Trigeminal Autonomic Cephalalgias

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ABSTRACT

Purpose of Review: This article reviews the clinical features of and treatment options for the trigeminal autonomic cephalalgias (TACs).

Recent Findings: The TACs are a group of primary headache disorders characterized by short-lasting episodes of severe unilateral headaches that are associated with ipsilateral cranial autonomic symptoms. The best known and most commonly seen TAC in clinical practice is cluster headache. The other syndromes within this group include paroxysmal hemicrania, hemicrania continua, and short-lasting unilateral neuralgiform headache attacks. Although these disorders share a similar phenotype, they are distinguished by differences in attack frequency and duration. Recognition of these clinical differences is paramount because treatment options vary; paroxysmal hemicrania and hemicrania continua demonstrate an absolute response to treatment with indomethacin, while the other syndromes respond to other agents.

Summary: Although much less common than other headache disorders seen in clinical practice, recognition of the TACs is especially important as they are among the most severe and disabling syndromes in headache medicine.

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INTRODUCTION

The trigeminal autonomic cephalalgias (TACs) (cluster headache, paroxysmal hemicrania, hemicrania continua, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing [SUNCT], and short-lasting unilateral neuralgiform headache attacks with cranial autonomic features [SUNA]) are a group of relatively uncommon headache disorders that are characterized clinically by short-lived attacks of recurrent unilateral headaches. These headaches are associated with one or more cranial autonomic symptoms, such as ptosis, conjunctival injection, lacrimation, nasal congestion, or rhinorrhea, ipsilateral to the pain. Hemicrania continua was recently reclassified as a TAC in the *International Classification of Headache Disorders, Third Edition, beta version* (*ICHD-3 beta*).[1]

Although these disorders seem similar on the surface, notable distinctions in attack frequency and duration set them apart, as does their response to different treatments (**Table 7-1**). On one end of the TAC spectrum lie the short-lasting unilateral neuralgiform headache syndromes SUNCT and SUNA, in which patients experience the most frequent and shortest attacks. At the other end is cluster headache, in which attacks are the longest and least frequent of the TACs. Paroxysmal hemicrania is at the midpoint of the spectrum, with attacks occurring more often than cluster headache but significantly less often than SUNCT/SUNA and with a duration between the two (**Figure 7-1**). Hemicrania continua is not characterized by individual attacks per se. Rather, it consists of a one-sided continuous headache of moderate intensity, with episodic exacerbations of more severe pain lasting several hours to days. It is during these painful exacerbations that ipsilateral cranial

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Dr Newman discusses the unlabeled/investigational use of intranasal sumatriptan, zolmitriptan, and dihydroergotamine and oxygen inhalation as acute therapy for cluster headache; prednisone, dexamethasone, methylprednisolone, and occipital nerve blocks as bridge therapy for cluster headache; and verapamil, lithium carbonate, topiramate, and sodium valproate as preventive therapy for cluster headache. Dr Newman discusses the unlabeled/investigational use of indomethacin, melatonin, topiramate, verapamil, piroxicam, naproxen, and acetazolamide for the treatment of paroxysmal hemicrania; indomethacin, topiramate, melatonin, occipital nerve block, and occipital nerve stimulation for the treatment of hemicrania continua; and gabapentin, lamotrigine, topiramate, and lidocaine for the treatment of unilateral neuralgiform headache attacks.

TABLE 7-1 Clinical Features of the Trigeminal Autonomic Cephalalgias

Feature	Cluster	Paroxysmal Hemicrania	SUNCT/SUNA	Hemicrania Continua
Sex ratio female:male	1:3	1:1 episodic, 2:1 chronic	1:1.5	2:1
Pain quality	Stabbing, boring	Throbbing, boring, stabbing	Burning, stabbing, throbbing	Baseline: steady ache Exacerbations: throbbing, stabbing
Pain severity	Very severe	Very severe	Severe	Baseline: mild to moderate Exacerbations: moderate to severe
Site of maximal pain	Orbit, temple	Orbit, temple	Orbit, temple	Orbit, temple
Attacks per day	1–8	1–40	1–100	Daily in 50%
Attack duration	15–180 minutes	2–30 minutes	1–10 minutes	30 minutes to 3 days
Autonomic features	Present	Present	Present	Present during exacerbations
Restlessness	90%	80%	65%	Infrequent
Usual temporal profile	Episodic	Chronic	Chronic	Unremitting
Circadian periodicity	Yes	No	No	No
Nocturnal attack	Yes	No	No	No
Triggers				
Alcohol	Yes	Yes	No	No
Nitroglycerin	Yes	Yes	No	No
Cutaneous	No	No	Yes	No
Cervical root pressure	No	Yes	No	No
Neck movement	No	Yes	Yes	No
Treatment response				
Oxygen	Yes	No	No	No
Sumatriptan	Yes	Partial	No	Partial
Indomethacin	Occasional	Yes	No	Yes

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

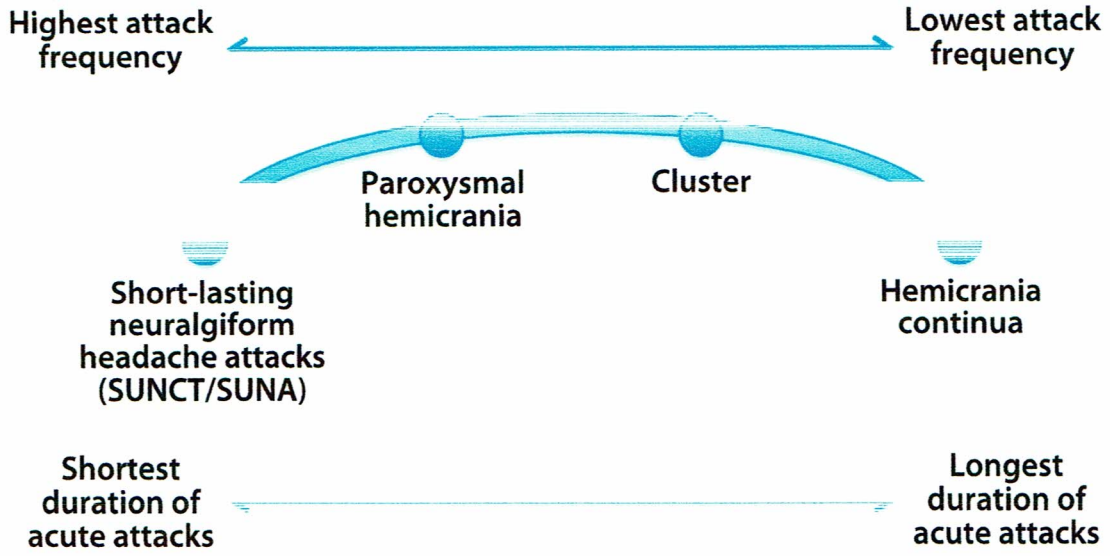

FIGURE 7-1 The clinical spectrum of the trigeminal autonomic cephalalgias.

