Cluster Headache: History, Mechanisms, and Most Importantly, Treatment Options

By Mark J. Burish, MD, PhD

The first clear descriptions of cluster headache came from 17th and 18th century Europe, with the first in-depth account from the Dutch physician Nicolas Tulp in 1641, and the first complete account that meets all International Classification of Headache Disorders criteria from the Dutch physician Gerard van Swieten in 1745. In the early 1900s, the disease was meticulously described by the German/Swiss neurologist Paul Robert Bing and the London neurologist Wilfred Harris. Modern treatments such as oxygen gas and parenteral dihydroergotamine were used by the American physician Bayard Horton. Cluster headache has enjoyed a dozen different names, from the mundane “sphenopalatine neuralgia” to the more colorful “erythroprosopalgia of Bing.” The current name of the disease was provided in 1952 by the American physician E. Charles Kunkle, who noticed that the headaches tend to “cluster” together. Cluster headache was often considered a variant of migraine until very recently and was established as its own disorder with the first International Classification of Headache Disorders (ICHD-I) in 1998. The ICHD have gone through three iterations with largely similar criteria for cluster headache throughout: only restlessness/agitation was added with the ICHD-II revision in 2004, and two new autonomic features were added in the current 2013 ICHD-III-beta revision in 2013.

The current criteria for cluster headache are:

A. At least five attacks fulfilling criteria B–D.
B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 minutes when untreated.
C. Either or both of the following:
   a. At least one of the following symptoms or signs, ipsilateral to the headache: conjunctival injection and/or lacrimation, nasal congestion and/or rhinorrhea, eyelid edema, forehead and facial sweating, forehead and facial flushing, sensation of fullness in the ear, miosis and/or ptosis.
   b. 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 diagnosis.

Cluster headache comes in two variants, described by the ICHD-III-beta as follows:

Episodic cluster headache: At least two cluster periods lasting from seven days to one year (when untreated) and separated by pain-free remission periods of greater than one month.

Chronic cluster headache: Occurring without a remission period, or with remissions lasting less than one month, for at least one year.

Cluster headache has a prevalence of 0.1 percent of the population, approximately the same rate as multiple sclerosis in the US. Cluster headache is more common in men than women at a rate of 3:1, with a typical onset between 20 to 40 years of age. About 90 percent of patients have the episodic form and usually have one to three headaches per day, lasting between two weeks and three months, with cycles occurring once or twice per year. There is some interchange between the episodic and chronic forms, as 13 percent of episodic cluster headache patients switch to chronic, and up to 33 percent of chronic cluster headaches change to episodic.
Diagnosis

The ICHD-III-beta criteria are listed above. The pain of cluster headache is exquisite, and anecdotally is regarded by patients as more painful than migraine, kidney stones, childbirth, or multiple bone fractures. The cluster headache cycle may start and end with headaches that are milder in intensity, as if the headache cycle is ramping up and cooling down. And 30 percent of patients with cluster headache report a low-level of interictal discomfort between attacks.

Features characteristic of cluster headache are the short time to maximal pain (generally within minutes) and the circadian pattern (82 percent of patients have headaches at the same time every day).5 There are also typical headache triggers which include alcohol, nitroglycerin, heat, exercise, and naps. For episodic cluster headache, there is a characteristic circannual pattern, with cluster periods usually occurring in the spring and fall. Interestingly the headache triggers only work during the cluster period for episodic cluster headache and have no effect in the headache-free period.

Cluster headache can be differentiated from migraine primarily based on cluster headache’s shorter duration, associated restlessness, and potential for multiple headaches per day. Many typical “migranous” and “trigeminal autonomic” symptoms are not helpful in distinguishing between migraine and cluster headache; about half of cluster headache patients have nausea, photophobia, and phonophobia (some even have auras and premonitory symptoms), and likewise about half of migraine patients have cranial autonomic symptoms.6-8

The differential diagnosis for cluster headache includes other primary headache disorders such as migraine, paroxysmal hemicrania, and hypnic headache; cranial neuralgias such as trigeminal neuralgia; and secondary headache disorders such as temporal arteritis, maxillary sinusitis, Tolosa-Hunt syndrome, and infections of the cavernous sinus.

Pathophysiology

The cause of cluster headache is poorly understood. About five to 10 percent of cluster headache patients have a family history of cluster headache, suggesting a genetic link. Presumably, cluster headache has multiple susceptibility genes. One of those genes may be the orexin/hypocretin receptor 2 (HCRTR2) which is implicated in sleep, narcolepsy, and hypothalamic functioning. Mutations in HCRTR2 were associated with cluster headache in two independent studies.9,10 but not in a third.11 Cluster headache patients are much more likely to use tobacco than the general population, and the rate of patent foramen ovale is higher, but a causative relationship with these factors has not been established.

A small proportion of cluster headaches are secondary, giving some insight into different areas of the brain that may be involved. Cluster headaches have been associated with hypothalamic and pituitary tumors, menigiomas (anywhere from the cavernous sinus to the upper cervical spine), carotid artery dissections, vascular malformations, and sleep apnea.12 These associations, and the clinical features of cluster headache, suggest that there are three brain systems involved.

