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Take Me to the River: The Agony of Cluster Headache

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Disclosure

- Advisory Board: Kalyra Pharma, Creative Biopeptides

Learning Objectives

- Cite The diagnostic criteria of cluster headache
- Describe the pathophysiology of cluster headache
- Summarize the various modes of treatment of cluster headache
- List the aspects of cluster headache that stand out from other primary headache disorders

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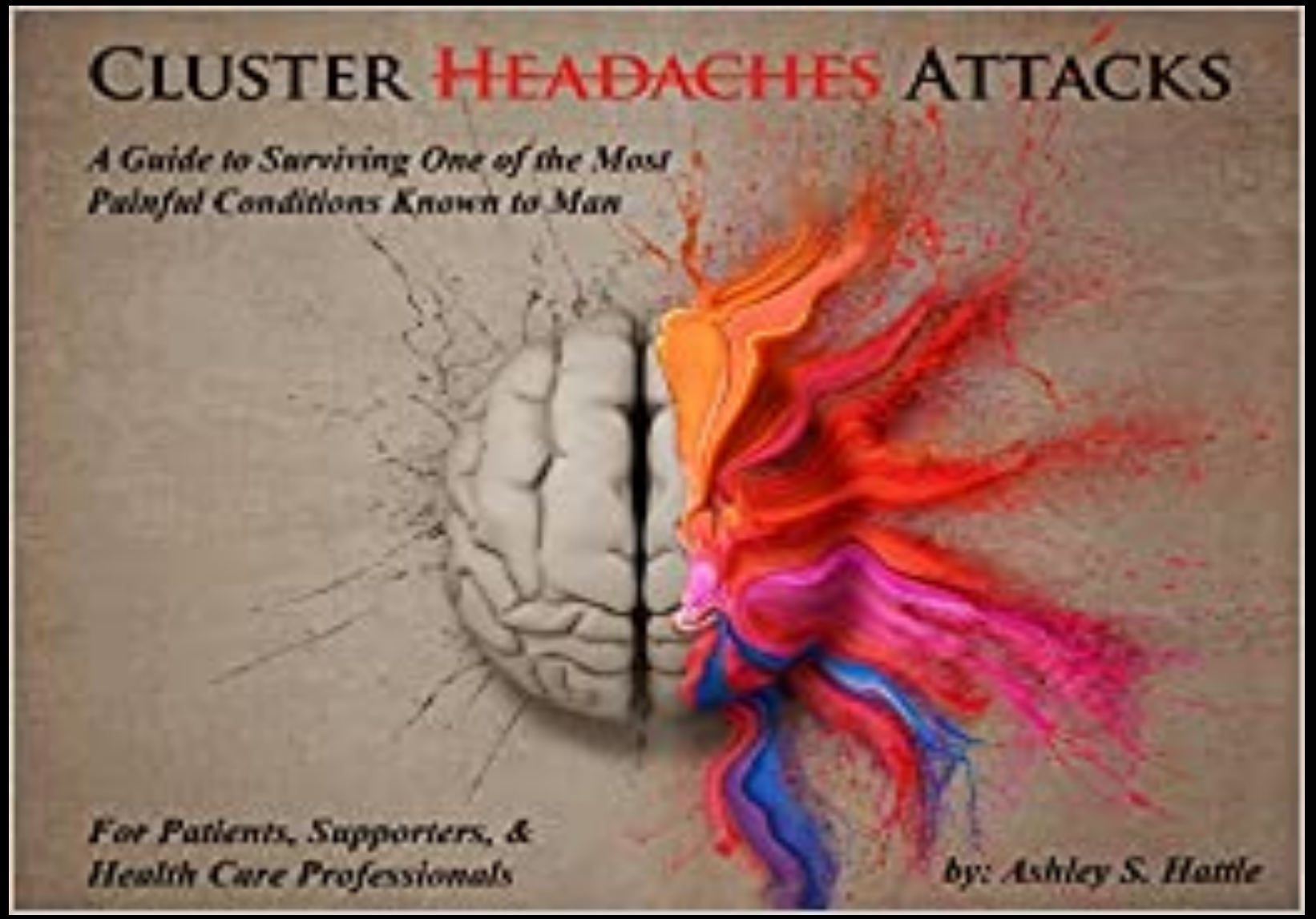
CLUSTER HEADACHES ATTACKS
A Guide to Surviving One of the Most Painful Conditions Known to Man
For Patients, Supporters, & Health Care Professionals
by: Ashley S. Hattle

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Prevalence

- 5 to 69 patients/100,000 people to 240-900/100,000 people=0.5-2 Mil Americans
- Diagnosis- average 6.6 years, with average 4.3 physicians, 3.9 incorrect DX
- Male predominance between 84% and 88% but changes, secondary to level of school education, smoking, employment rare, coffee and alcohol intake, M;F ratio fell from 6.2:1 before 1960 to 3.0:1 at onset of CH in 1990s
- Age of onset: between 20-40 YOA, peak between 25 and 30 YOA
- Rarely found in children between 7 and 14 YOA, then only in boys
- Can have onset of CH after 50 YOA, chronic CH more common in older patients
- Hypothesized autosomal dominant inherited disorder in some families: 3%-7% of CH patients have positive family hx
- Studies have reported CH patients have a greater incidence of smoking, drinking and illicit drug use than non-CH patients or controls

Kudrow L. Cluster headache: mechanisms and management. New York, NY: Oxford University Press; 1980; Klapper JA, Klapper A, Voss T. The misdiagnosis of cluster headache: a nonclinic, population-based, Internet survey. Headache. 2000;40(9):730–735; Rozen TD, Fishman RS. Cluster headache in the United States of America: demographics, clinical characteristics, triggers, suicidality, and personal burden.Headache. 2012;52(1):99–113;Manzoni GC. Gender ratio of cluster headache over the years: a possible role of changes in lifestyle. Cephalalgia. 1998;18(3):138–142;Arruda MA, Bonamico L, Stella C, Bordini CA, Bigal ME. Cluster headache in children and adolescents: ten years of follow-up in three pediatric cases. Cephalalgia.2011;31(13):1409–1414; Manzoni GC, Maffezzoni M, Lambru G, Lana S, Latte L, Torelli P. Late-onset cluster headache: some considerations about 73 cases. Neurol Sci. 2012;33(Suppl1):s157–s159; Russell MB, Andersson PG, Thomsen LL. Familial occurrence of cluster headache. J Neurol Neurosurg Psychiatry. 1995;58(3):341–343; Gaul C, Christmann N, Schröder D, et al. Differences in clinical characteristics and frequency of accompanying migraine features in episodic and chronic cluster headache. Cephalalgia. 2012;32(7):571–577; Zidverc-Trajkovic J, Podgorac A, Radojicic A, Sternic N Migraine-like accompanying features in patients with cluster headache. How important are they? Headache. 2013 Mar 27. [Epub ahead of print; Graham JR. Cluster headache. Headache. 1972;11(4):175–185. Rossi P, Allena M, Tassorelli C, et al. Illicit drug use in cluster headache patients and in the general population: a comparative cross-sectional survey. Cephalalgia.2012;32(14):1031–1040; Romberg MH. Lehrbuch der nervenkrankheiten des menschen. Berlin: Dunker; 1840:58–60.