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

autonomic features occur. A useful way to think about these disorders is to remember that as the attacks become more frequent and shorter in duration, the name of the syndrome becomes longer.

Several other primary headache syndromes may be mistaken for the TACs because of their short duration and high-intensity pain. Unlike the TACs, however, these disorders are not associated with prominent cranial autonomic symptoms (Table 7-2). Two other headache syndromes (both quite rare) may be mistaken for a TAC. Hypnic headache syndrome, although longer in duration than most TACs, may be mistaken for cluster because it occurs during sleep.[2] Headaches associated with airplane travel are typically severe jabbing or stabbing pains that occur during ascent or descent. These headaches are usually unilateral and orbitofrontal, and less than 5% of cases may be associated with ipsilateral lacrimation or nasal stuffiness.[3] Trigeminal neuralgia is a cranial neuralgia characterized by short-lasting unilateral attacks of severe lancinating pains affecting one or more branches of the trigeminal nerve. Rarely, trigeminal neuralgia may be associated with mild ipsilateral or bilateral cranial autonomic symptoms.[4] However, trigeminal neuralgia can be distinguished from SUNCT/SUNA by the ultrashort duration of individual attacks, involvement of the second or third division in 95% of cases, mild nature of the cranial autonomic symptoms, presence of a refractory period, and trigger zones.

Intracranial mass lesions have been reported to mimic the TACs, with a high proportion of lesions in or around the pituitary gland.[5–7] Because the TACs are relatively uncommon and the possibility of an underlying lesion exists, all patients with a TAC should have an MRI with special attention to the pituitary gland as part of their workup.[8] Neurologists' ability to differentiate between the various TACs and distinguish them from other primary and secondary

KEY POINTS

- On one end of the trigeminal autonomic cephalalgia spectrum lie the short-lasting unilateral neuralgiform headache syndromes (SUNCT and SUNA), in which patients experience the most frequent and shortest attacks. At the other end is cluster headache, in which attacks are the longest and least frequent of the trigeminal autonomic cephalalgias. Paroxysmal hemicrania is at the midpoint of the spectrum, with attacks occurring more often than cluster headache but significantly less often than SUNCT/SUNA and with a duration between the two.
- As the attacks of trigeminal autonomic cephalalgias become more frequent and shorter in duration, the name of the syndrome becomes longer.
- Headaches associated with airplane travel are typically severe jabbing or stabbing pains that occur during ascent or descent. These headaches are usually unilateral and orbitofrontal, and less than 5% of cases may be associated with ipsilateral lacrimation or nasal stuffiness.

TABLE 7-2 Headaches of Short Duration

▶ **With associated cranial autonomic features**
Cluster headache
Paroxysmal hemicrania
SUNCT/SUNA
Hemicrania continua (exacerbations)
▶ **Without associated cranial autonomic features**
Primary cough headache
Primary exercise headache
Primary stabbing headache
Primary headache associated with sexual activity
Primary thunderclap headache
Headache associated with airplane flights
Hypnic headache
Trigeminal neuralgia

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

headache disorders will help prevent unnecessary suffering and exposure to ineffective medications.

PATHOPHYSIOLOGY

It is not surprising that recent evidence suggests the TACs share a common pathophysiologic substrate as the clinical phenotype is very similar. However, some notable differences exist between the individual syndromes demonstrated by functional MRI (fMRI) and positron emission tomography (PET). Both cluster headache and SUNCT are associated with ipsilateral activation of the hypothalamus (SUNCT has also been reported to have bilateral hypothalamic activation), whereas contralateral hypothalamic activation is seen with paroxysmal hemicrania and hemicrania continua.[9–13] Additionally, PET scans in hemicrania continua reveal activation of the ipsilateral dorsal rostral pons.[12] The attack-related changes in the hypothalamus likely account for the circadian and circannual rhythmicity of individual attacks and seasonal rhythmicity of active and remission phases.

Several hypothalamic nuclei, via descending orexinergic pathways, are involved in pain modulation. Orexins are neuropeptides that are synthesized exclusively in the hypothalamus. In preclinical animal models of headache, orexin A and orexin B have demonstrated antinociceptive and pronociceptive properties, respectively.[14] A recent placebo-controlled study of filorexant, a dual orexin receptor antagonist, failed to demonstrate benefit for the preventive treatment of migraine.[15] Future well-powered studies should evaluate the effect of dual orexin receptor antagonists in patients with migraine with sleep disturbance and in cluster headache where hypothalamic dysfunction may play a more prominent role.

The trigeminovascular and cranial parasympathetic pathways are responsible for

the ipsilateral pain and cranial autonomic features that characterize these disorders.[5] The pain-sensitive intracranial structures are innervated by the ophthalmic branch of the trigeminal nerve, a pseudounipolar neuron that has its cell body arising in the trigeminal ganglion and which synapses in the trigeminal nucleus caudalis. Activation of this system presumably accounts for the elevated levels of calcitonin gene-related peptide (CGRP) in venous blood during cluster attacks.

Activation of the trigeminal nucleus caudalis results in a reflex excitation of the superior salivatory nucleus. The cranial parasympathetic system may also be activated by descending input from the hypothalamus. The cranial preganglionic parasympathetic fibers that innervate the intracranial blood vessels arise within the superior salivatory nucleus, exit the brainstem with the facial nerve, and synapse in the pterygopalatine ganglion. The second-order vasomotor neurons innervate the cerebral blood vessels, while the secretomotor efferents innervate the lacrimal and nasal mucosa glands, which produce the typical cranial autonomic symptoms seen during the TACs. Activation of this pathway is associated with the release of vasoactive intestinal polypeptide. Indeed, elevated levels of CGRP and vasoactive intestinal polypeptide have been demonstrated in jugular venous samples during acute episodes of cluster headache and chronic paroxysmal hemicrania.[5,16,17]

CLUSTER HEADACHE

Cluster headache is uncommon, affecting approximately 0.1% of the population, yet it is the most common of the TACs.[18] Cluster headache affects men 3 to 4 times more often than women, and recent evidence suggests that, at least in some families, a genetic predisposition exists.[5] A family history was reported in 5% to 20% of patients with cluster headache. The risk in first-degree relatives is 14 to 39 times that of the general population, and in second-degree relatives, a twofold to fourfold increased risk exists.[19,20]

Clinical Features

Although uncommon, these headaches are excruciatingly severe and a cause of significant disability. They have been referred to as "suicide headaches" because of the extreme severity and high frequency of attacks. The clinical history of these headaches is so classic it would seem difficult to miss the diagnosis, yet a recent review found that the correct initial diagnosis was made in only 21% of patients, and the time delay to reach the correct diagnosis was more than 5 years in 42% in a series of more than 1100 patients.[21]

This disorder is aptly named, as headaches occur in groups or clusters of attacks that recur on a daily or near-daily basis. The vast majority of patients with cluster headache experience the episodic form, in which cluster cycles (the period of time during which attacks occur) last from weeks to months, separated by pain-free remission periods lasting from several months to years. When attacks recur for a year or more without remission periods or when the remission periods last less than a month, the term chronic cluster is used. Most patients with chronic cluster began with the episodic form; however, in a minority of patients, chronic cluster headache begins spontaneously.

