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CASE VIGNETTE

"It's like, 'oh, I'm going to have a headache'—and bam! I have a headache."

Howard, a 57-year-old museum curator, was referred upon the retirement of his previous neurologist, who had treated him for the past 2 years. Howard has a 17-year history of severe, frequent headaches refractory to chlorpromazine, lithium, indomethacin, and methysergide. He is currently on a regimen of verapamil (240 mg q12h), gabapentin (Neurontin 900 mg tid), and acetaminophen/diphenhydramine (Tylenol PM). Vital signs and physical examination were normal. On neurological examination, a left-sided ptosis and conjunctival injection were noted.

Describe your typical headache, Howard. Where do you get the pain? How long does it last? Do you have any other symptoms with the attack? How frequent are these headaches?

Howard reports daily headaches in the left temporoparietal region—always the left side. The current frequency is about 3-5 headaches daily, duration 10 to 90 minutes. The pain is described as throbbing and of moderately severe intensity—"it's not terrible but it's there"—accompanied by tearing of the left eye. "Like clockwork," he almost always awakens with a headache and goes to bed with a headache. With the Tylenol PM he does not wake up during the night with headache.

Has the pattern or character of the headaches changed over time?

His headaches began abruptly in May of 1983, during a time of financial stress. He could only recall having had two headaches in his life prior to that time. Initially, these headaches were multiple daily attacks of a very severe stabbing pain—"like an icepick in my eye"—in the left orbital, supraorbital and temporal regions, accompanied by ipsilateral tearing and nasal congestion. He originally had anywhere from 2 to 10 of these attacks a day, lasting from 10 minutes to an hour. In the first few years there were periods of remission, then the pattern changed. He would have multiple daily attacks of a very brief but terrible stabbing pain in the left eye, about 5 to 10 attacks a day, every day, each lasting only a few seconds or minutes. These brief stabbing headaches are now very unusual, with a frequency of about 5 to 10 attacks a year.

Does anything seem to trigger your headaches? Do you have any warning signs that a headache is coming? What do you do for relief during an attack? What makes them better, or what will make them worse?

Bright light can bring on or exacerbate a headache. Noise and movement neither precipitate nor exacerbate an attack. There are no warning signs; the headache comes on rapidly and fades slowly. Applying pressure or holding his head under hot shower water will provide some relief. Usually he just endures. "Everyone has some pain in their life and this happens to be mine." On further questioning, Howard reports that he usually drinks wine or beer with dinner, but the amount of alcohol consumed does not appear to influence the headaches. He has a history of smoking but quit about 7 years before the onset of his headaches.

How well is your current treatment working? Are you able to function during an attack?

The medications are able to "muffle" the pain and he usually can continue to function at work and home. He experiences fatigue as a side effect of the gabapentin. He feels the current regimen is the best he has tried but there is room for improvement. Chlorpromazine 25 mg q12h and indomethacin 50 mg tid each produced an initial improvement in frequency and severity but were subsequently ineffective, according to the patient's records. Methysergide (Sansert) was briefly tried, but Howard was uncomfortable with the side effect profile. He started the current regimen of verapamil, with gabapentin subsequently added, about 2 years ago, with several subsequent dose escalations.

On further discussion, it was decided to try valproic acid (Depakote 125 mg bid for 1 week, then increasing to 250 mg bid) after first tapering gabapentin over a 30-day period. Unfortunately, his severe headaches returned as gabapentin was tapered and did not improve after 3 weeks of valproic acid. Valproic acid was tapered and gabapentin restarted. Given Howard's proportions (6′6″, 280 lbs) and his tolerance for the verapamil/gabapentin regimen, it was decided to increase the gabapentin gradually to a total dosage of 3600 mg/day.

PRETEST

1. What is the diagnosis?
2. Which of the following features were most important in making the diagnosis?
   a. Unilateral location of pain
   b. Periorbital location of pain
   c. Photophobia
   d. Tolerance for alcohol
   e. Attack duration (10-90 min)
   f. Attack frequency (3-5/day)
   g. Pain intensity (moderately severe)
   h. Tearing of ipsilateral eye
   i. History of extremely brief stabbing headaches
   j. Response to verapamil
3. What is the significance of the left-sided ptosis and conjunctival injection noted on neurological exam?
4. Is any further work-up advisable?

