Article 4: Acute Treatment of Migraine

Bert B. Vargas, MD, FAAN, FAHS. Continuum (Minneap Minn). August 2018; 24 (4 Headache):1032–1051.

ABSTRACT

PURPOSE OF REVIEW:

This article provides a framework to help providers formulate a plan for the acute treatment of migraine. Topics covered include the cost-effective patient-centered approach known as stratified care and a summary of evidence-based treatment options that are currently available. Strategies for improving treatment response, troubleshooting suboptimal results, and addressing the needs of special populations are also reviewed.

RECENT FINDINGS:

Both the American Headache Society and the Canadian Headache Society have released evidence-based assessments and reviews of acute treatments for migraine that can be used to help guide treatment decisions. Although several older medications have been re-released with new formulations or new delivery systems, several new medications have also become available or are in the final phases of study, further increasing the number of options available for patients.

SUMMARY:

The acute management of migraine should incorporate a stratified care model in concert with evidence-based treatment options. The response to treatment should be monitored regularly, and measures should be taken to identify suboptimal tolerability or efficacy.

KEY POINTS

- Inadequate acute treatment of migraine exerts a significant socioeconomic burden and has also been associated with transition from an episodic to a chronic pattern of migraine.
- Stratified care considers individual variance in headache severity and associated features such as nausea or vomiting and allows patients the ability to make their own treatment decisions based on their unique needs.
- Stratified care of patients with migraine is equated with higher patient satisfaction but also with decreased health care costs.
- Acute treatments of migraine with the highest level of evidence include all triptans as well as nonspecific analgesics including acetaminophen and certain nonsteroidal anti-inflammatory drugs.
- Triptans are contraindicated in individuals with a history of stroke, heart attack, coronary artery disease, hemiplegic migraine, uncontrolled hypertension, migraine with brainstem aura, and peripheral vascular disease.
- A number of nonspecific analgesics have been shown to be efficacious when compared to placebo in the acute treatment of migraine.
- In situations where standard evidence-based oral medications are ineffective, poorly tolerated, or contraindicated, it may be necessary to consider nonoral treatment options for migraine.
- Despite a relative lack of evidence, peripheral nerve blocks are easily performed in the outpatient setting, are generally accepted as safe and well tolerated, and continue to be a commonly employed treatment for acute migraine.
- A large body of research supports the significant role of calcitonin gene-related peptide in the pathophysiology of migraine, which has led to the development of a new class of calcitonin gene-related peptide antagonists.
- Existing data are conflicting or inadequate to support the concern that coadministration of triptans with selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors confer any additional risk of serotonin syndrome in patients treated for migraine.
- Some common causes of suboptimal treatment include (but are not limited to): inadequate dosing, delay in treatment, not repeating treatment, suboptimal route of administration, and headache with a rapid time to peak severity.

Article 5: Preventive Therapy of Migraine

Todd J. Schwedt, MD, FAAN. Continuum (Minneap Minn). August 2018; 24 (4 Headache):1052–1065.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the preventive therapy of migraine, including indications, strategies for use, and available treatments.

RECENT FINDINGS:

Lifestyle modifications and migraine trigger avoidance are recommended as preventive measures for all individuals with migraine. The decision to recommend additional migraine preventive therapy should consider the frequency of migraine attacks and headaches, extent of

migraine-associated disability, frequency of using acute migraine treatments and the responsiveness to such treatments, and patient preferences. Additional therapies include prescription medications, nutraceuticals, neurostimulation, and behavioral therapy. Considering evidence for efficacy and the risk of potential side effects and adverse events, treatments with the most favorable profiles include (in alphabetical order): amitriptyline, beta-blockers (several), biofeedback, candesartan, coenzyme Q10, cognitive-behavioral therapy, magnesium citrate, onabotulinumtoxinA (for chronic migraine only), relaxation therapy, riboflavin, and topiramate. In addition, erenumab, a calcitonin gene-related peptide (CGRP) receptor monoclonal antibody, received approval from the US Food and Drug Administration (FDA) for the prevention of migraine in May 2018.

SUMMARY:

Successful migraine preventive therapy reduces the frequency and burden of attacks while causing limited side effects. Individual treatment recommendations are determined based upon evidence for efficacy, side effect and adverse event profiles, medication interactions, patient comorbidity, costs, and patient preferences. Patients must be counseled on reasonable expectations for their preventive therapy and the importance of adhering to the recommended treatment plan for a period of time that is sufficient to determine outcomes.

KEY POINTS

- Migraine prevention is multifaceted and includes lifestyle modifications, migraine attack trigger identification and avoidance, avoidance of risk factors for developing more frequent migraine attacks, and, when indicated, medications, nutraceuticals, neurostimulation, and behavioral therapies.
- The goal of preventive therapy is to reduce the frequency of migraine attacks, days with migraine and headache, severity of symptoms, frequency of taking acute migraine therapy, and migraine-related disability.
- When formulating recommendations for specific preventive therapies, clinicians must consider the likelihood for effectiveness and side effects as well as other factors such as potential interactions with other therapies that the patient uses, the patient's comorbidities, the cost of the therapy, and the patient's ability to adhere to the recommended treatment schedule.
- Lifestyle modifications and migraine attack trigger identification and avoidance should be discussed with all patients with migraine.
- Moderate-intensity aerobic exercise (150 minutes per week, generally divided among three to five sessions) should be considered for migraine prevention in adults.
- Maintenance of a daily headache diary is recommended to obtain an accounting of migraine frequency, treatment patterns, and potential migraine attack triggers.
- Commonly cited migraine triggers include: high stress, stress let down (moving from high-stress to low-stress environments, such as might occur during a vacation), weather changes, sex hormone fluctuations in women, not eating, alcohol, sleep disturbance, odors, light, smoke, heat, and certain foods.
- Caffeine overuse and caffeine withdrawal are both associated with headaches and migraine.
- Several factors are associated with increased risk for developing more frequent headaches (eg, transitioning from episodic migraine to chronic migraine), including obesity, sleep disorders, excessive caffeine intake, psychiatric disease, higher baseline headache frequency, the frequent use of abortive migraine medications, female sex, lower socioeconomic status, comorbid pain disorders, major life events, history of head or neck injury, ineffective acute treatment of migraine attacks, and presence of cutaneous allodynia.
- A period of caffeine cessation lasting at least 2 to 3 months is recommended for individuals with frequent migraine.
- Medication overuse is a risk factor for developing more frequent headaches and can lead to medication-overuse headache.
- Sleep is an effective treatment for migraine attacks. Sleep disturbances are common among individuals

with migraine, and poor sleep is positively associated with the occurrence and frequency of migraine attacks.