United States Cluster Headache Survey: Summary of Results

- Significant diagnostic delay (average 5+ years- with only 21% getting correct diagnosis initially
- Suicidal ideation substantial, found in 55% of responders
- Most attacks occur between midnight and 3:00 am; the circadian periodicity of CH is present, but predominance may differ by country
- CH appeares to have a R side predominance
- Most common type of alcohol trigger in the United States is beer: also weather changes, and smells are common triggers
- Peptic ulcer is not highly prevalent in CH patients, but CH is associated with cardiac disease and Cerebrovascular disease- the majority of patients are heavy smokers, Pos. comorbidity with RLS
- CH extremely disabling, almost 20% lose jobs, and another 8% are out of work or on disability secondary to CH
- Survey on web, included 1,124 individuals, 816 M, 318 F

Rozen TD, Fishman RS. Cluster Headache in the United States of America: Demographics, Clinical Characteristics, Triggers, Suicidality, and Personal Burden. Headache 2012; 52(1):99-113.

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Clinical Features-1

- Romberg first described CH in 1840; Horton et al, in 1939 proposed the nosological entity Horton's Histaminic Cephalgia secondary to possible relationship to histamine; Kunkle named the disorder Cluster Headache.
- CH patients may have emotional prodrome: euphoria or hypomania, days or weeks prior to CH episode
  - The HA may start with unilateral or bilateral cervical pressure
  - Patients may report warmth over the ipsilateral temporal region for minutes prior to the CH
    - The ipsilateral eye or temple may develop mild pain and it may be associated with nasal stuffiness
    - As the pain increases, settles behind the eye or temple, it may become throbbing with increasing intensity possibly associated with stabbing pain in the temple, teeth or face
    - A clear discharge may begin from previously "stuffed nostril"

Jay GW, Barkin RL. Primary Headache Disorders Part I- Migraine and the Trigeminal Autonomic Cephalalgias. Disease a Month 2017;63: 308-338; Romberg MH. Lehrbuch der nervenkrankheiten des menschen. Berlin: Dunker; 1840:58–6Kunkle EC, Pfeiffer Jr JB, Wilhoit WM, Hamrick Jr LW. Recurrent brief headaches in cluster pattern. NC Med J. 1954;15(10):510–512; Horton BT, MacLean AR, Craig WM. A new syndrome of vascular headache: results of treatment with histamine: preliminary report. Mayo Clin Proc. 1939;14:257–26

Clinical Features-2

- CH patients do have ANS signs including ipsilateral lacrimation, conjunctival injection, ptosis and miosis, hyperhidrosis (partial Horner's syndrome)
- From all over the country, patients with CH describe the pain to the author the same way: it feels like " there is someone in my head, behind my eye, trying to push my eye out with a hot poker"
- The Physical appearance of the CH patient has been, over time, described as "leonine"
  - Patients appear to have a particularly masculine physiognomy and physique
  - Facial features include thick, course skin, peau d'orange, extreme wrinkling of forehead and face with deep furrows
  - Freitag noted that the "tall rugged male types frequently may be seen with a diminutive wife who, between she and her husband, has the dominant personality, frequently answering questions for the patient"
  - Female CH patients also tend to develop a "masculine" appearance with very creased or furrowed square faces

Jay GW, Barkin RL. Primary Headache Disorders Part I- Migraine and the Trigeminal Autonomic Cephalalgias. Disease a Month 2017;63: 308-338; Graham JR. Cluster headache. Headache. 1972;11(4):175–185; Freitag R. Cluster Headache. GW Jay, ed. Clinician's guide to chronic headache and facial pain. New York, NY: Informa Healthcare; 2009:76–95; Olesen J, Goadsby P, eds. Cluster headache and related conditions. eds. New York, NY: Oxford University
Press; 1999:23–26; Graham JR. Some clinical and theoretical aspects of cluster headache. In: Saxena PR, ed. Migraine and related headaches. Rotterdam; The Netherlands: Erasmus Universiteit; 1975:27–40.

The Headache Pattern-1

- Patients average 1-3 headaches/day, but this can range from 1-10/day
- Each HA has a duration of 45-180 minutes
  - If longer than 3 hours, must re-evaluate the diagnosis
- Peak intensity within a minute, while the pain may last from 10-60 minutes without gradually decreasing
- CH attacks frequently occur after working hours, most commonly 90-120 minutes after falling asleep, during the first assumed REM stage of sleep
- CH is seen over the oculofrontal or oculotemporal regions, unilaterally and is side locked- it does not switch sides
- Possible association with CH and OSA (if OSA treated, CH may improve)

Jay GW, Barkin RL. Primary Headache Disorders Part I- Migraine and the Trigeminal Autonomic Cephalalgias. Disease a Month 2017;63: 308-338; Jay GJ. Cluster headache. In: Jay GW, ed. The headache handbook: diagnosis and treatment. Boca Raton, FL: CRC Press; 1999:33–44; Barloese M, Jennum P, Knudsen S, Jensen R. Cluster headache and sleep, is there a connection? A review. Cephalalgia. 2012;32(6):481–491; Bender SD. Topical review: cluster headache and sleep-related breathing disorders. J Orofac Pain. 2011;25(4):291–297.

Headache Pattern-2

- CH period frequency appears to be related to seasonal photoperiod changes (length of daylight) with the cluster periods increasing during the shortening or lengthening photoperiods
- Commonly, Cluster periods peak within 2 weeks following the shortest and longest days of the year (in July and January) and decrease within 2 weeks after daylight savings and standard time changes
- CH may be provoked by vasodilators: alcohol, histamine, nitroglycerin
- Changes to a patient's sleep/wake (diurnal cycle) and extreme stress may trigger a cluster cycle
- During an attack, CH patient may pace the floors, become agitated to point of violence
  - They may strike their heads into a wall or strike the wall with their fists
  - Some may be driven to suicide by the pain, as well as the fear of future attacks that they can anticipate almost to the minute
- **Circadian rhythms** are generated by the suprachiasmatic nucleus (SCN) located within the hypothalamus of the **brain**
- **Headaches frequently occur same time daily during episode**

Jay GW, Barkin RL. Primary Headache Disorders Part I- Migraine and the Trigeminal Autonomic Cephalalgias. Disease a Month 2017;63: 308-338;

Classification of CH

- CH is the most recognized TAC
- 2 forms:
  - Episodic – most common form, 80% of patients; 1-5 mos., ave. 3 mos.
    - Remission- 6-24 mos., ave. 12 mos.; may have occasional CH during remission
  - Chronic (primary and secondary)- 10% of cases, rate varying between 5% and 22% in different series
  - Evolution from episodic to chronic HA increase in patients with onset at older age, esp. in Females: also in patients with 4 or more accompanying symptoms, mostly in men: Cluster period lasting more than 8 weeks; remission lasting less than 6 mos., cluster period having a higher frequency with sporadic CH
- Secondary Cluster Headache (next slide)

Jay GW, Barkin RL. Primary Headache Disorders Part I- Migraine and the Trigeminal Autonomic Cephalalgias. Disease a Month 2017;63: 308-338; Rasmussen BK. Epidemiology of cluster headache. In: Olesen J, Goadsby P, eds. Cluster headache and related conditions. (eds) Oxford University Press; 1999:23–26; Torelli P, Manzoni GC. What predicts evolution from episodic to chronic cluster headache? Curr Pain Headache Rep. 2002;6(1):65–70.

