

TRIGEMINAL AUTONOMIC CEPHALALGIAS

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A. Trigeminal autonomic cephalalgias

Trigeminal autonomic cephalalgias (TACs) defined

- Headaches characterized by pain in a trigeminal nerve distribution, associated with ipsilateral cranial autonomic features
- As concerns cluster headache (CH), paroxysmal hemicrania (PH), and short-lasting unilateral neuralgiform headache attacks (SUNCT): As the names get longer, the attack duration gets shorter and the attack frequency increases (source: Dr. Larry Newman)
- HC and PH completely respond to indomethacin

TAC classification 2013

- Cluster headache
- Paroxysmal hemicrania
- Short-lasting unilateral neuralgiform headache attacks
 - SUNCT
 - SUNA
- Hemicrania continua
- Probable TAC

B. Cluster headache

Cluster Headache International Headache Society 2013 Diagnostic Criteria

- At least 5 attacks of severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15-180 min untreated
- Frequency between 1 qod and 8/day for > half of the time when the disorder is active
- Either or both of the following:
 - Associated with ≥ 1 of:
 - ipsilateral conjunctival injection and/or lacrimation
 - ipsilateral nasal congestion and/or rhinorrhea
 - ipsilateral eyelid edema
 - ipsilateral forehead and facial sweating
 - Ipsilateral forehead and facial flushing
 - ipsilateral sensation of fullness in the ear
 - ipsilateral miosis and/or ptosis
 - Sense of restlessness or agitation
- Not attributed to another disorder

Episodic cluster headache (ECH) criteria

- Attacks fulfilling criteria for cluster headache and occurring in bouts (cluster periods)
- ≥ 2 cluster periods lasting 7 days to 1 year (when untreated) and separated by pain-free remission periods of ≥ 1 month

Chronic cluster headache (CCH) criteria

- Attacks fulfilling criteria for cluster headache and criterion below
- Occurring without a remission period, or with remissions lasting < 1 month, for ≥ 1 year

Cluster headache background

- Dutch physician Nicolaas Tulp (changed surname from Pieterszoon after tulips on facade of house) gave incomplete description in 1641 (? Exact duration, no clear clustering, no auto, not clearly unilateral)
- Probably first described by Austrian (initially Dutch) physician Gerhard van Swieten in 1745
 - Mentioned severity, unilaterality, short duration, ipsi autonomic features
 - Patient “cured” by Peruvian bark (quinine)--histamine of the past?
- Wilfred Harris and Bayard Horton largely made this disorder known to the medical world
- Kunkle proposed the term cluster headache in 1952, and it was widely accepted

Cluster headache epidemiology

- Prevalence 69-240 per 100,000 (rough estimate 0.1%)
- Incidence in Olmsted County 9.8 per 100,000 person-years
- M:F 2.5-7:1
- Usual onset in 20s-40s

Cluster headache clinical features

- Usually retro-orbital and temporal
- Can involve face or be extra-trigeminal
- Unilateral: 18% side shift within bout, 18% side shift between bouts, 1% side shift within attack
- Quality severe; boring, piercing, stabbing, tearing, burning, throbbing (less frequently)
- Attacks early and late in bout may be less severe
- Abrupt onset and cessation
- Interictal pain or discomfort sometimes present
- Tobacco use common; alcohol usage higher in CH patients vs. controls

Cluster headache autonomic symptoms

- Lacrimation (91%)
- Conjunctival injection (77%)
- Nasal congestion (75%)
- Ptosis or eyelid swelling (74%)
- Rhinorrhea (72%)
- May have partial Horner's syndrome that persists after frequent attacks

Cluster headache clinical features

- Restlessness or no exacerbation with movement (93%)
- Nausea (50%)
- Vomiting (23%)
- Photophobia (56%)--can be unilateral
- Phonophobia (43%)--can be unilateral
- Osmophobia (26%)
- Aura (14%)--mostly visual, 36% of these also had migraine

Cluster headache duration and frequency

- Individual attacks often last 1-2 hours
 - Average attack duration in Kudrow's series of 500 patients was 64 minutes
 - Bahra et al reported mean maximum attack duration of 159 min, mean minimum attack duration 72 minutes in a large review of 230 cluster headache patients
- Attack frequency usually 1-2 per 24 hours
 - Average attack frequency in 24 hours was 1 in Manzoni et al's study of 180 patients
 - Bahra et al reported a mean maximum # of attacks per 24 hours of 4-5
- Most patients report diurnal rhythmicity
 - Most common reported hour for attacks to occur in Barloese et al Danish study was 2 am