- Identification and treatment of sleep disturbances is recommended as part of a comprehensive preventive treatment plan for patients with migraine.
- Obesity is associated with a moderately higher risk of migraine and with an increasing number of headache days among those with migraine.
- Weight loss may be associated with reductions in headache frequency and severity.
- The decision to recommend migraine preventive therapy to a patient is based upon headache frequency, migraine attack frequency and duration, the severity of symptoms, the frequency of taking migraine acute therapies, a patient's responsiveness to migraine acute therapies, extent of migraine-related disability, and patient preference.
- Transcutaneous supraorbital nerve stimulation, transcranial magnetic stimulation, and caloric vestibular stimulation have received clearance from the US Food and Drug Administration for migraine prevention.
- Behavioral therapies for migraine are used with the intent of reducing the frequency of migraine attacks and the impact of such attacks on the individual, such as headache-related disability, quality of life, and psychological comorbidity.
- Although behavioral therapies should be considered for all patients significantly impacted by migraine, special consideration should be given when a patient prefers nonpharmacologic therapy; does not tolerate, respond well, or has contraindications to pharmacologic therapy; and when patient behaviors and stress are triggers for migraine attacks or add significantly to migraine-related disability.
- A combination of treatments can be used for migraine prevention when a patient has inadequate response to a single therapy.
- In addition to therapy with combinations of prescription medications, combination therapy that includes combining a medication with a nutraceutical or neurobehavioral therapy or noninvasive neurostimulation can be considered and may be necessary for the effective treatment of patients who are refractory to single treatments.
- Rates of adherence and persistence with migraine preventive therapies are low.
- When assessing response to migraine preventive therapy, it is essential to determine the patient's level of adherence with the treatment before determining that the therapy was ineffective.

Article 6: Headaches Due to Low and High Intracranial Pressure

Deborah I. Friedman, MD, MPH, FAAN. Continuum (Minneap Minn). August 2018; 24 (4 Headache):1066-1091.

ABSTRACT

PURPOSE OF REVIEW:

Headache disorders attributed to low and high intracranial pressure are commonly encountered in specialty headache practices and may occur more frequently than realized. While the headaches resulting from intracranial pressure disorders have what are conventionally thought of as defining characteristics, a substantial minority of patients do not manifest the "typical" features. Moreover, patients with intracranial pressure disorders may also have a preexisting primary headache disorder. Heightening the complexity of the presentation, the headaches of intracranial pressure disorders can resemble the phenotype of a primary disorder. Lastly, patients with so-called intracranial "hypotension" often have normal CSF pressure and neuroimaging studies. Thus, a high index of suspicion is needed. The published literature has

inherent bias as many types of specialists evaluate and treat these conditions. This article reviews the key points to emphasize the history, examination, and laboratory evaluation of patients with intracranial pressure disorders from a neurologist's perspective.

RECENT FINDINGS:

Lumbar puncture opening pressure in patients with spontaneous intracranial hypotension was low enough to meet diagnostic criteria (≤60 mm CSF) in only 34% of patients in one study. Most patients had an opening pressure in the low normal to normal range, and 5% had an opening pressure of 200 mm CSF or more. Diskogenic microspurs are a common cause of this syndrome. The Idiopathic Intracranial Hypertension Treatment Trial found that most participants had a headache phenotype resembling migraine or tension-type headache. No "typical" or characteristic headache phenotype was found, and headache-related disability was severe at baseline. Headache disability did not correlate with the lumbar puncture opening pressure at baseline or at the 6-month primary outcome period. Although participants who were randomly assigned to acetazolamide had a lower mean CSF opening pressure at 6 months, headache disability in that group was similar to the group who received placebo.

SUMMARY:

Significant overlap is seen in the symptoms of high and low CSF pressure disorders and in those of primary headache disorders. Neurologists are frequently challenged by patients with headaches who lack the typical clinical signs or imaging features of the pseudotumor cerebri syndrome or spontaneous intracranial hypotension. Even when characteristic symptoms and signs are initially present, the typical features of both syndromes tend to lessen or resolve over time; consider these diagnoses in patients with long-standing "chronic migraine" who do not improve with conventional headache treatment. While the diagnostic criteria for pseudotumor cerebri syndrome accurately identify most patients with the disorder, at least 25% of patients with spontaneous intracranial hypotension have normal imaging and over half have a normal lumbar puncture opening pressure. Detailed history taking will often give clues that suggest a CSF pressure disorder. That said, misdiagnosis can lead to significant patient morbidity and inappropriate therapy.