Secondary Cluster Headache

- Differential Diagnosis
  - Intracranial large artery aneurysms
  - Meningiomas
  - Brain arteriovenous malformations
  - Pituitary macroadenomas
  - Recurrent nasopharyngeal carcinoma
  - Metallic foreign body in the maxillary sinus
  - Aspergilloma in sphenoid sinus
  - Benign posterior fossa tumor

  Cavernous hemangioma
- With improvement post treatment of above: suggest Screening MRI of CH patients

Favier L, van Vliet JA, Roon KI, et al. Trigeminal autonomic cephalgias due to structural lesions: a review of 31 cases. Arch neurol 2007;:64:25

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ICHD III Diagnostic Criteria for Cluster Headache (International Classification of Headache Disorders)

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
        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
    B. A sense of restlessness or agitation
D. Attacks have a frequency between one every other dayt and 8 per day for more than half of the time when the disorder is active
E. . No better accounted for by another ICHD-3 diagnosis

Diagnosis

- Dx via thorough history and neurological examination
- If “CH” treated correctly but doesn’t help, question diagnosis
- Don’t use facial thermography to look for “cold spot” in the ipsilateral supraorbital region of the forehead- not needed
- MRI with/wo good idea when first diagnosed

Jay GW, Barkin RL. Primary Headache Disorders Part I- Migraine and the Trigeminal Autonomic Cephalalgias. Disease a Month 2017;63: 308-338; Klasser GD. Trigeminal autonomic cephalalgias. In: Jay GW, ed. Clinician's guide to chronic headache and facial pain. New York, NY: Informa Healthcare;
2009:96–117; Leone M, Proietti Cecchini AS, Franzini A, Messina G, Bussone G. From neuroimaging to patients' bench: what we have learnt from trigemino-autonomic pain syndromes. Neurol Sci. 2012;33(Suppl 1):s99–s102.

Major Clinical Features

- Predominantly found in men
- Severe or very severe pain
- Short duration (15-180 min, ave. 45-60 min)
- Clustering of attacks (1-10/day, 6-12 weeks ave)
- Unilateral pain in the orbital, supraorbital and temporal areas
- Headache accompanied by:
  - Ipsilateral tearing
  - Ipsilateral nasal congestion and/or runny nose
  - Ipsilateral eyelid swelling
  - Ipsilateral forehead or facial sweating
  - Ipsilateral miosis and/or ptosis (may be found on interictal examination)
- Patient extremely agitated and restless

Jay GW, Barkin RL. Primary Headache Disorders Part I- Migraine and the Trigeminal Autonomic Cephalalgias. Disease a Month 2017;63: 308-338; Jay GW. Cluster headache. Pr Pain Manag. 2013;13(6):55–

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Pathophysiology-1

- Pathways of CH may involve Cranial Nerves V, VIII, IX, and X
  - Changes in these nerves may induce the associated signs and symptoms of CH
- These changes can include hypothalamic dysfunction that can induce the chronobiological abnormalities
  - Leading to impaired sympathetic and parasympathetic activity
  - Decreases in autoregulatory function in vasomotor regulation
  - Chemoreceptor responses to hypoxemia
- Sustained hypoxemia, secondary to decreased carotid body activity can create the pathophysiological milieu needed for the cluster attack
- Hypothalamic activation, as seen on PET scanning, indicates an increase in regional cerebral blood flow during CH
- Other studies indicated that the hypothalamic activation in CH appears specific to CH
- Goadsby noted a difference in the structure of the hypothalamus specific to CH patients

Jay GW, Barkin RL. Primary Headache Disorders Part I- Migraine and the Trigeminal Autonomic Cephalalgias. Disease a Month 2017;63: 308-338;
A, Bahra A, Buchel C, Frakowiak RS, Goadsby PJ. Hypothalamic activation in cluster headache attacks. Lancet. 1998;352(9124):275–278; Morrow TJ, Koeppe RA, Casey KI. Involvement of the insular cortex in central autonomic regulation during painful thermal stimulation. J Cereb Blood Flow. 1995;15(Suppl 1):859;
Goadsby PJ, Edvinsson L. Human in vivo evidence for trigeminovascular activation in cluster headache. Neuropeptide changes and effects of acute attack therapies. Brain. 1994;117(pt 3):427–434;
2 10. Goadsby PJ. Current concepts of the pathophysiology of migraine. Neurol Clin. 1997;15(1):27–42

Pathophysiology-2

- Generalized hyperfunctioning of pain pathways in CH (lower cerebral blood flow was found to be lower in the contralateral primary sensory region and thalamic regions)
- The pattern of cerebral activation was changed in CH during the interictal period on the ipsilateral side to the HA, changing the central tonic pain mechanisms
- Gi proteins, which help modulate pain perception, are found to be decreased in the lymphocytes of migraine and CH patients, possibly representing a biological mechanism for cell hyperexcitability in primary headache disorders
- During an active Cluster cycle, neuroendocrine changes, including decreased plasma testosterone and luteinizing hormone, is seen in CH patients
  - Possibly secondary to a change in the HPA axis
  - Decreased response to thyrotropin-releasing hormone is also seen in CH patients
  - A change or loss of circadian rhythmicity of neuroendocrine substances has been seen, to include decreased melatonin levels during the night throughout active cluster periods
  - Also noted- during cluster periods- loss of normal circadian rhythms for blood pressure and temperature, beta-endorphins and plasma cortisol

Jay GW, Barkin RL. Primary Headache Disorders Part I- Migraine and the Trigeminal Autonomic Cephalalgias. Disease a Month 2017;63: 308-338; Di Piero V, Fiacco F, Tombari D, Pantano P. Tonic pain: a SPET study in normal subjects and cluster headache patients. Pain. 1997;70(2-3):185; Galeotti N, Ghelardini C, Zoppi M, et al. Hypofunctionality of Gi proteins as aetiopathogenic mechanism for migraine and cluster headache. Cephalalgia.2001;21(1):38–45.