COMMENTARY

Howard has chronic cluster headache evolving from episodic cluster headache. About 10% of patients with cluster headache have chronic symptoms with no remission periods. Like other patients who have progressed to a chronic daily headache, there are some mixed features to Howard's headaches. His current headache pattern could be alternatively described as a migraine variant, given his photosensitivity and the pulsating quality of the pain.

Describe your typical headache, Howard. Where do you get the pain? How long does it last? Do you have any other symptoms with the attack? How frequent are these headaches?

The pain quality and intensity are more suggestive of migraine than cluster headache. However, ipsilateral autonomic symptoms such as conjunctival injection, tearing, or ptosis, are hallmarks of cluster headache. The duration of a migraine attack is usually in the range of 4-72 hours, while cluster attacks are relatively brief, 15-180 minutes. Awakening with a headache is common among migraineurs, but people with cluster headache sufferers are more likely to note attacks that occur at the same time every day., particularly within 1-2 hours of going to sleep.

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Has the pattern or character of the headaches changed over time?
The initial attack frequency Howard describes is somewhat high for cluster headache (IHS diagnostic criteria specify 1-8 attacks per day). Otherwise, the severe, exclusively unilateral periorbital and temporal pain he describes and the associated ipsilateral symptoms are very clearly cluster headache. Patients with cluster headache frequently characterize the pain in similar terms as boring, stabbing or piercing. Chronic cluster headache often evolves from the episodic variety. The frequency and brevity of the attacks he initially experienced as the chronic pattern emerged might suggest a diagnosis of chronic paroxysmal hemicrania, a cluster variant seen more commonly in women than in men that is invariably responsive to indomethacin. As noted in the history, however, indomethacin proved ineffective.

This change in the headache pattern, with the development of chronicity and the reduced intensity of symptoms, probably due to medications, has sometimes been called a "modified cluster pattern." With modified cluster, especially with more severe symptoms than are found in this case, a secondary cause in the post-orbital region requires consideration. Since the pain is not worsening and the previous episodic attacks were more typical, an MRI is not indicated at present.

Does anything seem to trigger your headaches? Do you have any warning signs that a headache is coming? What do you do for relief during an attack? What makes them better, or what will make them worse?
The combination of light and sound sensitivity is characteristic of migraine, though either may sometimes be experienced with other headache conditions. Migraineurs commonly report that movement aggravates and rest or sleep alleviates the head pain, whereas patients with cluster headache patients tend to pace during attacks and obtain no benefit from rest. Application of pressure, heat or cold may provide mild relief for either cluster or migraine headache. A history of heavy smoking and/or drinking is reportedly common among people with cluster headache patients; however, smoking cessation generally provides little or no improvement in the headaches. Alcohol is often a potent trigger for cluster headache attacks, though not in this case.

How well is your current treatment working? Are you able to function during an attack?
Howard is at least fortunate to have been under excellent care for most of his long history of headaches, and the regimens that have been tried are all reasonable options for cluster headache prophylaxis. Howard's good response to gabapentin suggested he might benefit from valproic acid, an antiseizure medication with better documented efficacy for both cluster and migraine. This did not prove to be the case. Chronic cluster headache is often refractory to treatment, and while there are other options that could yet be explored, Howard is doing reasonably well on high-dose verapamil and gabapentin.

DIAGNOSIS OF CLUSTER HEADACHE

Tarvez Tucker, MD. Associate Professor, Department of Neurology, Case Western Reserve University School of Medicine; and Director, Headache Center, University Hospitals of Cleveland. Cleveland, OH

Cluster headache presents in an unmistakable fashion. Although far less common than migraine or tension type headache, the clinical features of cluster headache are singularly dramatic. Unique to all headache syndromes, the characteristics of cluster headaches are quite consistent from patient to patient, and for the same individual, the attacks are very stereotypic.

If a cluster headache patient presents in the throes of his attack, the diagnosis is virtually inescapable. He paces with the intensity of the periorbital pain, frequently holding his eye or even striking his head as distraction from the pain. He has ptosis or eyelid edema, tears stream from his eye, the ipsilateral nostril runs, the eye is red, the forehead sweaty.