KEY POINTS

- Although they represent opposite ends of a spectrum, spontaneous intracranial hypotension and pseudotumor cerebri syndrome share many clinical similarities.
- Neurologists are often faced with the dilemma of evaluating patients who may have either spontaneous intracranial hypotension or pseudotumor cerebri syndrome, but are "atypical."
- When evaluating a patient with possible spontaneous intracranial hypotension or pseudotumor cerebri syndrome, there is a fine line between being hypervigilant when considering the two diagnoses in clinical practice and overdiagnosing the conditions, which can lead to inappropriate investigations and treatments, potentially causing harm.
- Spontaneous intracranial hypotension is not necessarily spontaneous, is not of intracranial origin, and may not arise solely from low CSF pressure. CSF volume and compliance of the caudal dura may also be contributing factors.
- Typical orthostatic and "end of the day" headaches may be less prominent in spontaneous intracranial hypotension over time.
- A marked variability occurs in the location and character of spontaneous intracranial hypotension–related headaches.
- Patients with spontaneous intracranial hypotension may be asymptomatic or experience visual, vestibulocochlear, and cognitive problems, as well as an altered level of consciousness, movement disorders, and intracranial hemorrhage.
- Patients who have a typical headache pattern or abnormal brain imaging are generally identified early. The

lack or subtle nature of orthostatic symptoms coupled with normal brain imaging leads to considerable delay in diagnosis, sometimes for decades. Spontaneous intracranial hypotension should be considered in patients with headaches of any phenotype that are refractory to conventional headache therapies.

- Brain sag may be erroneously diagnosed as a Chiari malformation type I, leading to unnecessary surgery that may make the patient worse.
- In cases of spontaneous intracranial hypotension, the leak site cannot be identified in about half of cases, and intermittent leaking may occur, which can make identification of the leak site challenging.
- Nerve sheath diverticula and osseous changes are indirect signs of a potential leak site.
- In cases of spontaneous intracranial hypotension, a large pool of epidural contrast suggests a high-flow leak.
- CT myelography performed immediately after the instillation of intrathecal contrast is the preferred technique for detecting fast leaks in cases of spontaneous intracranial hypotension; delayed MRI myelography is more sensitive for detecting slow leaks.
- Close collaboration with a neuroradiologist who is experienced in the diagnostic imaging modalities, interpretation of findings, and interventional treatments of spontaneous intracranial hypotension is imperative.
- A retrospinal fluid collection at C1-C2 is a false localizing sign of a spinal CSF leak.
- A nontargeted lower thoracic or lumbar high-volume epidural blood patch is successful in alleviating symptoms in about 30% of patients with spontaneous intracranial hypotension. However, the symptoms may recur over time.
- Of the neurointerventional procedures for spontaneous intracranial hypotension, targeted epidural blood patches with fibrin sealant have the best chance of alleviating the patient's symptoms.
- Headache is the most common symptom of pseudotumor cerebri syndrome and may persist after other symptoms resolve and the CSF pressure normalizes.
- When present, the headache of pseudotumor cerebri syndrome is heterogeneous in phenotype, severe, and disabling.
- The presence of pulse-synchronous tinnitus and transient obscurations of vision supports a diagnosis of pseudotumor cerebri syndrome.
- A history of migraine was over twice as common in participants in the Idiopathic Intracranial Hypertension Treatment Trial as in the general population.
- Elevated CSF pressure in patients with pseudotumor cerebri syndrome may lead to skull base CSF leaks or intracranial hypotension.
- A comprehensive ophthalmic examination, including perimetry, is of prime importance for patients with suspected or confirmed pseudotumor cerebri syndrome. Confrontation visual field testing is inadequate to detect subtle defects, but the presence of a visual field abnormality on confrontation testing is highly concerning for significant visual loss.
- Body mass index has a negligible effect on lumbar puncture opening pressure.
- The position of the legs during a lumbar puncture has little impact (approximately 10 mm CSF) on the opening pressure, although the most accurate measurement is produced with the patient relaxed and legs extended.
- Sedation and Valsalva maneuvers can substantially increase the CSF opening pressure during a lumbar puncture.
- If the CSF pressure is elevated, remove enough CSF to achieve a closing pressure in the mid-normal range.
- Evaluate patients with pseudotumor cerebri syndrome for obstructive sleep apnea. This process may include screening questionnaires, asking the patient (and bed partner) about sleep apnea symptoms, assessing the Mallampati score, and polysomnography. Treatment of sleep apnea often helps lower the intracranial pressure.
- A randomized treatment trial comparing maximal medical therapy with and without ventriculoperitoneal shunting or optic nerve sheath fenestration was funded by the National Eye Institute and is expected to begin enrollment in 2018.
- Although headache disability improved overall in the Idiopathic Intracranial Hypertension Treatment Trial, no

benefit of acetazolamide treatment was shown compared to placebo in Headache Impact Test-6 scores. Lowering the CSF pressure does not always result in improvement in headaches; no correlation existed between Headache Impact Test-6 score and lumbar puncture opening pressure at baseline or at 6-month follow-up.

- Many patients with pseudotumor cerebri syndrome require headache treatment in addition to intracranial pressure–lowering therapies. Preventive therapies should be selected based on headache phenotype with attention to side effect profile.
- A team approach is needed for the management of patients with pseudotumor cerebri syndrome, with a neurologist (or neuro-ophthalmologist) directing the coordination of care.
- The visual prognosis in patients with pseudotumor cerebri syndrome is generally good, but up to 10% of patients have permanent severe visual loss. Male sex, high-grade papilledema, profound anemia, renal failure, and uncontrolled systemic hypertension are risk factors associated with a poor visual outcome. Patients who present with loss of visual acuity require aggressive treatment.
- Headaches may persist after the CSF pressure is controlled and pseudotumor cerebri syndrome seems otherwise quiescent. This may be related to central sensitization occurring early in the course.

Article 7: Headache in Pregnancy

Matthew S. Robbins, MD, FAAN, FAHS. Continuum (Minneap Minn). August 2018; 24 (4 Headache):1092–1107.

ABSTRACT

PURPOSE OF REVIEW:

Headache disorders are extraordinarily common and disproportionately impact women of childbearing age. This article reviews the importance of proper diagnosis, natural history, and management of headache disorders in pregnant and postpartum women.