Pathophysiology-3

- Neurochemical changes with CH:
  - Histamine was thought to be a mediator of CH, but still large debate
  - SP, CGRP, VIP- all may induce a rostral spread of nociception to the trigeminal nerve
  - Can get alleviation of CH attack with somatostatin- a SP inhibitor
  - Levels of CGRP, a marker of activation of the trigeminal pathway, are noted to be markedly increased during spontaneous CH and during CH induced by use of nitroglycerin
  - Use of O_2 and SQ sumatriptan normalizes the level of CGRP
  - Vasoactive intestinal polypeptide (VIP) is a marker of parasympathetic activity and its ictal increase was noted
  - Decreased plasma methionine-enkephalin is seen
  - Patients found to have higher levels of BDNF (associated with pain modulation and central sensitization)- found inside and outside of cluster episodes
    - It interacts with CGRP

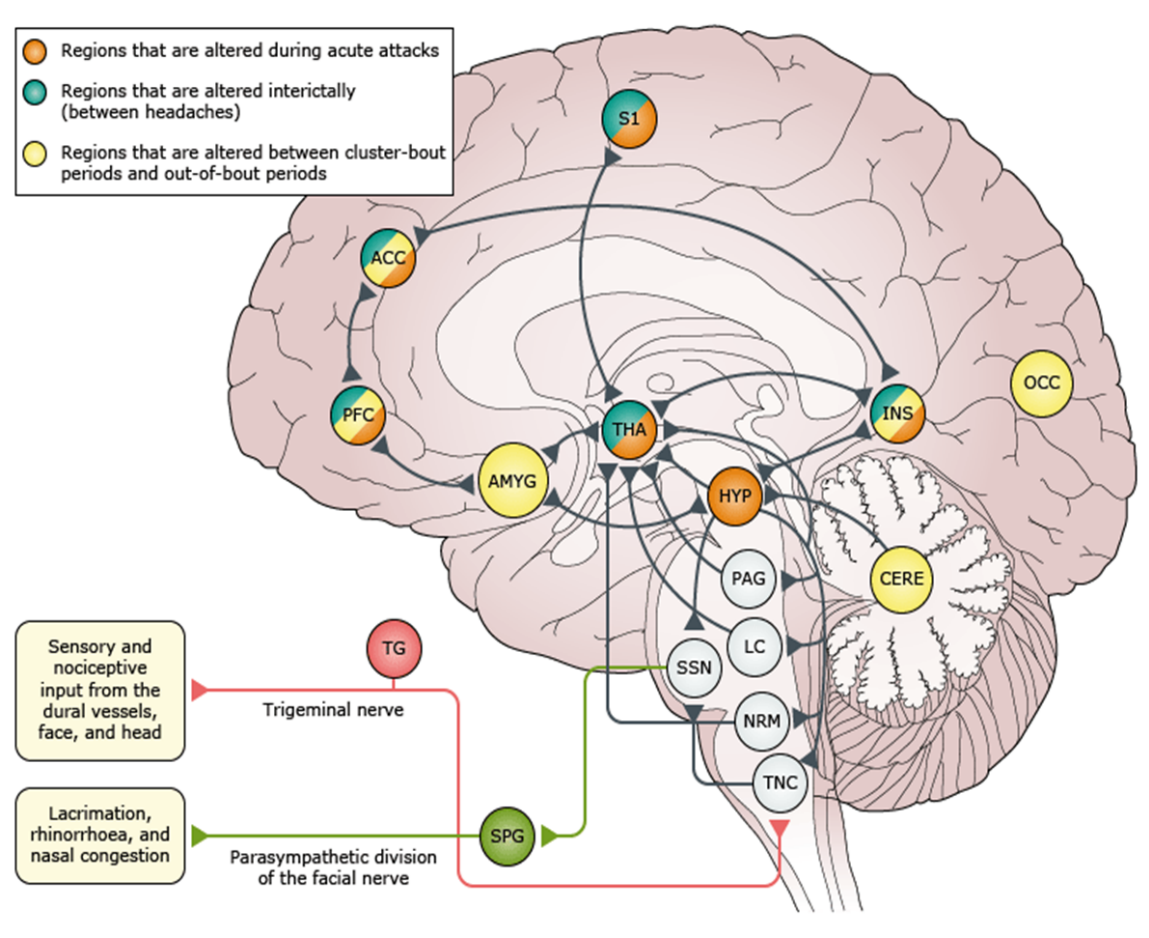
Jay GW, Barkin RL. Primary Headache Disorders Part I- Migraine and the Trigeminal Autonomic Cephalalgias. Disease a Month 2017;63: 308-338; Goadsby PJ, Edvinsson L, Ekman R. Release of vasoactive peptides in the extracerebral circulation of humans and the cat during activation of the trigeminovascular system. Ann Neurol. 1988;23(2):193–196; Fanciullacci M, Alessandri M, Figini M, Geppetti P, Michelacci S. Increases in plasma calcitonin gene-related peptide from extracerebral circulation during nitroglycerin-induced cluster attack. Pain. 1995;60(2):119–123; Treatment of acute cluster headache with sumatriptan. The Sumatriptan Cluster Headache Study Group. N Engl J Med; 1991. 325(5):322–326; Mosnaim AD, Maturana P, Puente J, Wolf ME. Decreased plasma methionine-enkephalin levels in cluster headache patients. Am J Ther. 2012;19(3):174–179; Fischer M, Wille G, Klien S, et al. Brain-derived neurotrophic factor in primary headaches. J Headache Pain. 2012;13(6):469–475; Steinberg A, Sjostrand C, Sominanda A, Fogdell-Hahn A, Remahl AI. Interleukin-2 gene expression in different phases of episodic cluster HA—a pilot study. Acta Neurol Scand. 2011;124(2):130–134.