During cluster cycles, attacks may recur from once every other day to 8 times a day. Attacks typically recur at the same time each day and may often awaken the patient from sleep, usually within 2 hours after falling asleep. The pain is maximal in, around, or behind the eye and may radiate into the ipsilateral temple, jaw, upper teeth, and neck. The pain is often described as boring or stabbing, often likened to a hot poker being thrust into the affected eye. The pain is excruciatingly severe, peaks

KEY POINTS

- All patients with a trigeminal autonomic cephalalgia should have an MRI with special attention to the pituitary gland as part of their workup.
- Both cluster headache and SUNCT are associated with ipsilateral activation of the hypothalamus, whereas contralateral hypothalamic activation is seen with paroxysmal hemicrania and hemicrania continua.
- Elevated levels of calcitonin gene-related peptide and vasoactive intestinal polypeptide have been demonstrated in jugular venous samples during acute episodes of cluster headache and chronic paroxysmal hemicrania.
- A recent review found that the correct initial diagnosis of cluster headache was made in only 21% of patients, and the time delay to reach the correct diagnosis was more than 5 years in 42% of patients.
- The vast majority of patients with cluster headache experience the episodic form, in which cluster cycles (the period of time during which attacks occur) last from weeks to months, separated by pain-free remission periods lasting from several months to years.

KEY POINTS

- Recumbency, the typical posture assumed by patients with migraine, often worsens the pain of cluster headache, which can be used as a distinguishing historical feature.
- Approximately 30% of patients with cluster headache report a low-level interictal discomfort between attacks, and migrainous symptoms occur in about half of all patients with cluster headache.
- Three categories of treatment for cluster headache exist: acute, preventive, and bridge therapies.
- Nonoral routes of administration are required for medications for acute cluster headache attacks, and parenteral formulations work fastest; however, medications delivered intranasally can also terminate attacks fairly quickly.

rapidly, and lasts from 15 to 180 minutes. During these painful attacks, at least one cranial autonomic symptom occurs ipsilaterally (conjunctival injection, lacrimation, nasal congestion or discharge, miosis, or ptosis). During acute attacks of cluster headache, patients are typically unable to keep still, preferring to pace, move about, sit upright holding their head and rocking, or even bang their head against a wall. Recumbency, the typical posture assumed by patients with migraine, often worsens the pain of cluster headache, which can be used as a distinguishing historical feature compared to migraine. In the absence of autonomic features, a sense of restlessness or agitation is required for the diagnosis. During an active cluster cycle, acute headaches may be triggered by alcohol, nitroglycerine, pungent odors, and daytime naps.[21] Approximately 30% of patients with cluster headache report a low-level interictal discomfort between attacks,[22] and migrainous symptoms occur in about half of all patients with cluster headache. When present, the photophobia or phonophobia is often ipsilateral to the headache, unlike the bilateral symptoms reported in migraine.[23] Table 7-3 lists the *ICHD-3 beta* criteria for cluster headache, including the new criterion of a sense of fullness in the ipsilateral ear.

Treatment Options

Three categories of treatment for cluster headache exist: acute, preventive, and bridge therapies.[24] Every patient with cluster headache requires some form of treatment, and most require all three at some point. The majority of medications used to treat cluster headache are used off-label. Only subcutaneous sumatriptan and parenteral dihydroergotamine (DHE) have a US Food and Drug Administration (FDA) indication for cluster headache. Because cluster headache attacks are relatively short lasting and reach peak intensity rapidly, acute therapies must work quickly and consistently. Preventive therapies are used in an attempt to stop recurrent attacks while the cycle is ongoing. In general, preventive agents do not induce a remission, but rather reduce or eliminate the acute attacks during the cluster period. In episodic cluster headache, these agents are continued for several weeks longer than the usual cycle duration, then gradually tapered and discontinued during the remission period. Because preventive agents require several weeks to exert their benefit, bridge therapies should be given concurrently with starting prevention. Bridging agents are usually employed for the first 10 to 14 days of a cycle, induce a rapid remission, and are tapered or discontinued when the preventive agents become therapeutic. Some patients have very short (1- to 3-week) cluster cycles. For these patients, a short course of a bridge therapy and an acute agent during the early part of the cycle are all that is required, as the cycle will have ended before a preventive medication would have exerted a beneficial effect.

Acute treatment options. During acute attacks of cluster headache, patients require medications that work quickly to rapidly terminate the excruciating pain. Nonoral routes of administration are required, and parenteral formulations work fastest; however, medications delivered intranasally can also terminate attacks fairly quickly. Oral medications should be avoided as they invariably take too long to work.

Subcutaneous injections of sumatriptan can produce relief within 15 minutes and are available in 4-mg and 6-mg doses. As the maximum daily dose is 12 mg, use of the 4-mg dose allows for an additional treatment. Injectable DHE (subcutaneous or IM) also provides fast relief but, unlike sumatriptan, is not available in prefilled syringes. Intranasal formulations of sumatriptan, zolmitriptan, and DHE may result in relief within 30 minutes.

TABLE 7-3 ***ICHD* 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 one 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. Forehead and facial flushing
   f. Sensation of fullness in the ear
   g. Miosis and/or ptosis
2. A sense of restlessness or agitation

D. Attacks have a frequency between one every other day and eight per day for more than half of the time when the disorder is active

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

▶ **Episodic Cluster Headache**

Description: Cluster headache attacks occurring in periods lasting from 7 days to 1 year, separated by pain-free periods lasting at least 1 month.

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 ≥1 month

▶ **Chronic Cluster Headache**

Description: Cluster headache attacks occurring for more than 1 year without remission or with remission periods lasting less than 1 month.

A. Attacks fulfilling criteria for cluster headache and criterion B below

B. Occurring without a remission period, or with remissions lasting <1 month, for at least 1 year

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

[a] Reprinted with permission from Headache Classification Committee of the International Headache Society (IHS), Cephalalgia.[1] © 2013 International Headache Society. *www.ihs-classification.org/_downloads/mixed/International-Headache-Classification-III-ICHD-III-2013-Beta.pdf.*

Oxygen inhalation via a nonrebreather face mask is also a first-line acute treatment option. The patient should be instructed to breath normally while seated and leaning forward, using 100% oxygen at a rate of 10 L/min to 15 L/min for approximately 15 to 20 minutes. This treatment can abort an acute attack of cluster in about 15 minutes and has the advantage of having no daily limit (unlike the triptans or DHE). A drawback of this treatment, however, is that for some patients, oxygen inhalation only delays the attack rather than aborting it permanently.