RECENT FINDINGS:

Red flags for secondary headache specifically among pregnant women include elevated blood pressure and lack of a previous headache history, as well as a prolonged duration of the headache attack in those with a prior history of migraine. Migraine improvement is typical for most pregnant women, but the prognosis for women who have migraine with aura or chronic migraine is less predictable. Migraine is now an established risk factor for the development of preeclampsia. Recent data suggest hazards for compounds containing butalbital and possibly a better safety profile for triptans than previously believed during pregnancy. Peripheral nerve blocks and noninvasive neurostimulation devices are procedural and emerging therapies that have promising safety profiles for pregnant women with headache disorders.

SUMMARY:

Acute headache occurring in pregnancy and the postpartum period is a red flag requiring diagnostic vigilance. Migraine frequency in women typically improves during pregnancy, although this trend is less certain when aura is present and after delivery. Acute and preventive treatment plans during pregnancy and lactation are plausible but may require shifts in therapeutic hierarchy. Relatively safe oral, parenteral, and procedural therapies are available for pregnant women. Noninvasive neuromodulation devices are already available and will likely play a greater role in the coming years. Migraine is associated with medical and obstetrical complications during pregnancy, and women with frequent migraine attacks may need to be considered high risk.

KEY POINTS

- Recent evidence suggests that new headache in pregnancy and in the puerperium (within 6 weeks postpartum) is a red flag for secondary headache.
- Among women with a history of headache, a changed feature of a longer attack duration was associated with a secondary headache disorder diagnosis.
- A diagnostic strategy for acute headache in pregnant women should feature liberal use of noncontrast MRI and monitoring for preeclampsia, particularly in those with an elevated blood pressure and without a headache history.
- Migraine without aura typically improves or remits altogether in most women when pregnant, with improvement or remission observed in nearly 47% of women during the first trimester, in 83% of women during the second trimester, and in 87% of women during the third trimester.
- Migraine with aura is less likely to improve during pregnancy than migraine without aura. New-onset migraine with aura and even aura without headache may occur in the later stages of pregnancy.
- Management of migraine during pregnancy always starts with preconception counseling whenever feasible.
- Nonpharmacologic therapies should always be emphasized as an important aspect of migraine management, especially during pregnancy.
- Migraine prophylactic medication may be unnecessary in pregnancy because of the generally good prognosis and should be avoided because of teratogenic concerns.
- Butalbital compounds that are used in combination with acetaminophen or aspirin and caffeine have recently been associated with congenital heart defects and are generally not recommended.
- The majority of evidence suggests triptans intrinsically may not adversely impact labor and delivery outcomes, but more studies among pregnant women stratified by migraine severity may provide further clarity.
- Occipital and trigeminal pericranial nerve blocks are a treatment used for migraine, cluster headache, and other headache disorders as an acute therapy as well as for short-term prevention and are appealing to use in pregnancy because of their peripheral administration and presumed safety.
- Headaches associated with spinal or epidural anesthesia could take two forms: post–dural puncture headache and pneumocephalus.
- Over half of all women who have migraine will have an attack postpartum, so the management of postpartum headache, particularly in breast-feeding women, is an important clinical problem.
- Of the triptans, eletriptan is likely the most compatible medication with breast-feeding based on its low milk to plasma ratio.
- The evaluation of a pregnant or postpartum woman with suspected preeclampsia is also confounded by migraine serving as a preeclampsia risk factor. The distinction is crucial as migraine and preeclampsia are managed differently, with antepartum severe preeclampsia managed by expedited delivery.

Article 8: Pediatric and Adolescent Headache

Amy A. Gelfand, MD. Continuum (Minneap Minn). August 2018; 24 (4 Headache): 1108–1136.

ABSTRACT

PURPOSE OF REVIEW:

This article provides the practicing neurologist with a comprehensive, evidence-based approach to the diagnosis and management of headache in children and adolescents, with a focus on migraine.

RECENT FINDINGS:

Four triptans are now labeled by the US Food and Drug Administration (FDA) for acute migraine treatment in adolescents, and rizatriptan is labeled for use in children age 6 and older. For preventive migraine treatment, the Childhood and Adolescent Migraine Prevention trial demonstrated that approximately 60% of children and adolescents with migraine will improve with a three-pronged treatment approach that includes: (1) lifestyle management counseling (on sleep, exercise, hydration, caffeine, and avoidance of meal skipping); (2) optimally dosed acute therapy, specifically nonsteroidal anti-inflammatory drugs and triptans; and (3) a preventive treatment that has some evidence for efficacy. For the remaining 40% of children and adolescents, and for those who would not have qualified for the Childhood and Adolescent Migraine Prevention trial because of having continuous headache or medication-overuse headache, the clinician's judgment remains the best guide to preventive therapy selection.

SUMMARY:

Randomized placebo-controlled trials have been conducted to guide first-line acute and preventive migraine treatments in children and adolescents. Future research is needed to guide treatment for those with more refractory migraine, as well as for children and adolescents who have other primary headache disorders.

KEY POINTS

- New headaches, or new types of headaches, are more concerning for secondary pathology than old headaches.
- By age 10, migraine prevalence in children is approximately 5%. This means that by fifth grade, almost every classroom contains at least one child with migraine.
- The Pediatric Migraine Disability Assessment questionnaire is a six-question validated instrument for measuring headache-related disability in children and adolescents.
- Common premonitory symptoms in pediatric migraine include fatigue, irritability/mood changes, neck stiffness, and facial change.
- Differentiating premonitory symptom from migraine triggers can be challenging.
- Chocolate does not appear to be a migraine trigger.
- Cannabinoid hyperemesis syndrome can mimic cyclic vomiting syndrome in adolescents.
- Combine cognitive-behavioral therapy with pharmacologic preventive treatment for chronic migraine in children and adolescents ages 10 to 17 years.
- First-line pharmacologic preventives for pediatric and adolescent migraine should have a side effect profile comparable to that of placebo.
- In the United States, 504 plans allow children and teenagers to have necessary accommodations at school for management of a medical condition, such as migraine. All children and adolescents with migraine should have an annual letter from their doctor stating their diagnosis and supporting accommodations for their 504 plan.
- Four triptans are labeled by the US Food and Drug Administration for acute migraine in adolescents 12 to 17 years of age: almotriptan (oral), zolmitriptan (nasal spray), rizatriptan (melt), and sumatriptan/naproxen (oral); and one medication, rizatriptan (melt), is labeled for use in children age 6 and older.
- Children and adolescents who are on selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors generally do not need to have their access to triptans restricted.
- While tension-type headache exists in the general pediatric population, it is not a common reason for clinical presentation.
- Nausea is not present in tension-type headache. The presence of nausea in children with headaches has high specificity for a diagnosis of migraine.
- Primary stabbing headache is a particularly common reason for clinical presentation in children younger than the age of 6 years.
- Primary stabbing headache pain intensity can be severe in children.