Annual rhythmicity

- 56% of patients reported annual rhythmicity in Barloese et al Danish study
 - The month during which cluster bouts (episodic cluster headache) or worsening of attacks (chronic cluster headache) was least likely to occur was June; November was the month when most patients reported cluster bouts or worsening of attacks
 - The fewer the number of daylight hours/month, the more likely that cluster bouts will occur that month
 - Longer days (June is the month with the highest number of daylight hours in Denmark) prevent penetration of cluster bouts
- In episodic cluster headache patients, Kudrow noted cluster bout peaks in winter and summer, Bahra spring and fall
- Bouts often last 1-2 months and occur 1-2 times per year
- Bahra noted that most patients had one bout per year, mean bout duration 8.6 weeks, longest remission period 20 years

Tip on episodic cluster headache diagnosis

- Patients with episodic CH typically have 1-2-hour-long, unilateral, severe attacks of pain associated with cranial autonomic features that recur 1-2 times per day in bouts lasting 1-2 months, with these bouts recurring 1-2 times per year
 - Attacks often occur at 1-2 am

Cluster headache triggers

- Alcohol
- Nitroglycerin
- Sildenafil
- Histamine
- Exercise
- Elevated environmental temperature
- Sleep apnea

Cluster headache natural history

- Evidence suggests that it is a lifelong disorder
- Most ECH patients remain episodic
- ~10% go from ECH to CCH
- ~30% go from CCH to ECH
- Some patients develop longer remission periods as they age

Cluster headache unusual

- Absence of autonomic features (3%)
- Autonomic symptoms without headache
- Persistent or unremitting cluster headache
 - severe unilateral headache present at all times plus attacks of pain exacerbation with cranial autonomic features
- Periodic or intermittent cluster headache
 - single attacks occur once a month or year
- Hemiplegic cluster headache
- Valsalva-induced cluster headache
- Cluster triggered by viewing television
- Bouts triggered by long-acting nitrates; remission of angina during cluster periods

Secondary cluster headache

- Vascular
 - carotid dissection or aneurysm
 - vertebral art dissection or aneurysm
 - ACOM aneurysm

- intracranial AVMs
- scalp AVM
- cervical cord infarct
- lateral medullary infarct
- frontotemporal subdural hematoma
- Post trauma or surgery
 - facial trauma
 - post enucleation
- Dental
 - impacted wisdom tooth
 - following dental extraction
- Tumors
 - prolactinoma
 - pituitary adenoma
 - parasellar/sphenoidal/tentorial/high cervical meningiomas
 - prepontine epidermoid
 - nasopharyngeal carcinoma
 - metastatic lung carcinoma
 - pheochromocytoma
- Infectious
 - maxillary sinusitis
 - orbito-sphenoidal aspergillosis
 - herpes zoster ophthalmicus
- Inflammatory
 - giant cell arteritis
 - posterior fossa inflammatory myofibroblastic pseudotumor
- Other
 - Glaucoma

Cluster headache differential diagnosis

- Migraine
 - photophobia/phonophobia typically bilateral in migraine; typically ipsilateral to headache in TACs
 - migraine can have autonomic features, but usually less prominent and bilateral
 - migraine usually 4-72 hours
 - usually no circannual periodicity
 - less often nocturnal
 - migraine pain usually worse with movement
 - alcohol trigger in hours (next am) rather than in the bar
- Temporal arteritis
 - headache usually continuous, often worse with cold exposure
 - fever, polymyalgia rheumatica, weight loss, jaw claudication
 - no autonomic features
- Hypnic headache
 - always awakened during sleep
 - frequently bilateral
 - usually no autonomic features
- TN
 - usually V2/V3
 - shock-like pain
 - triggered attacks
- SUNCT
 - Shorter duration
 - Higher frequency
- Hemicrania continua
 - continuous pain
 - autonomic features less robust
 - indomethacin responsive

Cluster headache vs. paroxysmal hemicrania

Feature	Cluster headache	Paroxysmal hemicrania
Gender (M:F)	2.5-7:1	~1:1
Duration (min)	15-180 Usual 60	2-30 Usual 17
Frequency	1-8 Usual 1	2-50 Usual 11
Indomethacin	-	+
Nocturnal predilection	+	-

