Cluster Headache and Other Trigeminal Autonomic Cephalalgias

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REVIEW ARTICLE

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RELATIONSHIP DISCLOSURE:
Dr Burish has received personal compensation for serving as a lecturer for the Midwest Pain Society and the North American Neuromodulation Society and has received research/grant support from the American Headache Society, the National Headache Foundation, and the Will Erwin Headache Research Foundation.

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.

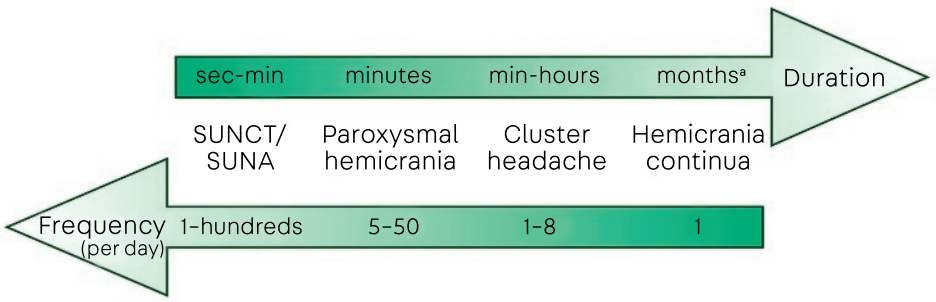

FIGURE 9-1

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.

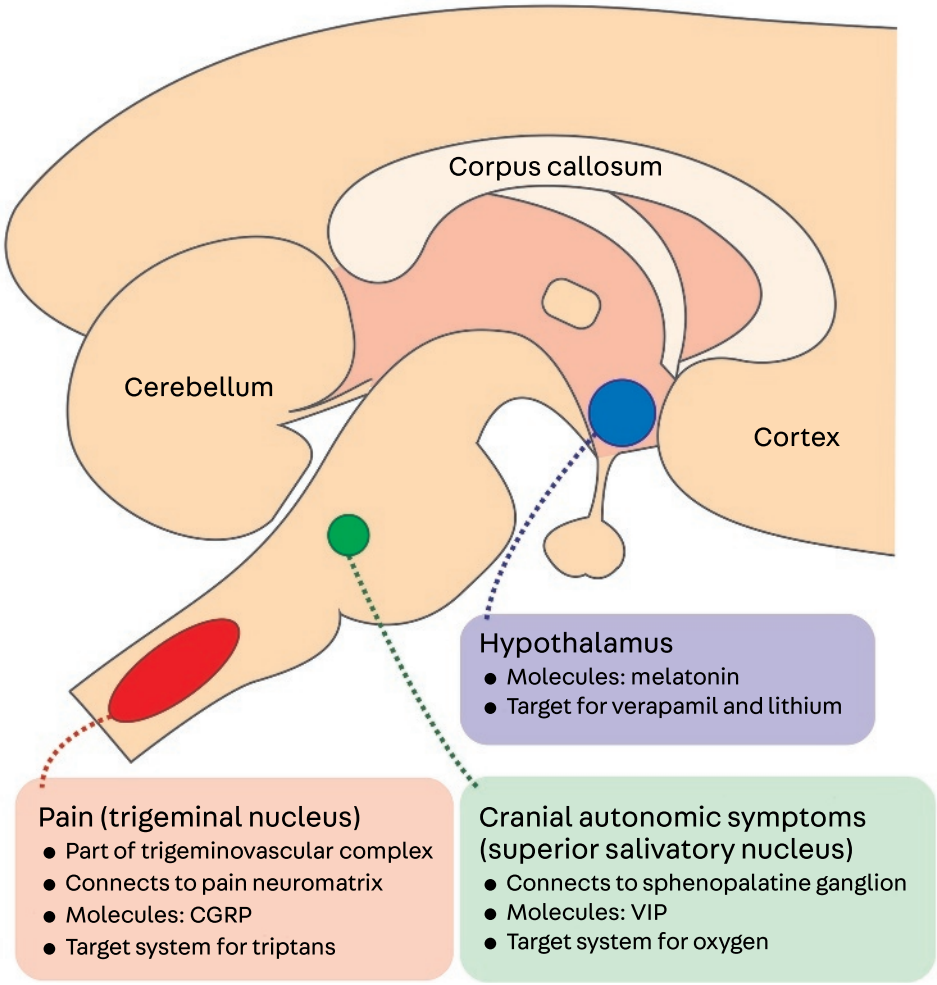

FIGURE 9-2

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**

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

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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)

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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**

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

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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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