Barring contraindications to its use, patients with cluster headaches should

KEY POINTS

- Barring contraindications to its use, patients with cluster headaches should be given a prescription for home oxygen therapy, to be used either as a first-line treatment or to supplement other treatments for high-frequency daily attacks.
- Bridge therapies are short-term treatments that are used to offer a respite to patients with cluster headache while the preventive agent reaches its therapeutic efficacy.

be given a prescription for home oxygen therapy, to be used either as a first-line treatment or to supplement other treatments for those with high-frequency daily attacks. Table 7-4 lists various treatment options for cluster headache.

Bridge therapies. Bridge therapies are short-term treatments that are used to offer a respite to patients with cluster headache until the preventive agent becomes effective. These agents are prescribed together with the daily preventives, continued for up to 2 weeks, and then tapered. Most patients respond to a short course of corticosteroids. Prednisone 60 mg per day to 80 mg per day may be started and decreased by 10 mg every 2 days; treatment with dexamethasone or methylprednisolone may also provide relief. A methylprednisolone wean using a methylprednisolone dose pack may be unsuccessful, as the dose supplied is too low.

Another useful stopgap measure is the use of a greater occipital nerve block; a mixture of 3 mL of 0.5% bupivacaine and

TABLE 7-4 Treatment Options for Cluster Headache

▶ **Acute**
Sumatriptan subcutaneous 4–6 mg[a]
Sumatriptan nasal spray 20 mg
Zolmitriptan nasal spray 5 mg
Dihydroergotamine (DHE) parenteral[a] or intranasal
Oxygen 10–15 L/min via nonrebreather face mask
▶ **Bridge**
Prednisone orally 60–80 mg/d tapered over 14 days
Dexamethasone orally 4 mg 2 times/d for 2 weeks, then 4 mg/d for 1 week
Greater occipital nerve block with 3 mL of 0.5% bupivacaine and 40 mg of methylprednisolone
DHE parenterally 1 mg/d for 1 week
Naratriptan orally 2.5 mg 2 times/d for 1 week
Ergotamine orally 2 mg 2 times/d for 1 week
▶ **Preventive**
Verapamil orally 240–480 mg/d administered in three divided doses (short-acting formulation preferred)
Lithium carbonate orally 300–900 mg/d
Sodium valproate orally 500–1500 mg/d
Topiramate orally 100–200 mg/d
Melatonin orally 9–25 mg at bedtime
Gabapentin orally 1200–2400 mg/d
Methylergonovine orally 0.2 mg 3 times/d
Indomethacin orally 75–150 mg/d

[a] US Food and Drug Administration approved for this indication.

40 mg of methylprednisolone (some prefer triamcinolone) is injected into the ipsilateral greater occipital nerve.

Preventive therapies. The majority of patients with episodic cluster headache and all patients with chronic cluster headache require prevention. When used in episodic cluster headache, the medications are continued for slightly longer than the typical cycle and then gradually discontinued; they are maintained indefinitely for chronic cluster headache. No evidence exists that maintaining patients with episodic cluster headache on daily medications will prevent subsequent cycles. In general, treatment should begin with one agent employed at a low dose and gradually increasing the dose over several days to weeks. If the cluster cycle shows a partial response but fails to remit and maximum doses have been achieved, another medication may be added to the first, rather than substituting one for another. It should be noted that none of the agents routinely used in clinical practice have an FDA indication for prevention of cluster headache, nor is there robust class I evidence for their use.[24]

Verapamil is widely considered the drug of choice for cluster headache prevention and is often given in doses higher than those required for blood pressure control (up to 960 mg per day). Verapamil is usually begun at a dose of 240 mg per day and can be increased by 80 mg per day every 10 to 14 days. Some clinicians raise the dose more quickly, but it has been reported that verapamil may cause heart block through its action on the atrioventricular node; this effect can be delayed for approximately 10 days, so it may be preferable to increase the dose more slowly. A baseline ECG, heart rate, and blood pressure should be obtained prior to treatment and repeated prior to each increase in dosage.[25] Because ECG abnormalities may be delayed, the ECG should also be repeated approximately 2 weeks after dosage changes. Although many patients are treated with the long-acting formulation of verapamil for convenience and to enhance compliance, the short-acting formulation, usually dosed 3 times a day may be more beneficial. Even some patients with refractory cluster headache may be switched to the short-acting form with excellent results.

Other preventive options include the use of topiramate, sodium valproate, and melatonin. Lithium carbonate can also be an effective prophylactic agent for cluster headache, especially the chronic subtype. The therapeutic dose ranges from 600 mg per day to 1200 mg per day. Prior to initiating treatment, serum measurements of thyroid and kidney function must be ascertained, and they should be repeated periodically following treatment. Indomethacin, the drug of choice for paroxysmal hemicrania and hemicrania continua, may also be useful at times.[26]

Potential New Therapeutic Options

Unfortunately, approximately 20% of patients with chronic cluster headache do not find relief, despite trials of all medications, alone and in combination, or because of other medical contraindications.[27] Until recently, the only options available for these patients involved surgical procedures that targeted either the parasympathetic pathways (eg, sphenopalatine gangliolysis, greater superficial petrosal neurectomy, sectioning of the nervus intermedius) or the trigeminal nerve . These therapies provide inconsistent results and may result in significant adverse events.

Neuromodulation. Neurostimulation of deep brain structures (eg, hypothalamus),[27,28] peripheral nerves (eg, occipital,[29] supraorbital, supratrochlear,[30] vagus[31]), or the sphenopalatine ganglion[32] has been reported to be effective for intractable cluster headache

KEY POINTS

- Although many patients with cluster headache are treated with the long-acting formulation of verapamil for convenience and to enhance compliance, the short-acting formulation, usually dosed 3 times a day, may be more beneficial.
- Approximately 20% of patients with chronic cluster headache do not obtain relief, despite trials of all medications, alone and in combination, or because of other medical contraindications.
- Neurostimulation of deep brain structures (eg, hypothalamus), peripheral nerves (eg, occipital, supraorbital, supratrochlear, vagus), or the sphenopalatine ganglion has been reported to be effective as treatment for intractable cluster headache.

KEY POINTS

- Occipital nerve stimulation using implantable devices has been reported to be effective in controlling cluster headache in approximately two-thirds of treated patients.
- Deep brain stimulation of the posterior hypothalamus is a very invasive procedure and should be reserved for only the most refractory patients with cluster headaches.
- Several important differences exist between cluster headache and paroxysmal hemicrania. Paroxysmal hemicrania has a higher daily attack frequency, shorter duration of individual attacks, and fewer nocturnal attacks; is more often chronic versus episodic; has less propensity to trigger with alcohol but greater propensity to mechanical trigger factors; and is responsive to treatment with indomethacin.
- Acute attacks of paroxysmal hemicrania may be triggered by head bending or rotation or by pressing on the C2 root, greater occipital nerve, or transverse process of C4-C5. Ingestion of alcoholic beverages, a classic cluster headache trigger, is an inconsistent trigger of paroxysmal hemicrania.

and, it is hoped, may supplant the need for neurolytic and other more invasive procedures.