The first is the hypothalamus, which may be the location where cluster attacks originate. Not only is the hypothalamus the site of the circadian pacemaker in the suprachiasmatic nucleus, but imaging data shows preferential activation of the posterior hypothalamus at the onset of a cluster headache.13 Anatomical and functional changes of the hypothalamus have also been seen in cluster headache patients, as have alterations in hypothalamic and pituitary molecules such as orexin, melatonin, and luteinizing hormone.14–16

The second system involved in cluster headache is the autonomic system, specifically the superior salivatory nucleus and the sphenopalatine ganglion, which includes molecules such as vasoactive intestinal peptide that have been shown to be altered in cluster headache. Stimulation of the sphenopalatine ganglion can trigger or abort a cluster headache attack, depending on the setting.

The third system is the trigeminal nucleus, sometimes grouped with the large cranial blood vessels and meninges (“the trigeminovascular system”), or grouped with the upper cervical dorsal horns (“the trigeminocephalocervical complex”). This area is likely involved in the pain component of cluster headache, and includes molecules such as calcitonin gene-related peptide, pituitary adenylate cyclase-activating peptide 38, and others that have been shown to be altered in cluster headache.

Management

A brain MRI, with particular focus on the pituitary and cavernous sinus, is recommended in all patients according to the European Headache Federation.17 Additional work-up for many cluster headache patients might include ESR and CRP for temporal arteritis, especially in the elderly. In some cases, referral to ophthalmology, otolaryngology, or dentistry can be considered. A trial of indomethacin is often warranted to rule out paroxysmal hemicrania, as the features of these two diseases are very similar, and indomethacin is completely effective in treating paroxysmal hemicrania. If indomethacin is only partially effective, you may still be dealing with cluster headache. For patients refractory to several medications, the European Headache Federation recommends vessel imaging of the head and neck (such as MRA), pituitary lab testing, and polysomnography for sleep apnea (continuous positive airway pressure has been helpful in treating headaches for some patients). For suspected secondary causes of cluster headache, please note that lesions such as pituitary microadenomas, menigiomas, and vascular malformations are common incidental findings that may be entirely unrelated to the cluster headaches. Patients should be counseled that treatment of these lesions may or may not have an effect on their head-
aches, and that surgical resection likely should be considered only in the most refractory cases.

A number of treatment options for cluster headache are available (table available at PracticalNeurology.com). For abortives, oxygen gas, injectable sumatriptan, and nasal zolmitriptan are the preferred treatments. Oxygen gas should be tried at 15L/min, via a non-rebreather mask, for 20 minutes and appears to work better if taken early in the headache attack. For bridging medications (i.e. several weeks or less), ipsilateral greater occipital nerve block with steroids plus local anesthetic can be effective for several weeks, however the exact dosage of these injected medications is not clear. For prophylaxis, verapamil is generally considered first line, though it often requires high doses (240-960mg daily divided TID), so a baseline EKG, and EKGs after each dose change and then every six months, are recommended to look for heart block. For treatment during pregnancy and lactation, options to discuss with the patient and with obstetrics include oxygen gas and intranasal lidocaine amongst others. Greater occipital nerve block with local anesthetic alone could also be considered; adding steroids to the injection requires more careful consideration.

For patients refractory to standard treatments, revisiting medications such as oxygen gas may also be helpful: there has been much importance placed on education of oxygen use: it requires 15L/min via non-rebreather for a full 20 minutes. Anecdotally, some patients require higher rates, up to 25 L/min via non-rebreather. Lifestyle changes should also be emphasized, including the avoidance of triggers such as alcohol. Other treatments not listed in the table that have some data include epleptriptan, frovatriptan, tizanidine, gabapentin, clonidine, Botox injections, pizotifen, chlorpromazine, histamine, clonipine, leuprolide, methylphenidate, methylsergide, dihydroergotamine (IV and nasal), and warfarin. Alternative therapies have not shown benefit in small retrospective studies, including acupuncture, chiropractic, hypnosis, and homeopathy.

Should any medications fail to provide benefit, occipital nerve stimulation and deep brain stimulation of the posterior hypothalamus have been described and guidelines for their use have been proposed that include one to two years of refractory headaches and extensive trials of medications. Enrollment in one of the current cluster headache trials is also an option. Patients may ask you about psilocybin and other psychedelic compounds, as some patients have found relief with sub-psychedelic dosages and a seemingly non-psychedelic formulation showed promise in a preliminary case series. Additional trials of psychedelics have been proposed, but the majority of these compounds are currently listed as Schedule I drugs and thus are illegal to prescribe.

**Treatments in Development**

Calcitonin gene-related peptide (CGRP) is a pain signaling molecule of the trigeminovascular system that is elevated in patients with cluster headache or migraine. Antibodies for CGRP have been developed by several companies, and are now in Phase 3 trials for both cluster headache and migraine. They do not appear to have the hepatotoxic effects of some of the earlier small molecule CGRP inhibitors. As of October 2016, the open clinical trial for CGRP antibodies for cluster headache, including participating trial locations and contact information, is ClinicalTrials.gov identifier: NCT02397473 (episodic cluster headache) and NCT02438826 (chronic cluster headache).

Sphenopalatine ganglion stimulation has been shown to be an effective abortive treatment for cluster headache in European studies. This stimulator is currently in trials for chronic cluster headache (ClinicalTrials.gov: NCT02168764), and is arguably more attractive than other stimulators in part because it is much smaller and can be powered wirelessly through a device held at the cheek. Separately, vagal nerve stimulation has also been shown to be effective for cluster headache, and a non-invasive vagal nerve stimulator is available.

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