Systematic review of cluster headache treatment endorsed by AAN in 2010

- Acute
 - Level A:
 - Sumatriptan 6 mg SC
 - Zolmitriptan 5, 10 mg NS
 - Oxygen 6-12 L/min
 - Level B:
 - Sumatriptan 20 mg NS
 - Zolmitriptan 5, 10 mg po
 - Level C:
 - Lidocaine IN
 - Octreotide 100 mcg SC
- Preventive
 - Level A:
 - Nothing
 - Level B:
 - ONB
 - Civamide 100 microliter IN (not commercially available)
 - Level C:
 - Verapamil
 - Lithium
 - Melatonin

2016 American Headache Society cluster headache treatment guidelines

- Acute:
 - Sumatriptan 6 mg SC (A)
 - Zolmitriptan 5 mg & 10 mg nasal (A)
 - 100% oxygen, 6-12 L/min (A)
 - Sumatriptan 20 mg nasal (B)
 - Zolmitriptan 5 mg & 10 mg oral (B)
 - Sphenopalatine ganglion stimulation (B)
 - Cocaine/Lidocaine intranasal (C)
 - Octreotide (C)
- Preventive:
 - Suboccipital steroids (A)
 - Civamide (B)
 - Lithium (C)
 - Verapamil (C)
 - Melatonin (C)
 - Prednisone (U)

2006 EFNS cluster headache guidelines

- Acute:
 - 100% oxygen, 15 l/min (A)
 - Sumatriptan 6 mg s.c. (A)
 - Sumatriptan 20 mg nasal (A)

- Zolmitriptan 5 mg nasal (A/B)
- Zolmitriptan 10 mg nasal (A/B)
- Zolmitriptan 10 mg oral (B)
- Zolmitriptan 5 mg oral (B)
- Lidocaine intranasal (B)
- Octreotide (B)
- Preventive:
 - Verapamil (A)
 - Steroids (A)
 - Lithium carbonate (B)
 - Methysergide (B)
 - Topiramate (B)
 - Ergotamine tartrate (B)
 - Valproic acid (C)
 - Melatonin (C)
 - Baclofen (C)
- A denotes effective, B denotes probably effective, C denotes possibly effective

Acute treatment of cluster headache

- Oxygen 7-15L/min for 15-20 min via non-rebreathing face mask (give them prescription and send them to oxygen supply store, not pharmacy)
- Sumatriptan 6 mg SC, limit 2 inj/ 24 hours (can also use 3 or 4 mg SC, limit is still 12 mg in 24 hours)
 - Generic 4 mg sumatriptan injections often on back order
 - Give them enough
 - 2016 study by Leone and Proietti Cecchini provided Class IV evidence that in selected patients with chronic cluster headache, the continuous use of ≥ 2 sumatriptan injections per day for at least 2 years did not cause serious adverse events.
- Sumatriptan 20 mg IN (only if attacks last at least 45 min)--used much less than SC because doesn't work as well
- Zomig 5 mg IN
- DHE 1 mg SC or IV
- Lidocaine 4-6% nasal drops, 2 drops in each nostril
 - patient has to lie down after dosing for 2-5 minutes, with head extended out of bed, bent downwards 30-45 degrees and rotated 20-30 degrees towards side of headache
 - rarely adequate on own as acute therapy, and difficult for cluster headache sufferers to tolerate as they are restless

Patient with vascular disease (who has failed oxygen and intranasal lidocaine) acute treatment options

- Olanzapine
 - 5 mg prn headache
 - If no help or too sedated 2.5 mg per headache
 - Max is 10mg per headache, two times per day (20mg per day)
 - Rarely can use up to 30mg per day (Rozen personal communication)
- Chlorpromazine suppository, 25 mg: 1 to 2 supp (25–50 mg) to abort a headache
- Indomethacin suppository, 50 mg: 1 supp every 30 minutes up to 150 mg total
- Greater occipital nerve block acutely

Transitional prevention of cluster headache

- Prednisone 60 mg qd X 3 days, then decrease by 10 mg q 3 days until off
 - typically used once starting maintenance prevention as maintenance prevention takes a while to work
 - usually limited to 3 courses per year
- Greater occipital nerve (GON) blockade
 - I typically use 1 injection, ipsilateral to pain
 - Can repeat every 3 months in CCH
- *Ergotamine 1 mg po TID or 2 mg supp qd X 1-3 weeks
 - avoid triptan use acutely