Occipital nerve stimulation using implantable devices has been reported to be effective in controlling cluster headache in approximately two-thirds of treated patients.[29] Clinical improvement as evidenced by pain relief may be delayed for up to 2 months following implantation.

In a study of an implantable on-demand sphenopalatine ganglion stimulator, nearly 70% of subjects with chronic cluster headache experienced significant improvement from acute attacks.[32] Occipital nerve stimulation for chronic cluster headache is not FDA approved, and no controlled trials for its use in chronic cluster headache have yet been performed or reported.

A recent open-label study of 19 patients with cluster headache (11 chronic, 8 episodic) employed a noninvasive handheld vagal nerve stimulator for both acute and preventive management. As acute therapy, 15 of 19 reported an overall improvement. When used as prevention, a significant reduction in attack frequency from 4.5 attacks per day to 2.6 attacks per day occurred.[31] Several studies using this device are currently in process in the United States.

Deep brain stimulation of the posterior hypothalamus has been shown to be successful in treating otherwise refractory cluster headache. It is a very invasive procedure, with the potential for serious adverse outcomes (eg, intracerebral hemorrhage, stroke, death), and should be reserved for only the most refractory patients with cluster headache.[27,28,33]

PAROXYSMAL HEMICRANIA

Paroxysmal hemicrania shares many features with cluster headache; initially, it may be difficult to distinguish between the two disorders (**Table 7-1**). Like cluster headache, paroxysmal hemicrania is characterized by recurrent short-lived headaches that are associated with ipsilateral cranial autonomic symptoms and two temporal profiles, chronic and episodic. **Table 7-5** lists the *ICHD-3 beta* criteria for paroxysmal hemicrania. **Case 7-1** depicts a typical case of episodic paroxysmal hemicrania and highlights the clinical overlap that exists between the TACs.

Clinical Features

Several important differences exist between cluster headache and paroxysmal hemicrania.[5] Paroxysmal hemicrania has a higher daily attack frequency, shorter duration of individual attacks, and fewer nocturnal attacks; is more often chronic versus episodic; has less propensity to trigger with alcohol but greater propensity to mechanical (eg, neck movement) trigger factors; and is responsive to treatment with indomethacin.

The headaches of paroxysmal hemicrania are typically one-sided, with pain in and above the eye, radiating into the ipsilateral temple. Headaches recur more than 5 times a day for more than half the time (mean 11) and last 2 to 30 minutes (median 19 minutes).[1,34] Unlike cluster, the *ICHD-3 beta* criteria for paroxysmal hemicrania does not list restlessness or agitation, yet 80% of patients in one series endorsed these symptoms.[23]

Acute attacks of paroxysmal hemicrania may be triggered by head bending or rotation or by pressing on the C2 root, greater occipital nerve, or transverse process of C4-C5.[5,34] Ingestion of alcoholic beverages, a classic cluster headache trigger, is an inconsistent trigger of paroxysmal hemicrania.

Although no sex predominance is noted in the episodic subtype, it seems that the chronic form of paroxysmal hemicrania may affect women more frequently. As a general rule, when a woman presents with features of cluster

TABLE 7-5 *ICHD* 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. At least one of the following 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. Forehead and facial flushing
    6. Sensation of fullness in the ear
    7. Miosis and/or ptosis
  - D. Attacks have a frequency above five per day for more than half the time
  - E. Attacks are prevented absolutely by therapeutic doses of indomethacin
  - F. Not better accounted for by another *ICHD-3 beta* diagnosis
- **Episodic Paroxysmal Hemicrania**

  Description: Attacks of paroxysmal hemicrania occurring in periods lasting from 7 days to 1 year, separated by pain-free periods lasting at least 1 month.
  - 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 ≥1 month
- **Chronic Paroxysmal Hemicrania**

  Description: Attacks of paroxysmal hemicrania occurring for more than 1 year without remission or with remission periods lasting less than 1 month.
  - A. Attacks fulfilling criteria for paroxysmal hemicrania, and criterion B below
  - B. Occurring without a remission period or with remissions lasting <1 month for at least 1 year

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

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headache, especially the chronic subtype, paroxysmal hemicrania should be strongly considered.

Treatment Options

Paroxysmal hemicrania demonstrates a complete and absolute response to treatment with indomethacin. Although the *ICHD-3 beta* guidelines suggest that indomethacin should be initiated at a dose of 150 mg per day and increased up to 225 mg per day if needed, in clinical practice, most patients are treated with 25 mg 3 times a day and increased to 50 mg 3 times a day in 1 week if the headache does not respond or only partially improves. In general, headaches remit within 2 days of reaching the effective dose, but at times this may be delayed for as long as 2 weeks. During an active cycle, delaying or skipping a dose usually results in headache recurrence.

KEY POINT

- As a general rule, when a woman presents with features of cluster headache, especially the chronic subtype, paroxysmal hemicrania should be strongly considered.

KEY POINTS

- Paroxysmal hemicrania demonstrates a complete and absolute response to treatment with indomethacin.
- In clinical practice, most patients with paroxysmal hemicrania are treated with indomethacin 25 mg 3 times a day and increased to 50 mg 3 times a day in 1 week if the headache does not respond or only partially improves.
- Indomethacin should be given with meals, and, if long-term use is anticipated, a proton pump inhibitor should be prescribed.

Case 7-1

A 56-year-old woman presented with a 15-year history of recurrent right-sided headaches. Her attacks occurred in 6-week cycles every 1 to 2 years, at various times of the year. During cycles, headaches recurred 3 to 5 times a day lasting from 10 to 30 minutes each. Her attacks never awakened her from sleep. The pain was stabbing, excruciatingly severe, and maximal in the right eye and temple. Her headaches were associated with ipsilateral ptosis, conjunctival injection, tearing, and nasal stuffiness. She was totally pain free between headache cycles, but during periods of headache, she noticed a constant dull right-sided discomfort. During attacks, she lay in bed. Alcohol did not trigger her headaches.

She had no other medical problems, and her general medical and neurologic examinations were unremarkable. A brain MRI with contrast was normal, as was her serum prolactin level.

Verapamil, lithium, sodium valproate, and subcutaneous sumatriptan were unsuccessful. Prednisone provided complete relief, but only at doses above 40 mg per day.

Comment. This case highlights the clinical overlap that exists between the trigeminal autonomic cephalalgias (TACs) (**Table 7-1**). The (relative) low-to-moderate frequency of daily attacks and the 10- to 30-minute duration of this patient's individual headaches suggests cluster headache or paroxysmal hemicrania. The background low-level interictal discomfort suggests hemicrania continua but has been reported with every TAC. The presence of both conjunctival injection and tearing eliminates short-lasting unilateral neuralgiform headache attacks with cranial autonomic features (SUNA), and her attack frequency never exceeding five per day in 15 years makes short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) unlikely.