Pathophysiology-4

- Sympathetic NS Hypofunction is noted and appears to be countered by parasympathetic hyperfunction during CH
- Efferent impulses from the greater superficial petrosal nerves (which originate in the parasympathetic nuclei in the hypothalamus) may induce CH.
- Excessive release of acetylcholine from the parasympathetic nerve terminals could stimulate histamine from mast cells, and this, along with other neurochemical pain mediators and pro-inflammatory cytokines (Il-1) would stimulator nociceptors directly leading to increased pain, the release of SP, inducing more pain, inflammation and histamine release
- Studies using diffusion tensor imaging found that patients with episodic CH have microstructural brain changes in regions in the pain matrix
  - Microstructural changes in the bilateral brainstem white matter, the frontal lobe, the temporal lobe, the occipital lobe, the internal capsule and the right side of the thalamus and cerebellum
  - Changes in grey matter volume was found in the right thalamus, the head of the right caudate nucleus, the right precentral gyrus, the right posterior cingulate cortex the bilateral middle frontal gyrus, the left inferior parietal lobule and the left insula
  - Decreased left middle frontal gyrus volume was felt to be secondary to duration of the disease

Jay GW, Barkin RL. Primary Headache Disorders Part I- Migraine and the Trigeminal Autonomic Cephalalgias. Disease a Month 2017;63: 308-338; Menzler K, Belke M, et al. Diffusion tensor imaging in episodic cluster headache. Headache. 2012;52(2):274–282; Seifert CL, Magon S, Staehle K, et al. A case-controlled study on cortical thickness in episodic cluster headache. Headache. 2012;52(9):1362–1368; Absinta M, Rocca MA, Colombo B, Falini A, Comi G, Filippi M. Selectiv decreased grey matter volume of the pain-matrix network in cluster headache. Cephalalgia. 2012;32(2):109–115; Iacovelli E, Coppola G, Tinelli E, Pierelli F, Bianco F. Neuroimaging in cluster headache and other trigeminal autonomic cephalalgias. J Headache Pain. 2012;13(1):11–20

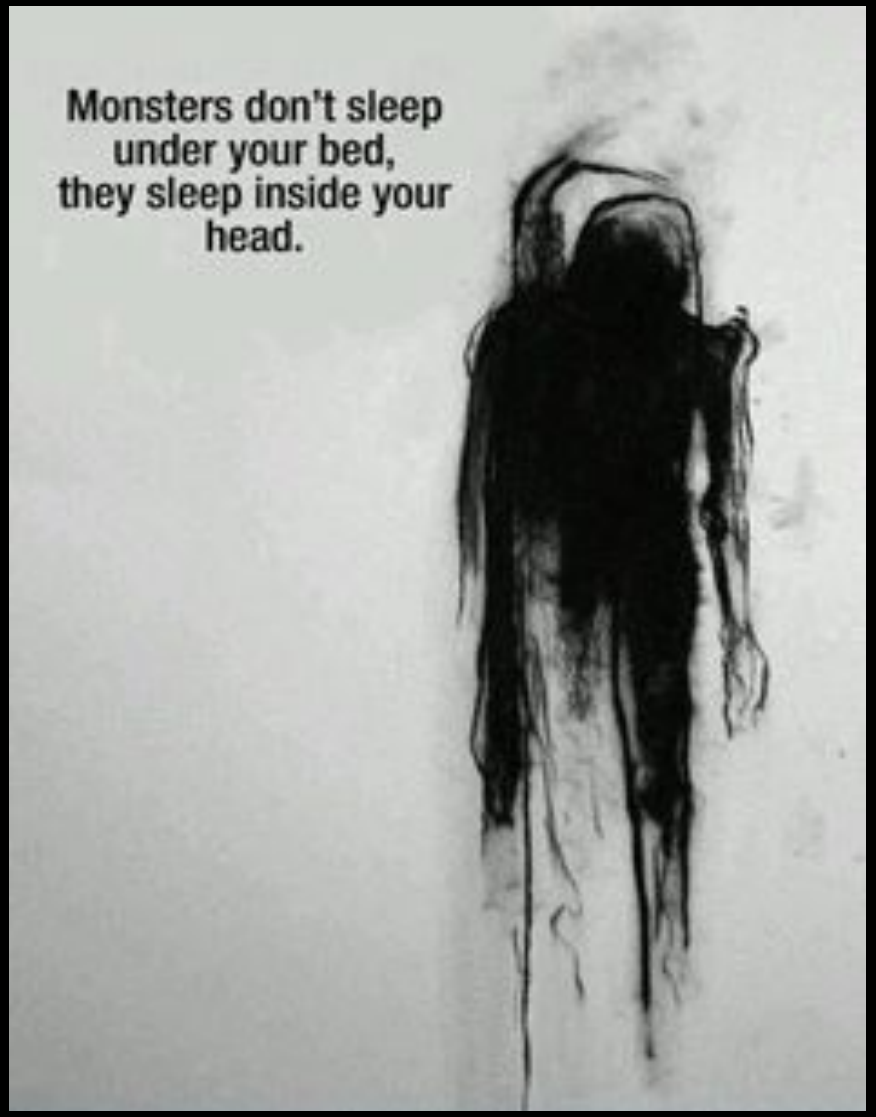
Pathophysiology-5



- Schematic peripheral and central pathway representation summarizing the pathogenesis of cluster headache. Pain and autonomic features in cluster headache probably arise from activation of peripheral structures, such as the trigeminovascular system. The pathophysiology initially involves structural and functional changes in the hypothalamus and specific brain networks that transmit nociceptive input, and these functional changes can differ between cluster-bout and out-of-bout periods. In addition, anatomical and functional links between the hypothalamus and brain areas that are traditionally not considered to be involved in pain processing (such as the occipital cortex and cerebellum) are altered in cluster headache and may have contributory roles in its pathophysiology.

- S1: primary sensory cortex; ACC: anterior cingulate cortex; OCC: occipital cortex; PFC: prefrontal cortex; THA: thalamus; INS: insular cortex; AMYG: amygdala; HYP: hypothalamus; PAG: periaqueductal grey; CERE: cerebellum; LC: locus coeruleus; TG: trigeminal ganglion; SSN: superior salivatory nucleus; NRM: nucleus raphe magnus; TNC: trigeminal nucleus caudalis; SPG: sphenopalatine ganglion.

- Macmillan Publishers Ltd: Nature Reviews Disease Primers. May A, Schwedt TJ, Magis D, et al. Cluster headache. Nat Rev Dis Primers 2018; 4:18006. Copyright © 2018. https://www.nature.com/nrdp/.