Article 9: Cluster Headache and Other Trigeminal Autonomic Cephalalgias

Mark Burish, MD, PhD. Continuum (Minneap Minn). August 2018; 24 (4 Headache): 1137–1156.

ABSTRACT

PURPOSE OF REVIEW:

This article covers the clinical features, differential diagnosis, and management of the trigeminal autonomic cephalalgias (TACs). The TACs are composed of five diseases: cluster headache, paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA), and hemicrania continua.

RECENT FINDINGS:

New classifications for the TACs have two important updates; chronic cluster headache is now defined as remission periods lasting less than 3 months (formerly less than 1 month), and hemicrania continua is now classified as a TAC (formerly classified as *other primary headache*). The first-line treatments of TACs have not changed in recent years: cluster headache is managed with oxygen, triptans, and verapamil; paroxysmal hemicrania and hemicrania continua are managed with indomethacin; and SUNCT and SUNA are managed with lamotrigine. However, advancements in neuromodulation have recently provided additional options for patients with cluster headache, which include noninvasive devices for abortive therapy and invasive devices for refractory cluster headache. Patient selection for these devices is key.

SUMMARY:

The TACs are a group of diseases that appear similar to each other and to other headache disorders but have important differences. Proper diagnosis is crucial for proper treatment. This article reviews the pathophysiology, epidemiology, differential diagnosis, and treatment of the TACs.

KEY POINTS

- The trigeminal and autonomic systems are connected through the trigeminal autonomic reflex.
- Functional imaging has shown activation of the posterior hypothalamus at the onset of a cluster headache attack.
- Cluster headache is 3 times more common in men, with a typical age of onset between 20 and 40 years of age. The two forms of cluster headache are an episodic version, where patients have a headache-free period of more than 3 months, and a chronic version, where the headache-free period is less than 3 months.
- The pain in cluster headache is excruciating, anecdotally worse than migraine, childbirth, or kidney stones.
- Cluster headache has well-defined criteria. Other features that are common in cluster headache include rapid escalation and de-escalation of pain, alcohol as a trigger during the headache period (but not during the remission period), a positive response to subcutaneous sumatriptan, a positive response to high-flow oxygen, and a clocklike daily pattern of headaches.
- Cluster headache may include short frequent headaches (mimicking paroxysmal hemicrania) or a mild interictal headache (mimicking hemicrania continua). An indomethacin trial is warranted in these situations.
- Patients with cluster headache may have migrainous features such as photophobia, phonophobia, and nausea. Patients with migraine likewise may have cranial autonomic symptoms.
- The differential diagnosis between cluster headache and migraine can often be made based on the duration, frequency, and associated factors such as restlessness.

- When using triptans to treat cluster headache, quicker routes are better: subcutaneous is more effective than nasal, which is more effective than oral.
- For the acute treatment of cluster headache, oxygen and noninvasive vagus nerve stimulation are good options for patients with multiple attacks per day.
- Unlike cluster headache, paroxysmal hemicrania has shorter and more frequent attacks, has a slight female predominance, is more likely to be chronic, is less likely to be circadian, can be triggered by neck movements, and responds completely to indomethacin.
- Indomethacin is not always well tolerated. A gastroprotective medication should be considered. In addition, indomethacin should be downtitrated to find the minimal effective dose, which is often less than a total daily dose of 100 mg.
- In comparison to short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms, trigeminal neuralgia does not have prominent cranial autonomic features, and has a refractory period for tactile stimuli.
- Hemicrania continua has more prominent migrainous features and less prominent cranial autonomic features than other trigeminal autonomic cephalalgias.
- Patients with hemicrania continua on indomethacin should be gradually downtitrated approximately every 6 months, as remissions have been reported for hemicrania continua.
- If indomethacin is not effective after a solid 1- to 2-week course at 75 mg 3 times a day, the diagnosis of hemicrania continua or paroxysmal hemicrania should be reconsidered.

Article 10: Cranial Neuralgias

Stewart J. Tepper, MD, FAHS. Continuum (Minneap Minn). August 2018; 24 (4 Headache):1157–1178.

ABSTRACT

PURPOSE OF REVIEW:

This article describes the clinical features and diagnostic criteria, pathophysiology (when known), and treatment strategies of the major cranial neuralgias.

RECENT FINDINGS:

Abnormal vascular loops compressing cranial nerves are the most common known pathogenesis associated with the primary neuralgias.

SUMMARY:

The most frequently encountered primary neuralgias are trigeminal neuralgia, occipital neuralgia, and, rarely, glossopharyngeal neuralgia. Nervus intermedius neuralgia is even more rare. All neuralgias merit a careful workup for secondary causes. Drug treatment generally relies on antiepileptic drugs, antidepressants, and baclofen. OnabotulinumtoxinA can be useful in treating some cranial neuralgias. Surgical and invasive treatments include ablation, gamma knife treatment, and microvascular decompression.

KEY POINTS

- The *International Classification of Headache Disorders, Third Edition* uses the term classical trigeminal neuralgia for what was previously called primary trigeminal neuralgia.
- Classical trigeminal neuralgia can occur in two forms: a purely paroxysmal form and a form with concomitant persistent interictal facial pain in a trigeminal distribution.
- Most cases of trigeminal neuralgia involve the second or third division of cranial nerve V.
- An abnormal examination suggests a secondary cause of trigeminal or other neuralgias, but this is not invariable.