Clues to the diagnosis lie in the history. The absence in this patient of circadian periodicity, nocturnal attacks, alcohol triggering, or restlessness during attacks (all hallmarks of cluster headache), suggest paroxysmal hemicrania, as does the failure to respond to verapamil and sumatriptan. Many patients with indomethacin-responsive TACs (eg, paroxysmal hemicrania, hemicrania continua) report partial response to treatment with corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs). Clinicians should first think paroxysmal hemicrania when a female patient presents with clusterlike headaches. The remitting form of hemicrania continua is uncommon, but remains a possibility in this case. Although this is likely a case of episodic paroxysmal hemicrania, instituting a trial of indomethacin is a good option, as it will treat both hemicrania continua and paroxysmal hemicrania.

Indomethacin should be given with meals, and, if long-term use is anticipated, a proton pump inhibitor should be prescribed. For the episodic form of paroxysmal hemicrania, indomethacin therapy should be continued for slightly longer than the usual cycle and then tapered. For the chronic subtype, periodic attempts to lower the dose should be made.

When indomethacin is poorly tolerated or contraindicated, treatment becomes challenging. Partial benefit has been reported with acetylsalicylic acid, celecoxib, piroxicam, naproxen, acetazolamide, topiramate, and verapamil. Melatonin

3 mg to 25 mg nightly is the author's preferred choice for patients unable to take indomethacin.

HEMICRANIA CONTINUA

Because of similar pathophysiology, clinical features, and treatment response, hemicrania continua has been classified in *ICHD-3 beta* as a TAC.

Clinical Features

Hemicrania continua is characterized by unilateral headache of mild to moderate intensity. This baseline discomfort is constant and unremitting, mild to moderate in intensity, and usually without other symptomatology. Exacerbations of more severe pain occur at varying intervals (daily to near daily) and last from 30 minutes to 3 days.[35,36] As with cluster headache, patients are often restless or agitated during the exacerbations. During these painful flare-ups, the cranial autonomic symptoms that typify the TACs occur ipsilaterally, and migrainous features such as nausea, photophobia, and phonophobia may also be present.[35] When present, photophobia and phonophobia tend to be ipsilateral to the pain.[23] Many patients with hemicrania continua also report superimposed episodes of brief stabbing pains (ice pick–like) and the sensation of a foreign body (eg, sand, grittiness) in the eye on the side of the headache.[35]

Two temporal profiles of hemicrania continua have been described, remitting and unremitting. The remitting form is characterized by headaches that are not daily or continuous but are interrupted by remission periods of 1 day or more without treatment. Most patients experience the unremitting form.

Hemicrania continua is frequently misdiagnosed. Focusing on the chronic hemicranial baseline discomfort, associated nausea, photophobia, or phonophobia often leads to a diagnosis of chronic migraine. Because many patients often only report severe flare-ups and associated autonomic symptoms, they may receive a diagnosis of cluster headache. **Case 7-2** describes a patient in whom the diagnosis of hemicrania continua was initially missed and reviews the pertinent features in the history that should always be addressed.

Treatment Options

Hemicrania continua, like paroxysmal hemicrania, is responsive to treatment with indomethacin. Treatment recommendations are similar to those described for paroxysmal hemicrania in this article, but doses of indomethacin much higher than those for paroxysmal hemicrania and higher than the FDA-approved maximum daily dose for indomethacin of 150 mg are sometimes required (300 mg per day to 500 mg per day).[36] Successful treatment with topiramate, melatonin, occipital nerve blocks, and occipital nerve stimulators have also been reported.[36]

SHORT-LASTING UNILATERAL NEURALGIFORM HEADACHE ATTACKS

SUNCT and SUNA, the two syndromes within this subcategory, are the rarest of TACs.

Clinical Features

Both SUNCT and SUNA are characterized by ultrabrief paroxysmal headache attacks typically lasting only seconds. The head pain in these syndromes is usually of a stabbing nature but may have a lancinating or burning quality, of moderate to severe intensity, and hemicranially located. Pain may occur anywhere in the head and is not limited to the orbitotemporal regions.[37] Attacks may occur as an isolated stab, in a series of stabs, or in a sawtooth pattern in which many stabs recur over several minutes superimposed over a baseline discomfort. Depending on the pattern, painful episodes can last from 1 to 600 seconds each and can recur from once to up to

KEY POINTS

- Many patients with hemicrania continua also report superimposed episodes of brief stabbing pains (ice pick–like) and the sensation of a foreign body (eg, sand, grittiness) in the eye on the side of the headache.
- Hemicrania continua, like paroxysmal hemicrania, is responsive to treatment with indomethacin.
- Short-lasting unilateral neuralgiform headache attacks may occur as an isolated stab, in a series of stabs, or in a sawtooth pattern in which many stabs recur over several minutes superimposed over a baseline discomfort.

KEY POINTS

- In general, a strictly side-locked headache suggests a trigeminal autonomic cephalalgia.
- Short-lasting unilateral neuralgiform headache attacks may occur spontaneously or be triggered by touching trigger zones within the trigeminal territory, talking, chewing, brushing teeth, coughing, or nose blowing.
- SUNCT attacks are associated with conjunctival injection and tearing (lacrimation), whereas SUNA has either one or will be associated with at least one of the other features that are characteristic of the trigeminal autonomic cephalalgias.
- Secondary mimics of SUNCT and SUNA include posterior fossa and pituitary lesions; therefore, all patients suspected of having these disorders require MRIs.

Case 7-2

A 28-year-old man with an 8-month history of headaches returned for his follow-up visit. At his first appointment, he reported strictly right-sided throbbing headaches of moderate intensity that were associated with photophobia, phonophobia, and nausea. His headaches occurred 3 to 4 times monthly, lasting 4 to 48 hours without treatment. Triggers included lack of sleep and weather changes. He had no family history of headaches.

The new onset of a side-locked headache and lack of family history prompted the neurologist to order an MRI, which was normal. He was initially diagnosed with migraine without aura and was prescribed topiramate for prophylaxis and sumatriptan 100-mg tablets for acute attacks. At follow-up, the headache frequency was unchanged, but he reported that sumatriptan had worked fairly well.

Comment. Is this truly a case of migraine that is not yet medically controlled, or has something been overlooked? In general, a strictly side-locked headache suggests a trigeminal autonomic cephalalgia (although migraine may occasionally be strictly one-sided), and the history should be reviewed in more detail, specifically asking about headache-free days rather than headache days, the presence of associated cranial autonomic features, ocular foreign body sensation, and localization of migrainous features.

Indeed, when the history was retaken, the patient reported that he always had some degree of right-sided pain that he "could live with"; it was the severe attacks that were distressing. He reported right nostril stuffiness during these severe episodes and that light sensitivity was only in the right eye.