In practice, patients rarely present in the midst of an attack. Cluster headaches are generally much shorter than migraine, commonly from 45 to 90 minutes. But just a few key questions will identify this very specific and frightening syndrome and contrast it to migraine headache.

CLUSTER HEADACHE CHARACTERISTICS

- More common in men
- Always unilateral and on the same side
- Orbital, supraorbital or temporal
- Short lasting pain: 15-180 minutes
- Associated with:
  - conjunctival injection
  - lacrimation
  - nasal congestion or rhinnorhea
  - facial sweating
  - partial Horner's (miosis and ptosis)
  - eyelid edema
- Attacks cluster in time, occurring a few times a day, daily, for several weeks, then disappearing for months or years.

MIGRAINE HEADACHE CHARACTERISTICS

- More common in women
- Often unilateral, but will sometimes switch sides
- Longer lasting pain: 4-72 hours
- Associated with:
  - GI disturbance (nausea, vomiting)
  - photophobia/phonophobia
- Attacks are periodic, but do not cluster together.

Diagnostic Pearl
Cluster patients pace and walk and are restless.

Migraine patients remain very quiet and still; motion and activity worsen the pain.

TEMPORAL AND SEASONAL CLUSTERING

The temporal "clustering" of this headache is fascinating and surprisingly similar from episode to episode.

- Attack phases occur in cluster periods: usually 1-2 per year
- Seasonal occurrence: attacks are most likely in January and July (shortest and longest days of the year)
- Remission periods last usually from 6 months to 2 years; these periods are consistent for the same patient
- Circadian periodicity: <8 attacks per day (usually 1-3/day) that occur usually at the same time of day: Most frequent time of onset: 1-2 AM, 1-3 PM, and 9 PM. Nocturnal attacks awaken patients from sleep.

PROFILE OF A CLUSTER HEADACHE SUFFERER

A number of curious clinical characteristics have been attributed to cluster patients, but careful clinical studies have not been performed to solidify these profiles:

- Heavy facial features
- Peau d'orange skin
- Hazel eyes
- Peptic ulcer disease
- Type A personality

Patients often use tobacco and drink alcohol (although having an alcoholic drink during the cluster period can often precipitate an attack). Howard is unusual in this regard. Many cluster patients tell me even the "thought of having a beer" brings on the periorbital pain.

Although cluster headache is most commonly episodic, a chronic form exists, as Howard exemplifies. Remissions shorten or disappear, and the patient is left with a daily refractory cluster headache. Chronic cluster, fortunately, occurs in just 10% of cluster patients. It is singularly difficult to treat.

DIFFERENTIAL DIAGNOSIS

Despite the striking clinical characteristics of cluster headache, it is sometimes misdiagnosed, particularly if the patient presents at the onset of the condition rather than—as in Howard's case—with a lengthy and consistent history of obviously benign, if agonizing, headaches.

Localization of pain to the retro-orbital and temporal region often causes confusion with the diagnosis of "sinus" headache, especially if the ipsilateral nostril is clogged during the attack. In fact, nasal drainage can signal the end of a cluster attack. It is not uncommon for patients to be treated for sinus headache during the "cluster," even for several cluster episodes. Since the cluster headache's natural course may end in a few weeks, the patient and physician can be fooled, thinking it was the antibiotics given for sinus headache that ended the attack.

One-sided orbital and temporal or frontal pain associated with a partial Horner's syndrome can also occur from ipsilateral dissection of the carotid artery. A history of recent trauma to the neck, for example, a whiplash injury in a motor vehicle or a sports-related injury, should arouse immediate consideration of carotid dissection. Of course, dissection usually would not produce episodic headache of a stereotypic nature.

Trigeminal neuralgia, oral-dental or ocular disease can also cause unilateral frontal head pain, but an accurate history of the pattern of headache and the pain characteristics usually permits correct distinction between these syndromes. For example, trigeminal neuralgia causes brief, lightening-like pains lasting just seconds and radiating in the distribution of the fifth cranial nerve.

Complete third nerve palsy with unilateral headache should arouse suspicion for compression of the third nerve by aneurysm, a true neurologic emergency. Again, the wise axiom regarding the "first or worst" headache mandates urgent diagnostic evaluation with head CT scan and possibly lumbar puncture. Fortunately, an accurate history of previous headache cycles will confirm the diagnosis of cluster headache in most cases.