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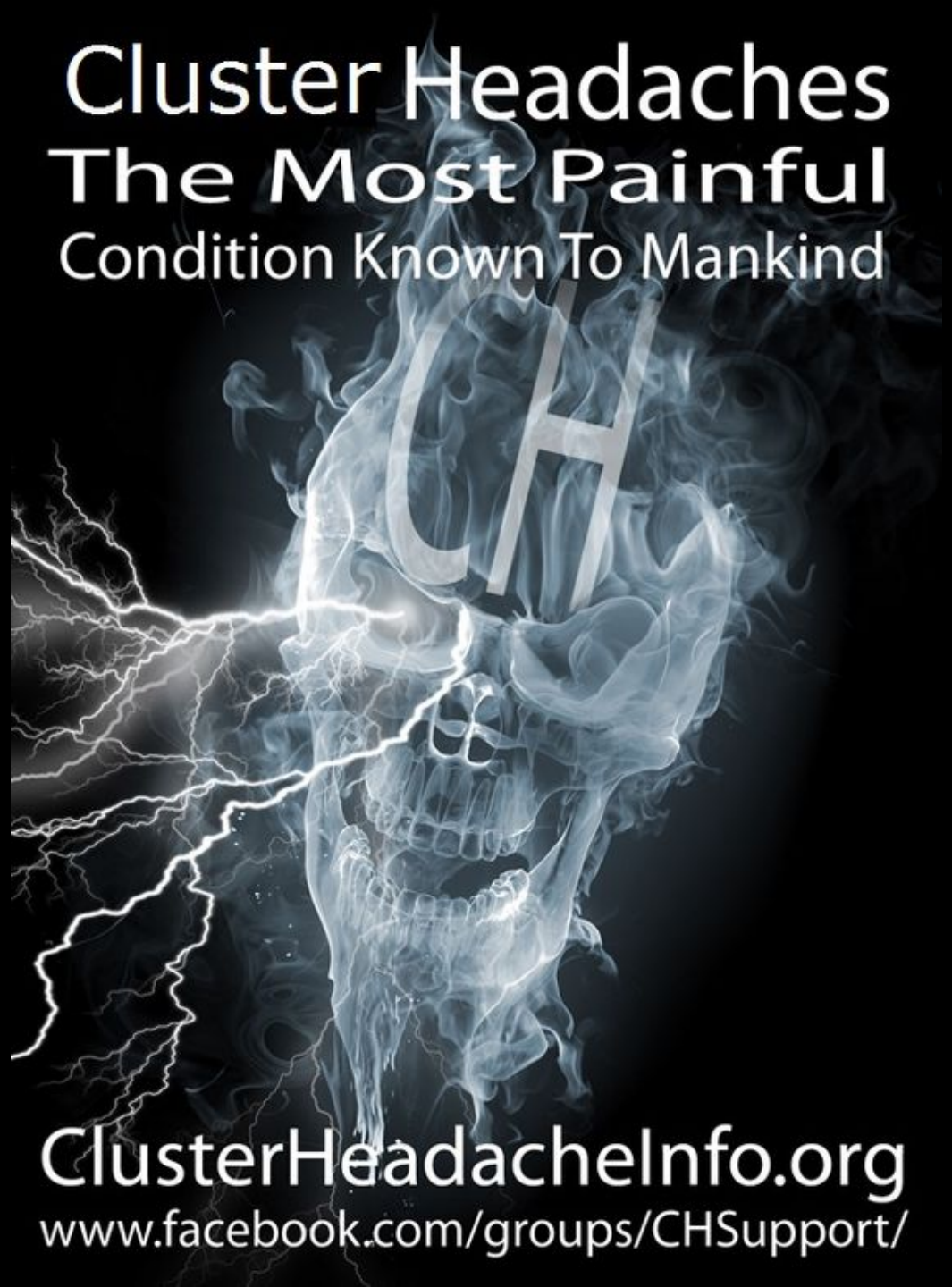

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Treatment-1

- Medication Management
- Interventionally
- Surgically

Medication-1

- Episodic CH- abortive
  - Oxygen
    - 100% O_2 via face mask at 12 Liter/min over 15 min can abort CH in about 15 min
      - Causes a decrease in cerebral blood flow
    - Clinical suspicion of oxygen overuse headache
    - Clumsy, large tank in bedroom, small tank taken out- dealing with medical
    - Medicare, most insurers won't cover it
  - Triptans
    - Sumatriptan considered first line abortive agent, I use rizatriptan
      - Evans et al found sumatriptan may inhibit TRPV1 ion channels in trigeminal neurons
      - Triptans also decrease CGRP
      - New study (Giana et al) notes sumatriptan doesn't always work- non-responders had longer and more frequent attacks- this group may not have $5HT_{1B/1D}$ involved, but other pain mechanisms
    - IN Sumatriptan or Zolmitriptan is also first line

Schoenen J. Deficient habituation of evoked cortical potentials in migraine: a link between brain biology, behavior and trigeminovascular activation? Biomed Pharmacother. 1996;50(2):71–78; Law S, Derry S, Moore RA. Triptans for acute cluster headache. Cochrane Database Syst Rev. 2010;14(4); Cittadini E, May A, Straube A, Evers S, Bussone G, Goadsby PJ. Effectiveness of intranasal zolmitriptan in acute cluster headache: a randomized, placebo controlled, double blind crossover study. Arch Neurol. 2006;63(11):1537–154 2 Evans MS, Cheng X, Jeffry JA, Disney KE, Premkumar LS. Sumatriptan inhibits TRPV1 channels in trigeminal neurons. Headache. 2012;52(5):773–784; Giani L, Cecchini AP, Astengo A, ety al. Cluster headache not responsive to sumatriptan: a retrospective study. Cephalalgia 2020; dow: 10.1177/0333102420956705 Online ahead of print. Accessed Sept. 19, 2020.

Medication-2

- Use a triptan at bedtime to abort the typical CH that occurs 90-120 min after sleep, presumed to be the first REM stage of sleep
  - 2 DHE IN Sprays or an oral triptan immediately before sleep will enable the medication to reach a peak plasma level and typically abort this HA
  - A Rapidly active DHE-45 preparation given IN is also good
  - DO NOT USE A DHE PREPARATION WITHIN 24 HOURS OF A TRIPTAN
- Intranasal butorphanol (mixed opioid agonist/antagonist)- works at kappa opioid receptor, also effective abortive agent, but must be used to avoid rebound headaches
  - This medication may cause a burning feeling in the sinuses- “weird feelings” and dysphoria, may have hallucinations- high addiction potential; may dilute to 50% without loss in stability

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Medication-3

- For Episodic CH and Chronic CH- Prophylaxis
  - You should know when the cluster cycle starts and ends (duration)- for episodic CH
  - See patient a month before the start and wean up on prophylactic medications
    - Verapamil 120 BID
      - May need 2 weeks to be affective at does 240-350 mg/day in Episodic CH; up to 4-5 weeks in Chronic CH ave. dose 572 mg/day in divided doses
      - May be associated with cardiac arrhythmias in CH patients so need baseline ECG
      - Nimodipine (another Ca Channel blocker) may be useful at 120 mg/day
    - Lithium carbonate 300 TID
      - May be used as single drug and then verapamil may be added if needed- the author starts with verapamil
      - Works in hypothalamus in region of the suprachiasmatic nucleus, helping to restore chronobiologic homeostasis
      - Does have serotonergic properties

Jay GW, Barkin RL. Primary Headache Disorders Part I- Migraine and the Trigeminal Autonomic Cephalalgias. Disease a Month 2017;63: 308-338;
Cohen AS, Matharu MS, Goadsby PJ. Electrocardiographic abnormalities in patients with cluster headache on verapamil therapy. Neurology.
2007;69(7):668–675

Medication-4

- And if needed, valproate sodium 500 -1000 mg/day
  - Alone or with ergots, possibly lithium for CH prophylaxis
  - May be more effective in patients with CH that have migraine like features: nausea, vomiting, photphonophobia
  - Black box warning- don't use in women of childbearing age/ability
  - May use topiramate 100-200 mg/day
    - SE- cognitive slowing
- Wean off of medications after end of cycle
- Patient may also use abortives for breakthrough CH