- Classical trigeminal neuralgia is almost never in a V1 distribution. Consider other diagnoses and ask about accompanying autonomic features to differentiate short-lasting unilateral neuralgiform headaches, which are usually in a V1 distribution.
- Most cases of classical trigeminal neuralgia are thought to be secondary to an abnormal vascular loop compressing the symptomatic trigeminal division around the dorsal root entry zone, also called neurovascular compression.
- Although most cases of classical trigeminal neuralgia respond initially to carbamazepine or oxcarbazepine, short-lasting unilateral neuralgiform headache attacks can also respond to these antiepileptic drugs, so that therapeutic response does not always yield a clear diagnosis.
- Numerous peripheral and central surgical and nonsurgical approaches can be tried for classical trigeminal neuralgias, including block or destruction of portions of the trigeminal nerve distal to the gasserian ganglia, percutaneous rhizotomies, gamma knife treatment, and microvascular
- The most common painful trigeminal neuropathy is herpetic.
- Pain related to any of the painful trigeminal neuropathies is best treated with antiepileptic drugs or tricyclic antidepressants. Early addition of gabapentin to the antiviral regimen in acute shingles may help prevent postherpetic trigeminal neuropathy.
- Proven pain-reducing medications for postherpetic trigeminal neuropathy begin with antiepileptic drugs. If these fail or are contraindicated, tricyclic antidepressants or serotonin norepinephrine reuptake inhibitors can be useful, as can topical capsaicin and lidocaine.
- Medical, not surgical, management is recommended for treatment of painful trigeminal neuropathies.
- Prevalence of painful trigeminal neuropathy attributed to a multiple sclerosis plaque ranges from 1.5% to 7.9% of patients with multiple sclerosis.
- The pain of glossopharyngeal neuralgia not only includes the distribution of the glossopharyngeal nerve but can extend into the pharyngeal and auricular vagal branches.
- Glossopharyngeal neuralgia is generally felt in the posterior tongue, pharynx, tonsillar fossa, or below the lower jaw angle and the ear. Clinical manifestations such as hoarseness, cough, neurocardiogenic bradycardia, sick sinus syndrome, asystole, seizures, and syncope suggest vagal involvement.
- Nervus intermedius neuralgia can present as either a set of brief, severe, stabbing, shooting, piercing, or sharp pains, or pains of longer duration, from 2 seconds to minutes in duration deep within the internal auditory canal. The patients usually have a trigger that occurs with touching the posterior wall of the external auditory canal or a zone around the ear.
- Occipital neuralgia is paroxysmal and generally occurs in the distribution of the greater occipital nerve. A different location or a continuous pain, especially with other associated symptoms, should call for a reconsideration of the diagnosis.
- Treatment of occipital neuralgia begins with a peripheral nerve block.

Article 11: Secondary Headache Syndromes

Denise E. Chou, MD. Continuum (Minneap Minn). August 2018; 24 (4 Headache): 1179–1191.

ABSTRACT

PURPOSE OF REVIEW:

This article is intended to assist clinicians in distinguishing benign primary headache syndromes from serious headache presentations that arise from exogenous causes.

RECENT FINDINGS:

Although most cases of severe headache are benign, it is essential to recognize the signs and symptoms of potentially life-threatening conditions. Patients with primary headache disorders can also acquire secondary conditions that may present as a change in their baseline headache patterns and characteristics. Clinical clues in the history and examination can help guide the diagnosis and management of secondary headache disorders. Furthermore, advances in the understanding of basic mechanisms of headache may offer insight into the proposed pathophysiology of secondary headaches.

SUMMARY:

Several structural, vascular, infectious, inflammatory, and traumatic causes of headache are highlighted. Careful history taking and examination can enable prompt identification and treatment of underlying serious medical disorders causing secondary headache syndromes.

KEY POINTS

- A potentially serious cause is more likely with a new severe headache than with a headache that has been recurrent over years.
- In contrast to common belief, brain tumors constitute a rare cause of headache and even less frequently present with severe pain. Approximately 30% of patients diagnosed with a brain tumor report headache on presentation; however, only 1% to 2% report headache as the sole clinical symptom.
- Distinguishing headache features in cases of nontraumatic subarachnoid hemorrhage include occipital location, a "stabbing" quality, a rapid peak of intensity (within 1 second of onset), and associated meningismus.
- Headache occurs in 60% to 95% of cases of carotid artery dissections, is usually unilateral with face/neck pain on the same side, and may be accompanied by ipsilateral Horner syndrome or amaurosis fugax.
- Reversible cerebral vasoconstriction syndrome headaches are often bilateral, brief in duration (1 to 3 hours), recurrent over a span of days to weeks, and are sudden in onset, rapidly reaching a maximal severe intensity (thunderclap).
- Distinguishing cardiac cephalalgia from migraine, which may also be aggravated by exertion, is essential to avoid the inappropriate administration of triptan or ergot medications, which are contraindicated in coronary syndromes because of their vasoconstrictive effects.
- Blindness can be a complication of untreated temporal arteritis in approximately half of patients because of involvement of the ophthalmic artery and its branches; however, visual loss can be prevented with prompt glucocorticoid treatment.
- Contrast-enhanced MRI may demonstrate granulomatous inflammation of the cavernous sinus, superior orbital fissure, or orbit in Tolosa-Hunt syndrome.
- Risk factors for the development of posttraumatic headache include a prior history of headache, milder degree of head trauma, and age younger than 60 years.
- Intermittent angle-closure glaucoma may be mistaken for migraine, as both conditions can present with unilateral eye pain, nausea/vomiting, light sensitivity, and visual disturbances.
- The occurrence of cranial autonomic symptoms in migraine (such as lacrimation, nasal congestion, and rhinorrhea) may contribute to the misdiagnosis of "sinus headache."
- Although relatively infrequent, sphenoid sinusitis is a serious condition because of the potential complication of cavernous sinus thrombophlebitis.
- Headache attributed to temporomandibular disorders is usually unilateral and should be ipsilateral to the pathology when the temporomandibular complex is the source of pain, but can be bilateral when muscular involvement is present.