Some migrainous headaches can have cluster features. In contrast to migraine, nausea in cluster headache is very uncommon, though it may occur secondary to the use of analgesics or ergotamine. Many patients with migraine headache describe eyelid ptosis or edema during their attack, but the periodicity of attacks resembles migraine rather than cluster and, again, the location of migraine pain in the head is far more variable than cluster.

Temporal arteritis should always be considered when frontal or temporal headache occurs in older individuals, usually over the age of 55. Pain is often at one or both temples and may be associated with a tortuous and tender palpable temporal artery; but the associated autonomic features and temporal pattern of cluster are lacking in giant cell arteritis. When in doubt, a Westergren sedimentation rate can help differentiate the two disorders.

Differential Diagnosis

- Sinus headache
- Trigeminal neuralgia
- Migraine headache with cluster features
- Carotid dissection
- Dental disease or glaucoma
- Temporal arteritis
- Compression due to aneurysm with third nerve palsy

At the time Howard's headaches began, he described a pattern more suggestive of chronic paroxysmal hemicrania (CPH) than cluster headache. These attacks are usually even shorter than cluster, lasting 2-45 minutes, and attack frequency is higher, usually >5/day with a range of 1-50. Difficulty in diagnosis occurs because patients with CPH have autonomic symptoms also, such as ptosis, eyelid edema, nasal congestion and lacrimation on the same side as the headache. Response to indomethocin is almost universal; in fact, responsiveness to indomethacin is part of the IHS criteria for the diagnosis of this syndrome. Another distinguishing feature: CPH is more common in women than men.

INVESTIGATIONS

Cluster headache is usually easily diagnosed by an accurate history of the nature of the head pain and its periodicity of attacks: several weeks, followed by months or years of headache-free periods. Most patients have a normal neurological examination, and special diagnostic or neuroimaging studies are usually not required. An exception to this is the patient who presents to you with his first headache. Perhaps he reports having had a strictly unilateral headache for several days or weeks with autonomic features that cause you to suspect cluster, but he does not have a history of prior head pain. New onset of unilateral headache due to tumor, AVM or expanding aneurysm usually, but not always, will be associated with atypical features in the history, or an abnormal neurologic examination. An MRI with enhancement is the best diagnostic test to exclude mass lesions; an MRA will demonstrate abnormalities of blood vessels. Simple tests to exclude glaucoma (measuring ocular pressure), or temporal arteritis (obtaining an ESR) will exclude other treatable causes of temporal or frontal pain. If trauma to the neck was present, however slight, a carotid ultrasound or magnetic resonance angiogram will exclude carotid dissection. If aneurysm, AVM or tumor is suspected on the basis of an atypical history or an abnormal examination, MRI of the brain or orbits will diagnose intracranial structural abnormalities.

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TREATMENT OF CLUSTER HEADACHE

Ninan T. Mathew, MD, FRCP(C). Houston Headache Clinic. Houston, TX

In the management of cluster headache, acute therapy has to be combined with prophylactic therapy. Patients with episodic cluster headache get 1-8 episodes in 24 hours during an active cluster period, and those with chronic cluster headache have a much higher number of episodes per day. Many have nocturnal attacks that interfere with their sleep and make them very tired during the day. Patients with cluster headaches are usually heavy smokers. Some of them may have hypertension as well. Those factors have to be evaluated before a treatment plan is chalked out.

THERAPY FOR ACUTE CLUSTER HEADACHE

Cluster headache attacks are of rapid onset and peak usually in 5-10 minutes. The whole attack may last on average about 45-60 minutes. Therefore, abortive agents used in acute cluster headaches should have a rapid onset of action. Only a few agents have been shown to be useful for acute cluster headache.

Abortive agents for acute cluster headache

Agent	*Dosage*
Oxygen inhalation	5-7 L/min for 10 min
Subcutaneous sumatriptan	6 mg
Nasal sumatriptan	20 mg
Oral zolmitriptan	10 mg
4% Lidocaine intranasal	1 ml

Oxygen inhalation. Breathing oxygen via mask at 5-7 liters per minute for 10 minutes at the very onset of headache has been shown to be effective in at least 70% of attacks. The effect of oxygen is rapid. In some patients, oxygen may simply postpone the development of an attack, and it is likely the headache may come back the same day. For some individuals, waiting to treat until the headache peaks may be the most effective strategy.

