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.**

CITE AS:
CONTINUUM (MINNEAP MINN) 2018;24(4, HEADACHE):1179–1191.

Address correspondence to Dr Denise E. Chou, 1 Amgen Center Dr, Thousand Oaks, CA 91320, *denise.chou@gmail.com*.

RELATIONSHIP DISCLOSURE:
Dr Chou has received personal compensation for serving on the advisory boards of Allergan, Amgen Inc, Eli Lilly and Company, Pernix Therapeutics, and Teva Pharmaceutical Industries Ltd; as a speaker for the American Academy of Neurology, Medscape Inc, and the PeerView Institute; and has received research/grant support as a principal investigator for Alder BioPharmaceuticals, Inc; Capnia, Inc; CEFALY Technology; and Teva Pharmaceutical Industries Ltd. Dr Chou is an employee of Amgen Inc.

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).

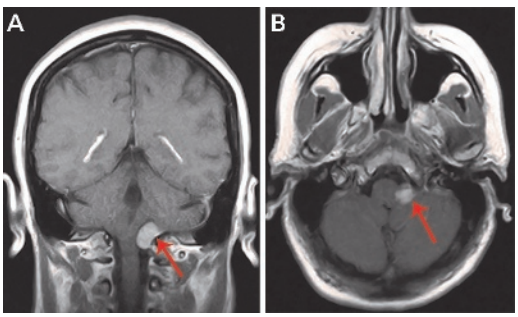

FIGURE 11-1
Brain MRI of the patient in CASE 11-1. Postcontrast T1-weighted coronal (*A*) and axial (*B*) images reveal a uniformly enhancing left foramen magnum dural-based mass consistent with a meningioma (*arrows*), causing crowding at the pontomedullary and medullary levels with minimal rightward 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.

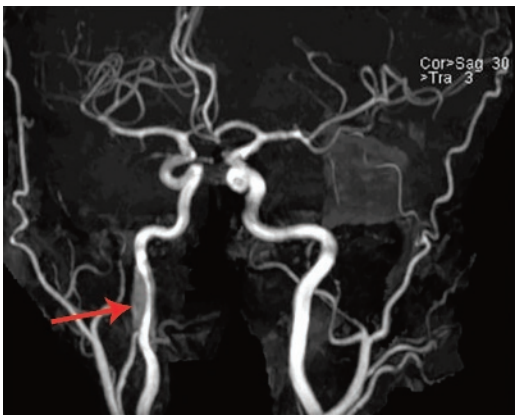

FIGURE 11-2
Magnetic resonance angiogram (MRA) of the head of the patient in CASE 11-2 showing an acute dissection of the right internal carotid artery with an intramural hematoma (*arrow*).

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.

REFERENCES

1 Dodick DW. Pearls: headache. Semin Neurol 2010; 30(1):74–81. doi:10.1055/s-0029-1245000.

2 Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition. Cephalalgia 2018;38(1): 1–211. doi:10.1177/0333102417738202.

3 Boiardi A, Salmaggi A, Eoli M, et al. Headache in brain tumours: a symptom to reappraise critically. Neurol Sci 2004;25(suppl 3):S143–S147. doi:10.1007/s10072-004-0274-8.

4 Burish M. Cluster headache and other trigeminal autonomic cephalalgias. Continuum (Minneap Minn) 2018;24(4 Headache):1137–1156.

5 Matharu MS, Cohen AS, McGonigle DJ, et al. Posterior hypothalamic and brainstem activation in hemicrania continua. Headache 2004;44(8): 747–761. doi:10.1111/j.1526-4610.2004.04141.x.

6 Goffaux P, Fortin D. Brain tumor headaches: from bedside to bench. Neurosurgery 2010;67(2): 459–466. doi:10.1227/01.NEU.0000372092.96124.E6.

7 Landtblom AM, Fridriksson S, Boivie J, et al. Sudden onset headache: a prospective study of features, incidence and causes. Cephalalgia 2002;22(5):354–360. doi:10.1046/j.1468-2982.2002.00368.x.

8 Edlow JA, Caplan LR. Avoiding pitfalls in the diagnosis of subarachnoid hemorrhage. N Engl J Med 2000;342(1):29–36. doi:10.1056/NEJM200001063420106.

9 Mac Grory B, Vu L, Cutting S, et al. Distinguishing characteristics of headache in nontraumatic subarachnoid hemorrhage. Headache 2018;58(3):364–370. doi:10.1111/head.13218.

10 Fine B, Singh N, Aviv R, Macdonald RL. Decisions: does a patient with a thunderclap headache need a lumbar puncture? CMAJ 2012;184(5):555–556. doi:10.1503/cmaj.110517.

11 Yamada SM, Tomita Y, Murakami H, et al. Headache in patients with chronic subdural hematoma: analysis in 1080 patients. Neurosurg Rev 2018;41(2):549–556. doi:10.1007/s10143-017-0889-x.

12 Silbert PL, Mokri B, Schievink WI. Headache and neck pain in spontaneous internal carotid and vertebral artery dissections. Neurology 1995;45(8):1517–1522.