- *DHE 0.5-1 mg SC or IM q 8-12 hours for 1-3 weeks or *repetitive IV DHE X 3 days
 - avoid triptan use acutely
- *Naratriptan 2.5 mg BID X 7 days or *eletriptan 40 mg BID X 6 days or *frovatriptan 2.5 mg qd X 7-20 days
 - avoid other triptan or ergot
- *placebo-controlled evidence lacking

Other prednisone protocols

- Becker Headache 2013;53:1191-6:
 - Prednisone 70 mg for 4 days
 - Dose is tapered by 5 mg every day
 - Total treatment time 17 day
- Rozen Neurologic Clinics 2009;27:537-556
 - Day 1 and 2: 80 mg
 - Day 3 and 4: 60 mg
 - Day 5 and 6: 60 mg
 - Day 7 and 8: 40 mg
 - Day 8 and 9: 20 mg
 - Day 10 and 11: 10 mg

Greater occipital nerve block

- 2 placebo controlled trials have assessed steroid plus local anesthetic
 - Ambrosini et al
 - Leroux et al
- Lambru and Matharu recommend methylprednisolone 80 mg plus 2 ml of 2% lidocaine
 - Can be repeated every 3 months in chronic cluster headache
 - If fail twice, likely don't need to try again
 - Cutaneous complication in 1 of 806 GON injections with this protocol

Maintenance prevention of cluster headache

- Short duration bouts may not require this
- Effective dose continued for typical duration of bout plus 2 weeks pain-free, then slow taper
- Baseline ECG, then **verapamil** 80 mg TID, increase by 80 mg q 2 weeks with ECG before each dose increase looking for PR-interval prolongation, initial target 480 mg/day but some need up to 960 mg/day
 - Routine 6-month ECGs after dose is established
- **Lithium** 300 mg TID, check trough level in approximately 1-2 weeks, trying to achieve a level of 0.7 to 1.0, may need to increase to 300/300/450 or 450/300/450
- ***Topiramate** 25 mg qhs, increase by 25 mg every 3-4 days up to max of 200 mg po BID
- **Melatonin** 10 mg qhs (some use 12-16 mg daily)
- *placebo-controlled evidence lacking

Other verapamil protocols

- Becker Headache 2013;53:1191-6:
 - Start 80 mg TID
 - Increase by 80 mg every week up to 480 mg/day
 - Above 480 mg/day, increase by 80 mg every 2 weeks
 - Do ECG when dose of 400 mg has been reached, and a week after each dosage increase above this level
 - Periodic ECGs once on stable dose
- Rozen Neurologic Clinics 2009;27:537-556:
 - Start 80 TID; increase by 80 mg every 3-7 days
 - If patient needs more than 480 mg/day, then ECG needed before each dose change thereafter

- Miller and Matharu The Practitioner 2013;257:15-20:
 - Do ECG, if normal then start 120 mg BID
 - Increase by 120 mg every 2 weeks (in three times daily regimen)
 - Max dose 960 mg per day
 - ECG to be performed before every dose increase
 - If prolonged PR or QT interval, dose decreased to last known dose with normal ECG

Cluster headache maintenance prevention tips

- For maintenance prevention, I start with verapamil first, followed by lithium, and then topiramate
- I often add melatonin early because it is well tolerated, but I have not been overwhelmed by its efficacy
- I am more likely to employ >1 maintenance preventive agent in cluster headache than in migraine
 - If I start verapamil and it does not work sufficiently at high doses, I will continue the verapamil, add lithium, and only start the verapamil taper once headaches are better
 - Might find that lithium in combination with a lower dose of verapamil can control the headaches
 - If a patient has a partial response to one agent, I will add another preventive rather than starting one and tapering the other
- In ECH, there is no evidence that staying on a preventive agent after the bout has ended prevents the appearance of the next bout
 - But if bordering on CCH, many patients do so
- With verapamil, maximum efficacious dose achieved during prior bout can be given at the beginning of subsequent bout, as long as baseline ECG is normal