This patient had hemicrania continua but, like many with this disorder, was initially misdiagnosed. Pitfalls in the diagnosis arise in several ways. Focusing on the pain of acute exacerbations without uncovering a history of the baseline discomfort, failure to inquire if the photophobia or phonophobia is ipsilateral to the pain, and not asking if total relief is obtained with triptans leads to the misdiagnosis of migraine. Focusing on the short duration of some exacerbations or on the autonomic features that accompany them leads to the misdiagnosis of cluster headache. Focusing on the constant pain (which is often associated with overuse of symptomatic medications) leads to the misdiagnosis of chronic migraine and medication-overuse headaches.

100 times per day. Attacks may occur spontaneously or be triggered by touching trigger zones within the trigeminal territory, talking, chewing, brushing teeth, coughing, or nose blowing. Some patients report that neck movements can induce an attack.

As the name implies, SUNCT is associated with conjunctival injection and tearing (lacrimation), whereas SUNA has either one, or will be associated with at least one of the other features that are characteristic of the TACs. The onset of pain often lags behind the appearance of the eye redness or tearing. Episodic and chronic forms of both disorders exist, with the chronic form being more common.

Secondary mimics of SUNCT and SUNA include posterior fossa and pituitary lesions; therefore, all patients suspected of having these disorders require brain MRI. Because of the frequent short-duration neuralgiform pain and the potential for

TABLE 7-6 The Author's Top Trigeminal Autonomic Cephalalgia Tips

- Always obtain MRI scans and pituitary testing to exclude secondary mimics.
- Migrainous features may accompany trigeminal autonomic cephalalgias, but they are more likely to be ipsilateral to the pain (versus bilateral in migraine).
- Cluster headache may respond better to short-acting verapamil given several times daily than to the extended release formulation.
- Verapamil may cause heart block through its action on the atrioventricular node; this effect can be delayed for approximately 10 days, so it may be preferable to increase the dose more slowly. A baseline ECG, heart rate, and blood pressure should be obtained prior to treatment and repeated prior to each increase in dosage. Because ECG abnormalities may be delayed, the ECG should also be repeated approximately 2 weeks after dosage changes.
- Cluster headache bridge therapies should be started simultaneously with prevention.
- Avoid oral formulations of acute therapies in cluster headache.
- Unless contraindicated, all patients with cluster headache should be given a trial of oxygen.
- Oxygen therapy must be given through a nonrebreather face mask at high flow rates (10–15 L/min); nasal cannulas will not work.
- If a clusterlike headache occurs in a woman, does not demonstrate circannual or circadian periodicity, and is not associated with restlessness or nocturnal attacks or precipitated by alcoholic beverages, think paroxysmal hemicrania.
- Cluster headache and SUNCT/SUNA are more likely to occur in men.
- Paroxysmal hemicrania and SUNCT/SUNA are more likely to have a chronic temporal pattern.
- Paroxysmal hemicrania and hemicrania continua are indomethacin responsive.
- A baseline, low-level headache is required for the diagnosis of hemicrania continua, but approximately 30% patients with any trigeminal autonomic cephalalgia report this.
- The cranial autonomic symptoms in hemicrania continua occur with the exacerbations, not the baseline pain.
- A sensation of a foreign body in the ipsilateral eye is often reported in hemicrania continua, but if you don't ask, you won't know.
- Indomethacin response may be delayed by up to 2 weeks.
- Consider a trial of indomethacin in any patient with side-locked headache.
- Headaches that only respond to high indomethacin doses or require frequent dose escalations are more likely to be due to a secondary mimic.
- Remember to use proton pump inhibitors or agents that offer gastrointestinal protection concurrent with indomethacin.
- Melatonin and greater occipital nerve blocks may help when indomethacin cannot be used.
- SUNCT/SUNA are differentiated from trigeminal neuralgia by their V1 location, longer duration and higher frequency of attacks, associated cranial autonomic features, and lack of a refractory period.
- Lamotrigine is the drug of choice for SUNCT/SUNA, followed by topiramate and gabapentin.

MRI = magnetic resonance imaging; ECG = electrocardiogram; SUNCT = short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; SUNA = short-lasting unilateral neuralgiform headache attacks with cranial autonomic features.

KEY POINT

- Lamotrigine is the first-line therapy for short-lasting unilateral neuralgiform headache attacks. Topiramate and gabapentin have also been reported to be beneficial.

cutaneous stimuli triggering an attack, SUNCT and SUNA are occasionally mistaken for trigeminal neuralgia. These disorders are distinguished from trigeminal neuralgia by their predilection for involving the ophthalmic division (V1), the absence of a refractory period following cutaneous stimulation, and the potential for longer-duration attacks (up to 10 minutes).

Treatment Options

Lamotrigine is the first-line therapy for these disorders, with up to 75% of patients experiencing relief. Effective daily doses range from 100 mg to 400 mg, slowly titrated to avoid serious adverse reactions. Topiramate (50 mg per day to 400 mg per day) and gabapentin (600 mg per day to 3600 mg per day) have also been reported to be beneficial.[38] A 10-day course of IV lidocaine (1.3 mg/kg per hour to 3.3 mg/kg per hour) may induce a temporary remission for intractable SUNCT.[39] IV lidocaine requires cardiac and blood pressure monitoring and therefore must be given in an intensive care unit (ICU) or other inpatient monitored setting.

CONCLUSION

The TACs are uncommon primary headache disorders that are frequently misdiagnosed. Their recognition is important as they are among the most disabling of the primary headaches and require individualized treatment with different therapies. The author's top TAC tips are reviewed in Table 7-6.