Oxygen therapy is not associated with any adverse side effects, except in those with chronic obstructive pulmonary disease. The main drawback of oxygen therapy is the inconvenience. Many of our patients are asked to rent a small portable oxygen tank or bottle, which they can carry around. Many keep it available in their offices or workplaces as well as at home because it has to be used at the very onset of the attack.

Oxygen is a powerful vasoconstrictor of the dilated cranial blood vessels. It is also known to reduce the CGRP levels in the external jugular vein in patients during cluster headache.

Subcutaneous sumatriptan (Imitrex). Subcutaneous sumatriptan is the drug of choice for acute episodes of cluster headache; 6 mg sc begins to be effective in a few minutes and within 10-15 minutes patients become headache free. Subcutaneous sumatriptan is well tolerated by cluster headache patients and the usual triptan chest symptoms are very rarely seen in patients with cluster headache.

Because cluster headache patients are often heavy smokers, a baseline evaluation of cardiovascular status is necessary before sumatriptan is prescribed. But, overall, patients with cluster headaches appear to tolerate sumatriptan injections better than those with migraine.

A maximum of 2 injections (12 mg) is allowed in a 24-hour period. Sumatriptan has not been shown to produce tachyphylaxis when used repeatedly, and there is no evidence of any rebound with Imitrex injection in cluster headache. Long-term treatment has not been shown to be associated with any cumulative side effects.

Sumatriptan nasal spray. A recent study has shown that 20 mg sumatriptan nasal spray is useful in the treatment of acute cluster headache. Nasal spray sumatriptan begins to be effective in about 10-15 minutes. Here again the medicine has to be used early and patients should be advised to keep the Imitrex nasal spray with them all the time so that they can use it as early as possible. It is advised to use the spray in the opposite nostril, as the ipsilateral nostril is often congested.

Zolmitriptan (Zomig). 10 mg zolmitriptan tablets (double the usual migraine dose) has been shown to have some beneficial effect in the treatment of acute cluster headache. However, the study involved only a few patients and the effect was obvious only in 30 minutes, which in general is too slow to be considered a very effective treatment.

Zolmitriptan nasal spray, which is being developed at the present time, is known to have a much faster onset of action and may eventually become a better choice than zolmitriptan tablets. None of the other triptans have been studied for the treatment of cluster headache.

Intranasal lidocaine. 4% lidocaine drops to the ipsilateral nostril have been reported to be useful for patients during acute attacks. The patient is supposed to lie down with the head extended and turned slightly to the side of the headache while lidocaine drops are instilled into the ipsilateral nostril. The patient should lie in that position for a few minutes after instilling lidocaine. The sphenopalatine ganglion gets anesthetized, which in turn may reduce the pain. The long-term effectiveness of this treatment has not been evaluated. Long-term effects of repeat use of lidocaine solution on the nasal mucosa have not been studied.

Opioids. There is no place for opioid treatment in routine management of cluster headache. The attacks are multiple, particularly in chronic cluster headache, and repeat use of any opioid will only result in dependency problems. There is no evidence that opioids have any specific effects on cluster headache pain.

PROPHYLACTIC TREATMENT OF CLUSTER HEADACHE

Almost all patients with cluster headache, whether it is episodic or chronic, need prophylactic therapy. The only difference is that, in the episodic variety, treatment can be tapered and stopped when the patient goes into remission.

Medications for cluster headache prophylaxis

Agent	*Dosage*
Verapamil	240-480 mg/day
Methysergide	4-8 mg/day div dose during active cluster period
Corticosteroids	e.g., prednisone starting w/ 60 mg/day or dexamethasone 4.5 mg/day, tapering doses for 12-15 days
Lithium carbonate	600-900 mg/day
Ergotamine tartrate	1-2 mg/day during active cluster period
Topiramate	50-300 mg/day
Valproate (divalproex sodium)	500 mg bid

The choice of prophylactic treatment would depend on whether cluster headache is episodic or chronic. For chronic cluster headache, a single prophylactic agent may not be enough. Triple therapy, which involves verapamil, lithium and methysergide, may be necessary.