Other cluster headache preventive options

- Nimodipine 60-120 mg/day
- *Nifedipine 30-180 mg/day
- *Methysergide (outside U.S.)
 - usually in ECH
 - up to 12 mg/day
 - start 1 mg qhs, then increase by 1 mg q 3d (in a tid regimen) until on 5 mg qd; then increase by 1 mg q 5 d up to 12 mg/day total; need one month break every six months or testing for fibrotic complications q 6 months
 - used less because of belief that you need to avoid triptans and ergots
- *Methylergonovine 0.2-0.4 mg TID; some need QID; max dose 1.6 mg/day
 - If use for 3-6 M, need 1 M drug holiday
- Pizotifen (outside U.S.) 3 mg qd
- IN capsaicin and civamide
- *OnabotulinumtoxinA
- *Naratriptan 2.5 mg BID
 - must avoid other triptans or DHE acutely
- *Valproic acid 500-2000 mg/day
 - placebo-controlled trial negative but methodological issues
- *Gabapentin 800-3600 mg/day
- *Baclofen 10 mg TID
- *Chlorpromazine 75-700 mg/day
- *Transdermal clonidine 0.2-0.3 mg/day
- *Tizanidine 12-24 mg/day
- Leuprolide 3.75 mg IM X 1
- *Clomiphene 50 mg/day; increase by 25 mg q 2 wks if needed to max 100 mg/day
- *Levetiracetam 1-3 grams daily
- *placebo-controlled evidence lacking

Cluster headache neuromodulation

- Consider in those with refractory CCH
- Occipital nerve stimulation
 - Open-label studies
 - Most headache docs would do this before hypothalamic stim

- Trial stimulation before permanent implantation is debated
 - Some improve within a few days of implant, others take weeks to months
 - Note ICON study (prospective, randomized, double-blind, parallel-group study of high vs. low amplitude bilateral ONS) has no trial stim
- Most patients need to continue their cluster headache preventive meds
- Response to occipital nerve block does not predict response to occipital nerve stimulation
- Noninvasive vagal nerve stimulation
- Sphenopalatine ganglion stimulation
- Hypothalamic stimulation (~66 patients, 63% responded)
- Other surgery

C. Hemicrania continua

Hemicrania Continua IHS 2013 Criteria

- Unilateral headache fulfilling criteria below
- Present >3 months, with exacerbations of moderate or greater intensity
- Either or both of the following:
 - ≥1 of the following ipsilateral symptoms or signs:
 - 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
 - a sense of restlessness or agitation, or aggravation of pain by movement
- Responds absolutely to therapeutic doses of indomethacin
- Not better accounted for by another diagnosis

Hemicrania continua, remitting subtype criteria

- Headache fulfilling criteria for hemicrania continua, and criterion below
- Headache is not daily or continuous, but interrupted by remission periods of ≥1 d without treatment

Hemicrania continua, unremitting subtype criteria

- Headache fulfilling criteria for hemicrania continua, and criterion below
- Headache is daily and continuous for ≥1 y, without remission periods of ≥1 d

Hemicrania continua background

- 1981 Entity described by Medina and Diamond
- 1983 Boghen and Desaulniers also report
- 1984 Term HC coined by Sjaastad and Spierings
- 2004 IHS gives diagnostic criteria

Hemicrania continua epidemiology

- F:M ~ 2:1
- Average age onset late 30s
- Range of onset 5-67

Hemicrania continua clinical features

- Continuous moderate unilateral baseline headache
- Exacerbations of more severe pain
- Temple, orbit, frontal, occipital/parietal

Hemicrania continua baseline headache

- Range 1-10/10 (mean 6)
- Patient may complain of a foreign body sensation in the eye
- Cittadini and Goadsby believe this is a cranial autonomic feature (itching eye), and found it in 32% of their 39 patients
- Post-traumatic in 23%

Hemicrania continua exacerbations

- Range 7-10/10 (mean 9)
- Seen in nearly all patients
- Last 30 min to several days (usually several hours)
- Throbbing, sharp
- Photo (74%), phono (79%), nausea or vomiting (53%)
- Autonomic features in 95%
- 69% agitated and/or restless, but 69% also reported exacerbation of pain with motion
- Nocturnal attacks in 50%

Hemicrania continua and primary stabbing headache

- In a recent series of 39 HC patients, 36% had primary stabbing headache (Cittadini and Goadsby Brain 2010)
- Some state incidence of primary stabbing headache as high as 75% in HC
- Stabbing often occurs during exacerbation