Article 12: Unusual Headache Disorders

Amaal Jilani Starling, MD, FAHS. Continuum (Minneap Minn). August 2018; 24 (4 Headache):1192–1208.

ABSTRACT

PURPOSE OF REVIEW:

Unusual headache disorders are less commonly discussed and may be misdiagnosed. These headache disorders frequently have a benign natural history; however, without reassurance, therapeutic education, and treatment, they can negatively affect the health and function of patients.

RECENT FINDINGS:

This article reviews the clinical features, diagnosis, workup, and proposed treatments for several unusual headache disorders including primary cough headache, primary headache associated with sexual activity, primary exercise headache, cold-stimulus headache, primary stabbing headache, nummular headache, hypnic headache, and headache attributed to travel in space. Exploding head syndrome is also discussed, which is a sleep disorder commonly confused with a headache disorder.

SUMMARY:

Unusual headache disorders are usually benign, yet without the correct diagnosis can be very worrisome for many patients. Through greater awareness of these headache disorders, neurologists can evaluate and effectively manage unusual headache disorders, which offers significant benefits to patients and practice satisfaction to neurologists.

KEY POINTS

- Given that primary cough headache is rare, when a patient presents with a headache triggered by cough or some other Valsalva maneuver that may raise intracranial pressure, the most essential first step is to rule out a secondary cause based on red flags identified on history and examination.
- Since primary cough headaches are benign attacks of short duration, often reassurance is the only treatment needed.
- An explosive attack just before or with orgasm is a thunderclap headache, which is a headache red flag and a neurologic emergency.
- A diagnosis of primary headache associated with sexual activity can be considered once more alarming causes of headache have been ruled out; thus, it is a diagnosis of exclusion.
- Anticipatory treatment 30 minutes prior to sexual activity with indomethacin can be an effective treatment plan for most patients with primary headache associated with sexual activity. However, if longer term prevention is needed, beta-blockers have also been used successfully.
- Primary exercise headache is unique in that it is precipitated by sustained physically strenuous activity rather than short-duration precipitating factors such as cough, Valsalva maneuver, or orgasm.
- Given the high prevalence in athletes, primary exercise headache should be considered when evaluating an athlete with headache.
- Precipitation of headache by exercise or exertion is a headache red flag and should raise concern for a secondary cause of headache.
- Cardiac cephalalgia should be considered in older adults with vascular risk factors who present with a headache precipitated by exercise. The headache is a result of myocardial ischemia and can be the sole manifestation of ischemia. A stress test is diagnostic, and revascularization of coronary vessels is curative.
- Given that primary exercise headache is a self-limited, benign disorder, once a workup has been completed,

treatment is often as simple as trigger avoidance. However, exercise is essential for healthy living, and if primary exercise headache is a barrier to exercise, then pharmacotherapy is available and typically effective.

- In headache attributed to ingestion or inhalation of a cold stimulus, intense pain typically begins within a few seconds of the rapid ingestion or inhalation of cold material and is short lasting, persisting only for seconds.
- In headache attributed to ingestion or inhalation of a cold stimulus, the exposure of the palate or the posterior pharyngeal wall to a very cold substance may trigger rapid constriction and dilation of vessels, thus activating the nociceptors in the vessel wall, resulting in referred pain to the head.
- Aside from trigger avoidance, no specific treatment is required for headache attributed to ingestion or inhalation of a cold stimulus. Cold substances should be ingested slowly while avoiding rapid exposure of cold substances to the posterior aspect of the palate if possible.
- Clinically, primary stabbing headaches are headaches with the shortest duration, with studies demonstrating that 80% of stabbing pains last 3 seconds or less.
- The differential diagnosis for primary stabbing headache includes trigeminal neuralgia and trigeminal autonomic cephalalgias, specifically short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms.
- Idiopathic primary stabbing headache is benign and typically does not require any specific treatment aside from reassurance. However, if the stabbing pains are more frequent, indomethacin is the medication of choice.
- Nummular headache is an unusual primary headache disorder characterized by head pain that occurs in a small, fixed, very well-circumscribed coin, oval, or elliptical shape.
- Entities to consider in the differential diagnosis for nummular headache include primary stabbing headache, although this is typically multifocal and not unifocal as in nummular headache; epicrania fugax, although this head pain is in motion and not a focal, coin-shaped area as occurs in nummular headache; and other cranial neuralgias, although these would follow the relevant nerve distribution and respond to anesthetic blocks, both of which do not occur in nummular headache.
- Hypnic headache is a recurrent primary headache disorder of short duration that typically occurs in older persons, typically after the age of 50. These headaches occur only during sleep and will cause the person to awaken.
- The differential diagnosis for nocturnal headaches includes nocturnal hypertension, increased intracranial pressure (mass lesion or idiopathic intracranial hypertension), trigeminal autonomic cephalalgias (specifically cluster headache), caffeine withdrawal headache and medication-overuse (rebound) headache, or sleep apnea headache.
- Treatment options for hypnic headache include caffeine, melatonin, and lithium. Although effective, lithium may be problematic especially for older patients because of the possibility for lithium toxicity. Fortunately, caffeine and/or melatonin are typically effective, thus avoiding use of lithium altogether.
- Space headache has been reported in all phases of space flight. It typically has a moderate to severe intensity with an exploding or heavy quality of pain requiring analgesics.
- During an acute attack of exploding head syndrome, the patient has a perception of a loud, explosive noise in the absence of objective acoustic stimulation that usually occurs during sleep transitions when going to sleep or awakening. It is sudden, causes fear, but is not associated with head pain.
- Exploding head syndrome is benign, and reassurance is the cornerstone of treatment.