Patients should be cautioned about the use of triptan therapy, such as sumatriptan (a serotonin agonist) as abortive treatment if they are on methysergide (a serotonin antagonist). Patients on methysergide should rely upon oxygen or lidocaine as symptomatic therapy instead of triptans or ergots.

For episodic cluster headache, usually verapamil combined with ergotamine is useful. Ergotamine 1-2 mg can be used on a daily basis during the episodic cluster headache period. However, for chronic cluster headache, ergotamine is not recommended on a long-term basis. Verapamil has to be used in higher doses than usual, usually approximately 480 mg/day. Constipation and water retention are the main side effects of verapamil.

Corticosteroids (prednisone or dexamethasone) are useful in breaking the cycle of headache in many patients. A short course of prednisone for 12 to 15 days in decreasing doses is useful. Many physicians start a tapering course of prednisone initially in conjunction with verapamil and ergotamine or methysergide. After the corticosteroid is tapered off, verapamil and ergotamine or methysergide will be continued. Long-term use of corticosteroids in chronic cluster headache is not recommended, as there have been case reports of bone necrosis associated with use of corticosteroids in cluster headache patients.

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Topiramate has recently been shown to have beneficial effects in patients with cluster headaches. Topiramate can be used as an add-on therapy or as initial monotherapy. Slow titration topiramate as recommended for migraine therapy may not be necessary in cluster headache.

Even though there are reports of valproate being useful for cluster headache prophylaxis, the general clinical impression is that it is not very effective. Finally, there is no evidence that cessation of smoking will reduce cluster headache pain.

SURGICAL CONSIDERATIONS

What is the option when medical therapy fails in chronic cluster headache? Over the past 20 years we have accumulated a great deal of experience in dealing with patients with persistent intractable cluster headache who have not responded to any of the prophylactic medications after having tried combinations of these medications for reasonable periods of time. The experience indicates that surgical intervention directed to the trigeminal nerve is probably the most effective form of treatment for chronic cluster headache.

Surgical treatment for cluster headache

- Radiofrequency trigeminal rhizotomy
- Gamma knife surgery on the trigeminal nerve
- Retrogasserian glycerol injection
- Microvascular decompression of the trigeminal nerve
- Sensory trigeminal nerve root section

Indications for surgery include: (1) strictly unilateral chronic cluster headache, (2) patients who are totally resistant to adequate trials of preventive medications, and (3) patients with intractable chronic cluster headache with stable psychological and behavioral patterns.

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Radiofrequency trigeminal rhizotomy is preferred. Approximately 75% of patients in our series of 120 patients obtained freedom from headache. Failures were mostly due to technical reasons when the surgeon was not able to obtain good analgesia in the 1st division of the trigeminal nerve. Repeat attempts have been successful in some.

Complete analgesia, particularly of the ophthalmic division, is essential. If relapse of pain occurs after a number of years, repeat surgery is workable.

Corneal analgesia is a sequela of the surgery and therefore care should be taken by the patient not to injure the cornea.

PATHOPHYSIOLOGY OF CLUSTER HEADACHE

Joel R. Saper, MD. Michigan Head Pain & Neurological Institute. Ann Arbor, MI

An adequate explanation of the mechanisms of cluster headache must encompass all the acute attack features, including the severe unilateral pain distributed along the ophthalmic division of the trigeminal nerve and the 2nd cervical root, as well as account for the diagnostic autonomic symptoms, which include sympathetic impairment (miosis, ptosis, impaired sweating) and parasympathetic activation (rhinorrhea, lacrimation). The periodicity of the condition—its seasonal variation and the frequent clockwise regularity of the attacks—must also be explained. Contending theories invoke peripheral versus central mechanisms.

PERIPHERAL EVENTS

The cavernous sinus has been discussed as a possible site of origin for both the pain and the autonomic signs, as the internal carotid artery and the ophthalmic and maxillary divisions of the trigeminal nerve pass through it. Hardebo has proposed that cluster may be explained by a chronic or relapsing inflammatory process in which the inflammation blocks venous outflow from the cavernous sinus on one side and injures adjacent sympathetic fibers supplying the eye, upper eye lid, forehead skin, and the intracranial internal carotid artery and its branches.