Hemicrania continua subtypes

- Hemicrania continua, unremitting
 - ~85%
 - 2/3 continuous from onset
 - 1/3 initially episodic
 - Continuous pain rarely becomes episodic (~10%)
- Hemicrania continua, remitting
 - ~15%
 - Episodes of unilateral headache lasting weeks to months interrupted by remissions for 1-2 days to weeks to months

Hemicrania continua unusual

- Side-alternating attacks
- Bilateral pain
- Association with FHM
- Aura
- Masking by analgesic rebound
- Contralateral episodic cluster headache

Secondary hemicrania continua

- Mesenchymal tumor sphenoid
- Lung malignancy
- HIV
- C7 root irritation reported to aggravate
- Left lateral medullary infarct and left vertebral artery occlusion on MRI/A (head pain contralateral to infarct)
- Pontine infarction
- Internal carotid artery dissection
- Prolactinoma--headache exacerbation with dopamine agonists
- Venous malformation right masseter

Hemicrania continua differential diagnosis

- Other CDH
 - CTTH usually bilateral, no exacerbations
 - Unilateral chronic migraine and NDPH do not have prominent indomethacin response
- Some patients with cluster, PH, SUNCT have dull interictal pain between attacks
 - Exacerbations in HC last longer and have less robust auto features
- Trochleitis

Headache attributable to trochleitis IHS criteria

- A. Periorbital and/or frontal headache fulfilling criterion C
- B. Clinical and/or imaging evidence of trochlear inflammation
- C. Evidence of causation demonstrated by at least two of the following:
 - 1. unilateral ocular pain
 - 2. headache is exacerbated by movement of the eye, particularly downward in adduction
 - 3. headache is significantly improved by injection of local anaesthetic or steroid agent into the peritrochlear region
 - 4. in the case of a unilateral trochleitis, headache is localized ipsilateral to it
- D. Not better accounted for by another ICHD-3 diagnosis

Trochlear headaches

- Primary trochlear headache also described (no swelling)
- Some combine both into trochlear headache
 - Typically new daily from onset headache
 - Worse with eye movement like reading
 - Migraines may worsen when have trochlear headache
 - Often need 2 injections

Hemicrania continua treatment with **indomethacin**

- 25-300 mg per day
- Most need 150 mg per day
- Typical trial (25 mg po TID X 3 days, if no relief then 50 mg po TID X 3 days, if no relief then 75 mg po TID X 3 days)
- If there is a partial response, 300/day can be tried for a short time
- Headache usually resolves within 1-2 days of initiating the effective dose; skipping doses may result in recurrence
- Dose adjustments often needed to address clinical fluctuations; patients should be on lowest dose that controls the pain
- Gastric mucosa protective agents employed (omeprazole over the counter every day)
- Taper treatment q 3 months (decrease 25 mg q 3 days)
- If HC-remitting, treat for 2 weeks beyond typical headache episode duration, then taper

Hemicrania continua other treatment

- Complete response with:
 - **rofecoxib** (25-50 mg/day), **celecoxib** (200 mg BID-300 mg BID), aspirin, naproxen, ibuprofen, diclofenac, piroxicam
- Other meds reported to be effective:
 - DHE, methysergide, corticosteroids, acetaminophen with caffeine, lamotrigine (25-200 mg/day), **gabapentin** (600-3600 mg/day), lithium, **melatonin** (7-9 mg qhs; Rozen starts 3 mg qhs, increasing by 3 mg q 3-5 nights up to 24 mg po qhs), **verapamil** (120-480 mg/day), **topiramate** (100-200 mg/day), onabotulinumtoxinA
- Radiofrequency ablation of the C2 ventral ramus, C2 dorsal root ganglion, or sphenopalatine ganglion
- **Occipital nerve block, occipital nerve stimulation can help**

D. Paroxysmal hemicrania

Paroxysmal Hemicrania IHS 2013 Criteria

- At least 20 attacks fulfilling criteria below
- Severe unilateral orbital, supraorbital and/or temporal pain lasting 2-30 min
- ≥1 of the following ipsilateral symptoms or signs:
 - 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
- Frequency >5/d for > half the time
- Prevented absolutely by therapeutic doses of indomethacin
- Not better accounted for by another diagnosis

Episodic paroxysmal hemicrania criteria (EPH)

- Attacks fulfilling criteria for paroxysmal hemicrania and occurring in bouts
- ≥2 bouts lasting 7days to 1 year (when untreated) and separated by pain-free remission periods of ≥1 month