REFERENCES

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013;33(9):665–671. doi:10.1177/0333102413485658.
2. Newman LC, Lipton RB, Solomon S. The hypnic headache syndrome: a benign disorder of the elderly. Neurology 1990;40(12):1904–1905. doi:10.1212/WNL.40.12.1904-a.
3. Mainardi F, Lisotto C, Maggioni F, Zanchin G. Headache attributed to airplane travel ('airplane headache'): clinical profile based on a large case series. Cephalalgia 2012;32(8):592–599. doi:10.1177/0333102412441720.
4. Simms HN, Honey CR. The importance of autonomic symptoms in trigeminal neuralgia. Clinical article. J Neurosurg 2011;115(2):210–216. doi:10.3171/2011.4.JNS101843.
5. Goadsby PJ, Lipton RB. A review of paroxysmal hemicranias, SUNCT syndrome and other short-lasting headaches with autonomic features, including new cases. Brain 1997;120(pt 1):193–209.
6. Favier I, van Vliet JA, Roon KI, et al. Trigeminal autonomic cephalalgias due to structural lesions: a review of 31 cases. Arch Neurol 2007;64(1):25–31. doi:10.1001/archneur.64.1.25.
7. Levy M, Matharu MS, Meeran K, et al. The clinical characteristics of headache in patients with pituitary tumors. Brain 2005;128(pt 8):1921–1930. doi:10.1093/brain/awh525.
8. Cittadini E, Matharu MS. Symptomatic trigeminal autonomic cephalalgias. Neurologist 2009;15(6):305–312. doi:10.1097/NRL.0b013e3181ad8d67.
9. May A, Bahra A, Buchel C, et al. Hypothalamic activation in cluster headache attacks. Lancet 1998;352(9124):275–278.
10. May A, Bahra A, Buchel C, et al. Functional magnetic resonance imaging in spontaneous attacks of SUNCT: short-lasting neuralgiform headache with conjunctival injection and tearing. Ann Neurol 1999;46(5):791–794.
11. Sprenger T, Valet M, Platzer S, et al. SUNCT: bilateral hypothalamic activation during headache attacks and resolving of symptoms after trigeminal decompression. Pain 2005;113(3):422–426. doi:10.1016/j.pain.2004.09.021.
12. 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.
13. Matharu MS, Cohen AS, Frackowiak RS, et al. Posterior hypothalamic activation in paroxysmal hemicrania using PET. Cephalalgia 2005;25:859.
14. Holland PR, Goadsby PJ. Cluster headache, hypothalamus, and orexin. Curr Pain Headache Rep 2009;13(2):147–154. doi:10.1007/s11916-009-0025-x.
15. Chabi A, Zhang Y, Jackson S, et al. Randomized controlled trial of the orexin receptor antagonist filorexant for migraine prophylaxis. Cephalalgia 2015;35(5):379–388. doi:10.1177/0333102414544979.

16. Goadsby PJ, Edvinsson L. Human in vitro evidence for trigeminovascular activation in cluster headache. Neuropeptide changes and effects of acute attacks therapies. Brain 1994;117(pt 3):427–434.

17. Goadsby PJ, Edvinsson L. Neuropeptide changes in a case of chronic paroxysmal hemicrania—evidence for trigemino-parasympathetic activation. Cephalalgia 1996;16(6):448–450.

18. Fischera M, Marziniak M, Gralow I, Evers S. The incidence and prevalence of cluster headache: a meta-analysis of population based studies. Cephalalgia 2008;28(6):614–618. doi:10.1111/j.1468-2982.2008.01592.x.

19. Russell MB, Andersson PG, Thomsen LL. Familial occurrence of cluster headache. J Neurol Neurosurg Psychiatry 1995;58(3):341–343.

20. Leone M, Russell MB, Rigamonti A, et al. Increased familial risk of cluster headache. Neurology 2001;56(9):1233–1236. doi:10.1212/WNL.56.9.1233.

21. Rozen TD, Fishman RS. Cluster headache in the United States of America: demographics, clinical characteristics, triggers, suicidality and personal burden. Headache 2011;52(1):99–113. doi:10.1111/j.1526-4610.2011.02028.x.

22. Bahra A, May A, Goadsby PJ. Cluster headache: a prospective clinical study with diagnostic implications. Neurology 2002;58(3):354–361. doi:10.1212/WNL.58.3.354.

23. Irimia P, Cittadini E, Paemeleire K, et al. Unilateral photophobia or phonophobia in migraine compared with trigeminal autonomic cephalalgias. Cephalalgia 2008;28(6):626–630. doi:10.1111/j.1468-2982.2008.01565.x.

24. Francis GJ, Becker WJ, Pringsheim TM. Acute and preventive pharmacologic treatment of cluster headache. Neurology 2010;75(5):463–473. doi:10.1212/WNL.0b013e3181eb58c8.

25. Cohen AS, Matharu MS, Goadsby PJ. Electrocardiographic abnormalities in patients with cluster headache on verapamil therapy. Neurology 2007;69(7):668–675. doi:10.1212/01.wnl.0000267319.18123.d3.

26. Prakash S, Shah ND, Chavda BV. Cluster headache responsive to indomethacin: case reports and a critical review of the literature. Cephalalgia 2010;30(8):975–982. doi:10.1177/0333102409357642.

27. Sillay KA, Sani S, Starr PA. Deep brain stimulation for medically intractable cluster headaches. Neurobiol Dis 2010;38(3):361–368. doi:10.1016/j.nbd.2009.05.020.

28. Leone M, Franzini A, Broggi G, Bussone G. Hypothalamic stimulation for intractable cluster headache: long-term experience. Neurology 2006;67(1):150–152. doi:10.1212/01.wnl.0000223319.56699.8a.

29. Burns B, Watkins L, Goadsby PJ. Treatment of medically intractable cluster headache using occipital nerve stimulation: long-term follow-up of eight patients. Lancet 2007;369(9567):1099–1106. doi:10.1016/S0140-6736(07)60328-6.

30. Vaisman J, Lopez E, Muraoka NK. Supraorbital and supratrochlear stimulation for trigeminal autonomic cephalalgias. Curr Pain Headache Rep 2014;18(4):409–416. doi:10.1007/s11916-014-0409-4.

31. Nesbitt AD, Marin JCA, Tomkins E, et al. Initial use of a novel noninvasive vagal nerve stimulator for cluster headache treatment. Neurology 2015;84(12):1249–1253. doi:10.1212/WNL.0000000000001394.

32. Schoenen J, Jensen RH, Lanteri-Minet M, et al. Stimulation of the sphenopalatine ganglion (SPG) for cluster headache treatment. Pathway CH-1: a randomized, sham-controlled study. Cephalalgia 2013;33(10):816–830. doi:10.1177/0333102412473667.

33. Tepper SJ, Stillman MJ. Cluster headache: potential options for medically refractory patients (when all else fails). Headache 2013;53(7):1183–1190. doi:10.1111/head.12148.

34. Cittadini E, Matharu MS, Goadsby PJ. Paroxysmal hemicrania: a prospective clinical study of 31 cases. Brain 2008;131(pt 4):1142–1155. doi:10.1093/brain/awn010.

35. Newman LC, Lipton RB, Solomon S. Hemicrania continua: ten new cases and a review of the literature. Neurology 1994;44(11):2111–2114. doi:10.1212/WNL.44.11.2111.

36. Cittadini E, Goadsby PJ. Hemicrania continua: a clinical study of 39 patients with diagnostic implications. Brain 2010;133(pt 7):1973–1986. doi:10.1093/brain/awq137.

37. Cohen AS, Matharu MS, Goadsby PJ. Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) or cranial autonomic features (SUNA)—a prospective clinical study of SUNCT and SUNA. Brain 2006;129(pt 10):2746–2760.

38. Cohen AS, Matharu MS, Goadsby PJ. Suggested guidelines for treating SUNCT and SUNA. Cephalalgia 2005;25:1200.

39. Matharu MS, Cohen AS, Goadsby PJ. SUNCT syndrome responsive to intravenous lidocaine. Cephalalgia 2004;24(11):985–982.