Issue Overview

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Continuum: Lifelong Learning in Neurology® is designed to help practicing neurologists stay abreast of advances in the field while simultaneously developing lifelong self-directed learning skills.

Learning Objectives

Upon completion of this *Continuum: Lifelong Learning in Neurology* Headache issue, participants will be able to:

- Review the phenotype and possible neurobiological basis for premonitory symptoms of migraine, and recognize the importance of asking patients about these symptoms
- Apply current knowledge regarding migraine aura to clinical practice
- Recognize the key symptoms and salient features of the migraine postdrome
- Formulate an evidence-based, individualized, acute treatment plan for patients with migraine
- Discuss the indications and options for preventive therapy of migraine
- Recognize typical and atypical clinical features of spontaneous intracranial hypotension and the pseudotumor cerebri syndrome
- Discuss the symptoms, signs, risks, and management of headache disorders that present in pregnant and postpartum women
- Differentiate secondary from primary headache disorders in children and adolescents, diagnose the common primary headache disorders that present clinically in this age group, and apply evidence-based treatment strategies for headache in children and adolescents
- Diagnose and treat the trigeminal autonomic cephalalgias

- Discuss the clinical features, diagnostic criteria, pathophysiology, and treatment strategies of cranial neuralgias
- Recognize the clinical features of secondary headache syndromes and evaluate their underlying causes
- Discuss the epidemiology, clinical features, differential diagnosis, recommended workup, and treatment for less commonly discussed unusual headache disorders
- Review the legal issues a physician must consider when moving to a new medical practice

Core Competencies

This *Continuum: Lifelong Learning in Neurology* Headache issue covers the following core competencies:

- Patient Care
- Medical Knowledge
- Practice-Based Learning and Improvement
- Interpersonal and Communication Skills
- Professionalism
- Systems-Based Practice

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Goadsby reports no disclosure.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Bose reports no disclosure.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Burish discusses the unlabeled/investigational use of baclofen, corticosteroids, deep brain stimulation, lithium, occipital nerve stimulation, oxygen, sphenopalatine ganglion stimulation, sumatriptan, topiramate, valproate, verapamil, and zolmitriptan for the treatment of cluster headache; indomethacin, topiramate, and verapamil for the treatment of paroxysmal hemicrania; carbamazepine, duloxetine, gabapentin, lamotrigine, lidocaine, oxcarbazepine, and topiramate for the treatment of short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; and celecoxib, gabapentin, ibuprofen, indomethacin, melatonin, occipital nerve stimulation, onabotulinum toxin injections, topiramate, and verapamil for the treatment of hemicrania continua.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Charles discusses the unlabeled/investigational use of ketamine for the treatment for migraine aura.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Chou discusses the unlabeled/investigational use of glucocorticoids for the treatment of giant cell arteritis and Tolosa-Hunt syndrome, indomethacin for the treatment of hemicrania continua, and nonsteroidal anti-inflammatory drugs and oral or locally injected steroids for the treatment of primary trochlear headache (trochleitis).

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Friedman discusses the unlabeled/investigational use of acetazolamide for the treatment of pseudotumor cerebri syndrome, the use of gadolinium for MRI myelography for the diagnosis of spontaneous intracranial hypotension, and the use of zonisamide for the treatment of associated headache.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Gelfand discusses the unlabeled/investigational use of all listed medications for the treatment of headache in children and adolescents, with the exceptions of almotriptan oral tablets, sumatriptan/naproxen combination tablets, and zolmitriptan nasal spray for adolescents 12 to 17 years of age for the treatment of acute migraine as well as topiramate in adolescents 12 to 17 years of age for migraine prevention. Rizatriptan is labeled for acute migraine treatment in children age 6 and older.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Karsan reports no disclosure.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Kass reports no disclosure.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Robbins discusses the unlabeled/investigational use of medications and devices for the treatment of headache disorders in pregnant and breast-feeding women, including all analgesics, neuromodulation devices, preventive therapies, and triptans.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Schwedt discusses the unlabeled/investigational use of numerous medications for the treatment of migraine; none of the therapies discussed are approved by the US Food and Drug Administration except for caloric vestibular stimulation, divalproex sodium, erenumab, propranolol, timolol, topiramate, transcranial magnetic stimulation, and transcutaneous supraorbital nerve stimulation for the treatment of migraine and the use of onabotulinumtoxinA for the treatment of chronic migraine.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Starling discusses the unlabeled/investigational use of acetazolamide, beta-blockers including nadolol and propranolol, caffeine, celecoxib, clomipramine, clonazepam, cyclobenzaprine, ergotamine, flunarizine, gabapentin, indomethacin, lithium, melatonin, nifedipine, nonsteroidal anti-inflammatory drugs, onabotulinumtoxinA, topiramate, and tricyclic antidepressants including amitriptyline for the treatment of unusual headache disorders.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Tepper discusses the unlabeled/investigational use of all listed medications for the treatment of neuralgias.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Vargas discusses the unlabeled/investigational use acetaminophen, acetylsalicylic acid, dexketoprofen, diclofenac, dipyrone, droperidol, haloperidol, ibuprofen, ketorolac, lasmiditan, metoclopramide, naproxen, peripheral nerve block, prochlorperazine, and valproate for the acute treatment of migraine.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Lynn reports no disclosure.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Weathers reports no disclosure.

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The goals of *Continuum* include disseminating up-to-date information to the practicing neurologist in a lively, interactive format; fostering self-assessment and lifelong study skills; encouraging critical thinking; and, in the final analysis, strengthening and improving patient care.

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The review articles emphasize clinical issues emerging in the field in recent years. Case reports and vignettes are used liberally, as are tables and illustrations. Audio interviews with the authors of *Continuum* articles are published alongside each article, and video material relating to the issue topic accompanies issues when applicable.

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