- If patient seen in middle of cluster episode, use prednisone, an 80 mg/day, weaning down to 0 in ten days- start prophylactics during this time
  - May use methylergonovine for prevention of CH, acts as an ergot preparation
    - Take patients off drug in 3-6 mos. as AE of retroperitoneal fibrosis and fibrotic changes in the lungs and heart valves may occur
  - Baclofen may be used as a preventative (15-30 mgs/day)- start low, increase slowly- wean off slowly

Jay GW, Barkin RL. Primary Headache Disorders Part I- Migraine and the Trigeminal Autonomic Cephalalgias. Disease a Month 2017;63: 308-338
FDA warns pregnant women to not use certain migraine prevention medicines. (https://migraine.com/?P=40098). Accessed 12/7/2016; Wheeler S, Carrazana EJ. Topiramate-treated cluster headache. Neurology. 1999;53(1):234–236; Lainez MJ, Pascual J, Santonja JM, et al. Topiramate in the prophylactic treatment of cluster headache. Cephalalgia. 2001;21:369.

Medication-5

- Cluster patients metabolize medications differently:
  - No rebound from a triptan QHS
  - No AEs from lithium carbonate 300 mg TID
    - While a bipolar patient at this dose may experience shakiness, dizziness, subjective cognitive changes

- In past, histamine desensitization used via IV histamine infusions of 5.5 mg of histamine phosphate for 24 h for 10 days
  - May be helpful in intractable CH, as well as those who no longer respond to verapamil or lithium carbonate

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Medications-6

- Galcanezumab-gnlm- 300 mg for episodic CH
  - Reduces number of weekly CH attacks (8.7 fewer CH attacks vs. 5.2 (PBO) over weeks 1-3)
  - Dosing: 300 mg at onset of cluster period and then monthly until end of cluster period (3 SQ injections of 100 mg)
  - Injection site reactions possible
- One study showed CGRP humanized antibodies effective for chronic CH in 55% of Chronic CH patients (off label)
- Not approved by European Medicines Agency as ? Significance of results

Emgality web site: emgality.com/cluster, assessed 9/19/2020; Giani L, Cecchini AP, Leone M. Anti-CGRP monoclonal antibodies in cluster headache: what can we learn from recent clinical trials. Neurological Sciences. Published online 26 August 2020. https://doi.org/10.1007/s10072-020-04668-z accessed Sept 19, 2020; Ruscheweyh R, Broessner G, GoBrau G, et al. Effect of calcitonin gene-related peptide (-receptor) antibodies in chronic cluster headache: Results from a retrospective case series support individual treatment attempts. Cephalalgia; acceped 9 July 2020; DOI: 10.1177/0333102420949866 Accessed Sept 14, 2020

Interventional-1

- Sphenopalatine ganglion block with 4% lidocaine applied by dropper or pledget to the SP Ganglion via ipsilateral nostril
  - Abortive- in past, used long pledget with cocaine (Codden)-
  - Patients can be taught to use themselves
- Sphenopalatine ganglion stimulation good for patient with chronic refractory CH
- Percutaneous radiofrequency lesioning of the ipsilateral gasserian (trigeminal) ganglion- does abolish corneal reflex, with 66% change of pain relief, lasts until corneal reflex recovers, over several years
- Sectioning of the nervus intermedius can lead to sterile inflammatory reactions secondary to parasympathetic discharges
- Retro-gasserian injection of glycerol
- Trigeminal root sectioning in posterior fossa- last resort
  - Risk of anesthesia dolorosa (painful numbness)

Bakbak B, Gedik S, Kiktekir BE, Okka M. Cluster headache with ptosis responsive to intranasal lidocaine application: a case report. J Med Case Rep. 2012;6:64; Jay GW, Barkin RL. Primary Headache Disorders Part I- Migraine and the Trigeminal Autonomic Cephalalgias. Disease a Month 2017;63: 308-338; Lainez MJA, Marti AS. Sphenopalatine ganglion stimulation in cluster headache and other types of headache. Cephalalgia. 2016;36(12):1149–1155; Taha JM, Tew Jr JM. Tong-term results of radiofrequency rhizotomy in the treatment of cluster headache. Headache. 1995;35(4):193–196; Mathew NT, Hurt W. Percutaneous radiofrequency trigeminal gangliorhizolysis in intractable cluster headache. Headache. 1988;28:328–331.

Interventional-2

- Other neurostimulation for chronic CH include:
  - Occipital nerve stimulation
  - Greater occipital nerve injections
  - High cervical cord stimulation for chronic CH has been shown to decrease the mean attack frequency as well as mean intensity and duration of attacks
  - Microvascular decompression of the pterygopalatine ganglion in patients with refractory CCH did not provide pain relief

Wolter T, Kaube H. Neurostimulation for chronic cluster headache. Ther Adv Neurol Disord. 2012;5(3):175–180; Fontaine D, Christophe Sol J, Raoul S, et al. Treatment of refractory chronic cluster headache by chronic occipital nerve stimulation. Cephalalgia. 2011;31(10):1101–1105; Gantenbein AR, Lutz NJ, Riederer F, Sandor PS. Efficacy and safety of 121 injections of the greater occipital nerve in episodic and chronic cluster headache. Cephalalgia. 2012;32(8):630–634; Leroux E, Ducros A. occipital injections for trigemino-autonomic cephalalgias: evidence and uncertainties. Curr Pain Headache Rep. 2013;17(4):325; Wolter T, Kiemen A, Kaube H. High cervical spinal cord stimulation for chronic cluster headache. Cephalalgia. 2011;31(11):1170–1180; Oomen K, Av Wijck, Hordijk, Ru G, Microvascular JD. decompression of the pterygopalatine ganglion in patients with refractory cluster headache. Cephalalgia. 2011;31(11):1236–1239.

Surgical-1

- Electrodes placed in the posterior inferior hypothalamus
  - Good therapeutic value
  - Shoenen et al- after 4 years, the hypothalamic stimulation was helpful in most but not all patients with treatment resistant chronic CH
    - Another group found the same
  - Case report found that secondary chronic CH was treated well by hypothalamic stimulation in a drug-refractory patient with a 2-year follow-up

Leone M, Franzini A, D'Amico D, et al. Intractable chronic cluster headache relieved by electrode implant to posterior inferior hypothalamus. Cephalalgia. 2001;21:503; Schoenen J, Di Clemente L, Vandenheede M, et al. Hypothalamic stimulation in chronic cluster headache: a pilot study of efficacy and mode of action. Brain.2005;128(pt 4):940–947; Starr PA, Barbaro NM, Raskin NH, Ostrem JL. Chronic stimulation of the posterior hypothalamic region for cluster headache: technique and 1-year results in four patients. J Neurosurg. 2007;106(6):999–1005; Messina G, Rizzi M, Cordella R, et al. Secondary chronic cluster headache treated by posterior hypothalamic deep brain stimulation: first reported case. Cephalalgia. 2013;33(2):136–138.