13 Biousse V, D'Anglejan-Chatillon J, Massiou H, Bousser MG. Head pain in non-traumatic carotid artery dissection: a series of 65 patients. Cephalalgia 1994;14(1):33–36. doi:10.1046/j.1468-2982.1994.1401033.x.

14 Tentschert S, Wimmer R, Greisenegger S, et al. Headache at stroke onset in 2196 patients with ischemic stroke or transient ischemic attack. Stroke 2005;36(2):e1–e3. doi:10.1161/01.STR.0000151360.03567.2b.

15 Stam J. Thrombosis of the cerebral veins and sinuses. N Engl J Med 2005;352(17):1791–1798. doi:10.1056/NEJMra042354.

16 Terazzi E, Mittino D, Rudà R, et al. Cerebral venous thrombosis: a retrospective multicentre study of 48 patients. Neurol Sci 2005;25(6):311–315. doi:10.1007/s10072-004-0363-8.

17 Ducros A. Reversible cerebral vasoconstriction syndrome. Lancet Neurol 2012;11(10):906–917. doi:10.1016/S1474-4422(12)70135-7.

18 Goddeau RP, Alhazzani A. Headache in stroke: a review. Headache 2013;53(6):1019–1022. doi:10.1111/head.12116.

19 Lance JW, Hinterberger H. Symptoms of pheochromocytoma, with particular reference to headache, correlated with catecholamine production. Arch Neurol 1976;33(4):281–288.

20 Lipton RB, Lowenkopf T, Bajwa ZH, et al. Cardiac cephalgia: a treatable form of exertional headache. Neurology 1997;49(3):813–816. doi:10.1212/WNL.49.3.813.

21 Torres-Yaghi Y, Salerian J, Dougherty C. Cardiac cephalgia. Curr Pain Headache Rep 2015;19(4):14. doi:10.1007/s11916-015-0481-4.

22 Ness T, Bley TA, Schmidt WA, Lamprecht P. The diagnosis and treatment of giant cell arteritis. Dtsch Arztebl Int 2013;110(21):376–385. doi:10.3238/arztebl.2013.0376.

23 Klein RG, Campbell RJ, Hunder GG, Carney JA. Skip lesions in temporal arteritis. Mayo Clin Proc 1976;51(8):504–510.

24 Amrutkar C, Burton EV. Tolosa-Hunt syndrome. StatPearls. Treasure Island, FL: StatPearls Publishing, 2017.

25 Richie MB, Josephson SA. A practical approach to meningitis and encephalitis. Semin Neurol 2015;35(6):611–620. doi:10.1055/s-0035-1564686.

26 Lucas S. Posttrumatic headache: clinical characterization and management. Curr Pain Headache Rep 2015;19(10):48. doi:10.1007/s11916-015-0520-1.

27 Schankin CJ, Gall C, Straube A. Headache syndromes after acoustic neuroma surgery and their implications for quality of life. Cephalalgia 2009;29(7):760–771. doi:10.1111/j.1468-2982.2008.01790.x.

28 Ringeisen AL, Harrison AR, Lee MS. Ocular and orbital pain for the headache specialist. Curr Neurol Neurosci Rep 2011;11(2):156–163. doi:10.1007/s11910-010-0167-6.

29 Lee AG, Al-Zubidi N, Beaver HA, Brazis PW. An update on eye pain for the neurologist. Neurol Clin 2014;32(2):489–505. doi:10.1016/j.ncl.2013.11.007.

30 Jarrín E, García-García Á, Hurtado-Ceña FJ, Rodríguez-Sánchez JM. Clinical characteristics, treatment, and outcome of trochleitis. Strabismus 2017;25(1):1–4. doi:10.1080/09273972.2016.

31 Perry BF, Login IS, Kountakis SE. Nonrhinologic headache in a tertiary rhinology practice. Otolaryngol Head Neck Surg 2004;130(4):449–452. doi:10.1016/j.otohns.2004.01.005.

32 Cady RK, Dodick DW, Levine HL, et al. Sinus headache: a neurology, otolaryngology, allergy, and primary care consensus on diagnosis and treatment. Mayo Clin Proc 2005;80(7):908–916. doi:10.4065/80.7.908.

33 Abu-Bakra M, Jones NS. Prevalence of nasal mucosal contact points in patients with facial pain compared with patients without facial pain. J Laryngol Otol 2001;115(8):629–632. doi:10.1258/0022215011908685.

34 Bieger-Farhan AK, Nichani J, Willatt DJ. Nasal septal mucosal contact points: associated symptoms and sinus CT scan scoring. Clin Otolaryngol Allied Sci 2004;29(2):165–168. doi:10.1111/j.0307-7772.2004.00774.x.

35 McNeill C, Mohl ND, Rugh JD, Tanaka TT. Temporomandibular disorders: diagnosis, management, education, and research. J Am Dent Assoc 1990;120(3):253, 255, 257 passim. doi:10.14219/jada.archive.1990.0049.