A variety of supportive evidence can be adduced. Orbital phlebography has demonstrated signs of inflammation in the superior ophthalmic vein and cavernous sinus, particularly on the painful side, in most patients examined during cluster periods. Vasoactive peptides are elevated during a cluster attack, and nitroglycerin, alcohol, and other vasodilators reliably induce an attack during an active period. A recent PET scan study has shown cluster-like pain and autonomic symptoms experimentally produced by injection of capsaicin in the forehead, which results in changes in cavernous sinus blood flow.

A partial Horner's syndrome is a frequent accompaniment of cluster headache, presumably resulting from distention of the internal carotid artery that compromises the ocular sympathetic nerve supply. The distention could result from the release of vasoactive peptides in the internal carotid ganglion occurring in response to the greater superficial petrosal nerve discharge that is thought to produce the autonomic symptoms such as lacrimation and rhinorrhea.

CNS EVENTS

Peripheral mechanisms cannot account for the diurnal and the seasonal pattern of attacks. Hypothalamic involvement has been suspected based on the temporal patterns of the disorder, the autonomic symptoms, and several neuroendocrine changes observed during the active cluster period, including reduced response to thyrotropin-releasing hormone, reduced nocturnal melatonin secretion, and reduced testosterone levels in men.

PET scanning studies have identified activation of the inferior gray hypothalamic region ipsilateral to the pain during a cluster headache attack. In these studies, nitroglycerin has been used to elicit an attack during the active cluster period of patients. It produces only mild headache—with no hypothalamic activation—during a remission period.

Using voxel-based morphometry of MRI images, May and colleagues have reported increased gray matter in the inferior posterior hypothalamus of all 25 cluster headache patients investigated, 14 of whom were in an active cluster period and 11 were in remission. The area of hypothalamic activation detectable by PET scan localized to the same stereotaxic coordinates as the area of increased density detected by morphometry in the patients for which they had PET studies. While it is possible this increase in gray matter is a consequence rather than a cause of recurrent cluster headache attacks, the discovery was interpreted as the first demonstration of an anatomic abnormality underlying a benign primary headache disorder.

While these observations lend strong support to a central hypothalamic mechanism, the possibility that the observed hypothalamic activation during the acute attack is triggered by the pain has been raised. However, hypothalamic activation is not noted in experimental pain induced by capsaicin injection into the forehead, which produces some of the same autonomic symptoms as cluster headache in addition to severe pain along the ophthalmic division of the trigeminal nerve. Nor is it evident in PET studies of spontaneous migraine with aura, where increased brainstem, but not hypothalamic, activity has been observed.

One as yet unresolved issue concerns a central hypothalamic mechanism for the pain itself. The hypothalamus projects to motor, but not sensory, trigeminal nerve fibers. One possible explanation, suggested by Schoenen, would be that the hypothalamic generator activates autonomic nuclei that in turn trigger perivascular changes that produce the pain.

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Answers—Pretest

1. Chronic cluster headache evolving from episodic cluster.
2. The diagnosis is based on a, b, e, f, and h.
3. Ptosis and conjunctival injection are among the ipsilateral autonomic symptoms seen in acute attacks and are presumably chronically present for this patient.
4. No, because the patient has a long history of benign headache and has not reported any change in headache severity or attack pattern that might suggest emergence of an underlying organic disorder.

Answers—Posttest

1. Onset of severe headaches with no history of significant headache; new onset or changed pattern in an older patient; recent neck/head trauma with new onset or change in headache pattern; a marked increase in severity with onset of chronic pattern; atypical features or an abnormal neurological exam.
2. Rapid onset of action, since attacks are brief; evaluation of cardiovascular status before prescribing triptans; potential drug interactions as with methysergide and triptans; patient acceptability—e.g., willingness to use injections or to keep oxygen tank or bottles near at hand.
3. Almost always, since the multiple daily attacks cannot be controlled by repeated use of abortives; in episodic cluster headache, preventives are prescribed at the onset of an active cluster period or when a seasonal cluster period is anticipated.
4. Yes, the male preponderance is useful, though not diagnostic, in distinguishing cluster from migraine. Onset in patients over age 50 is relatively uncommon and should prompt a more careful work-up. Patients should be questioned about smoking and alcohol intake. Avoiding alcohol during active cluster periods may be particularly helpful; it is not clear that smoking cessation will have a specific benefit for headache prevention.