Cluster Headache
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Just One
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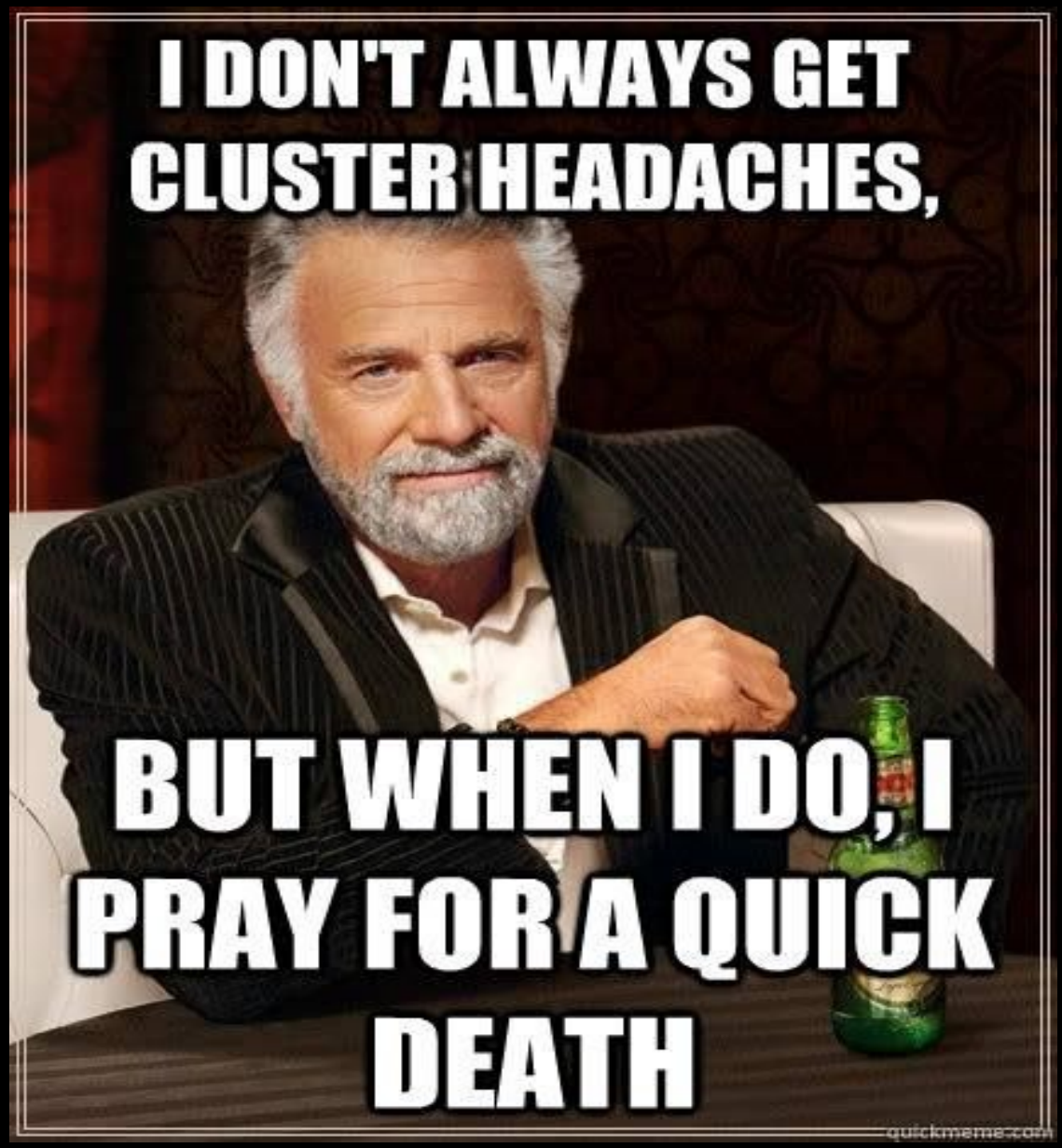

Pinterest.com

Other Trigeminal Autonomic Cephalalgias (TACs)

Paroxysmal Hemicrania-1

A. At least 20 attacks fulfilling criteria B-E
B. Severe unilateral and/or temporal pain lasting 2-30 min
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 rhinorrhoea
    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

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Paroxysmal Hemicrania-2

D. Attacks have a frequency of more than 5/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 diagnosis

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Hemicrania Continua-1

A. Unilateral headache fulfilling criteria B-D
B. Present for > 3 months, with exacerbation of moderate or greater intensity
C. Either or both of the following:
    1. At least one of the following symptoms or signs ipsilateral to the headache:
        a. Conjunctival injection and/or lacrimation
        b. Nasal congestion and/or rhinorrhoea
        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

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Hemicrania Continua-2

2. A sense of restlessness or agitation or aggravation of the pain by movement

D. Responds absolutely to therapeutic doses of indomethacin

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

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Short-lasting unilateral neuralgiform headache Attacks (with conjunctival injection and tearing/cranial autonomic symptoms (SUNA/SUNCT)-1

- At least 20 attacks fulfilling criteria B-D
- Moderate or severe unilateral head pain, with orbital, supraorbital, temporal and/or other trigeminal distribution lasting for 1-600 secs and occurring as single stabs, series of stabs or in a sawtooth pattern
- At least one of the following cranial autonomic symptoms or signs, ipsilateral to the pain:

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Short-lasting unilateral neuralgiform headache Attacks (with conjunctival injection and tearing/cranial autonomic symptoms (SUNA/SUNCT)-2

1. Conjunctival injection and/or lacrimation
2. Nasal congestion and/or rhinorrhoea
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

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Short-lasting unilateral neuralgiform headache Attacks (with conjunctival injection and tearing/cranial autonomic symptoms (SUNA/SUNCT)-3

- D. Attacks have a frequency of at least one a day for more than half the time when the disorder is active
- E. Not better accounted for by another ICHD-3 diagnosis

- Treatment-lamotrigine for most, may need topiramate and gabapentin- found to be useful
- May have up to 300 attacks an hour

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Pathophysiology-Hints

- All, per positron emission tomography (PET) and fMRI have shown areas of activation in the posterior hypothalamus
- Hypothalamic activation, keeping to the side of pain:
  - Cluster Headache- ipsilateral posterior hypothalamus
  - PH- contralateral hypothalamus
  - HC-contralateral hypothalamus and ipsilateral upper brainstem
  - SUNCT- ipsilateral hypothalamus
  - SUNA- absent in patients with extraocular autonomic phenomena

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