EPIDEMIOLOGY OF CLUSTER HEADACHE

Todd D. Rozen, MD. Assistant Professor of Neurology, Jefferson Headache Center/Thomas Jefferson University Hospital. Philadelphia, PA

1. Prevalence and incidence of cluster headache

Cluster prevalence is believed to be about 0.4%, compared with 6% for migraine[1]

Reported cluster prevalence rates:

Hardman and Hopkins (1966)	England	0.05%
Heyck (1976)	Germany	0.4%
D'Alessandro (1986)	San Marino	0.7%
Kudrow (1980)	United States	2.4%

Study: Swanson et al (1994),[2] Olmsted County, Minnesota:
Age-adjusted incidence rates:
Males: 15.6 per 100,000 person-years
Females: 4.0 per 100,000 person-years
Total: 9.8 per 100,000 person-years

2. Cluster headache is a male predominate disorder, but the gender ratio may be decreasing over time

Typically quoted male to female gender ratio: 6-7: 1

Study: Manzoni (1998),[3] Parma, Italy:
482 patients (374 men, 108 woman):

Years	*Male: female ratio*
Before 1960	6.2:1
1960-1969	5.6:1
1970-1979	4.3:1
1980-1989	3.0:1
1990-1995	2.1:1

The Manzoni study may reflect either a true increase in the incidence of cluster in females or a better recognition of cluster in women by physicians, and thus a higher diagnosis rate.

Cluster headache is strongly tied to alcohol consumption and cigarette smoking. As more women adopt the vices of men, their risk of developing cluster will increase.

3. Cluster demographics

a. Age of onset
- Older age of onset for cluster than migraine, but still a young person's disorder
- 80% of cluster patients have their first attack between the 2nd and 4th decades
- Women appear to have an earlier age of onset than men
- Women have 2 age peaks of cluster onset (3rd and 5th or 6th decade) while men have only 1 age peak (3rd decade)

b. Race
- Cluster appears to occur in all racial groups, although prevalence rates vary
- Kudrow[1] and Rozen et al[4] have shown that African-American women develop cluster more often than African-American men

c. Cluster subtypes (episodic or chronic cluster headache)
- 80% of cluster patients have episodic cluster
- 4% to 20% experience chronic cluster
- Older studies suggested that women never developed chronic cluster, but newer investigations have found an almost equal prevalence of chronic cluster in women and men

4. Genetics of Cluster

Cluster can be an inherited disorder, but much less frequently than migraine.

Study: Russell et al (1995),[5] Denmark:
370 probands:
- Positive family history found in 7%
- Autosomal dominant pattern
- 14-fold increased risk of developing cluster in first-degree relatives
- 2-fold increased risk in second-degree relatives

References

1. Kudrow L. Cluster headache: Mechanisms and management. New York: Oxford University press, 1980.
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3. Manzoni GC. Gender ratio of cluster headache over the years: possible role of changes in lifestyle. Cephalalgia 1998; 18:138-42.
4. Rozen TD, Niknam R, Shechter AL, Young WB, Silberstein SD. Cluster headache in women: clinical characteristics and comparison to cluster headache in men. Neurology 1999; 52:A471 (abstract)
5. Russell MB, Andersson PG, Thomsen LL, Iselius L. The inheritance of cluster headache investigated by complex segregation analysis. Cephalalgia 1995; 15(suppl 4):198. [*See also* Russell MB. Genetics of Cluster Headache. Olesen J, Tfelt-Hansen P, Welch KMA, eds. The Headaches. Philadelphia, Lippincott Williams and Wilkins, 2000; pgs: 679-682.]

POSTTEST

1. Under what circumstances should a patient with apparent cluster headache be given further work-up to rule out organic syndromes?
2. What are the important considerations in selecting an abortive agent for cluster headache?
3. When are preventive medications indicated?
4. Does the epidemiology of cluster headache provide any guidance for diagnosis and treatment?