Chronic paroxysmal hemicrania (CPH)

- Attacks fulfilling criteria for paroxysmal hemicrania
- Occurring without a remission period, or with remission periods lasting <1 month, for ≥1 year

Paroxysmal hemicrania background

- 1974 Described by Sjaastad and Dale
- 1976 Sjaastad and Dale coin term CPH
- 1987 Kudrow coins term EPH
- 1988 IHS gives criteria for CPH
- 2004 IHS classifies CPH and EPH as forms of PH

Paroxysmal hemicrania epidemiology

- 1-3% in relation to cluster headache (cluster prevalence 1 in 1,000, so PH prevalence 1 in 50,000)
- F:M 1.6-2.36 to 1 historically, although recent 31 patient series found F:M ratio of ~ 1 to 1
- Mean onset in the 30s

Paroxysmal hemicrania clinical features

- Usually V1 distribution, can be extra-trigeminal
- Sharp, stabbing, throbbing
- 80% agitated and/or restless
- Phonophobia (65%), photophobia (65%), nausea and/or vomiting (39%)
- Ipsi autonomic features (lacrimation and conjunctival injection most common)
- Bilateral auto features occur, can be dissociation

Paroxysmal hemicrania duration and frequency

- In a study by Cittadini et al, mean length of attacks was 17 minutes and the median was 19 minutes
- In same study, mean frequency was 11 attacks in 24 hours, and median was 9 attacks in 24 hours

Paroxysmal hemicrania clinical features

- Duration range 10 seconds-4 hours
- Frequency range 2-50/day
- No clear preponderance of nocturnal attacks
- Interictal pain in 58%
- Can be precipitated by neck movements
- Alcohol trigger in 19% (90% in cluster)

Paroxysmal hemicrania subtypes

- CPH
 - 80%
 - CPH from onset most common
 - Evolved from EPH less common
 - Can evolve into EPH

- EPH
 - 20%
 - Duration of headache phase 4-24 weeks
 - Remission range from 12-376 weeks
 - Can stay episodic for up to 35 years

Paroxysmal hemicrania unusual

- Side-alternating attacks
- Bilateral or center of forehead pain
- Absence of autonomic features
- Ear pain with external acoustic meatus obstruction
- May have sense of aural fullness or aural swelling
- Red ear syndrome
- Aura

Secondary paroxysmal hemicrania

- Vascular
 - Ectatic vertebro-basilar junction/basilar artery in close relation to trigeminal nerve
 - circle of Willis aneurysm
 - occipital, MCA infarcts
 - parietal AVM
 - Post carotid aneurysm embolization
- Tumor
 - malignant frontal tumor
 - cavernous sinus meningioma
 - petrous ridge meningioma
 - gangliocytoma sella
 - pituitary adenoma
 - parotid epidermoid mets
 - Pancoast tumor
- Miscellaneous
 - collagen vascular disease
 - intracranial hypertension
 - maxillary cyst
 - ophthalmic herpes zoster
 - essential thrombocythemia

Paroxysmal hemicrania vs. cluster headache

Feature	Cluster headache	Paroxysmal hemicrania
Gender (M:F)	2.5-7:1	~1:1
Duration (min)	15-180 Usual 60	2-30 Usual 17
Frequency	1-8 Usual 1	2-50 Usual 11
Indomethacin	-	+
Nocturnal predilection	+	-

Paroxysmal hemicrania treatment

- **Indomethacin**
 - Typical trial as in hemicrania continua
 - Some CPH cases do not recur after stop indomethacin
 - Periodically withdraw (q 3 months decrease by 25 mg q 3 days)
 - Treat for two weeks beyond typical EPH bout, then taper
 - Some “classic” patients do not respond, and those patients likely have another TAC

- Others
 - **celecoxib (200 mg BID)**
 - **rofecoxib (25-50 mg/day)**
 - verapamil (240-320 mg/day)
 - onabotulinumtoxinA
 - nocardipine
 - flunarizine
 - ibuprofen
 - ketoprofen
 - ASA
 - piroxicam
 - naproxen
 - diclofenac
 - phenylbutazone
 - **acetazolamide (250 mg TID)**
 - **topiramate (150-350 mg/day)**
 - prednisone
 - lithium
 - ergotamine
 - oxygen
 - **greater occipital nerve block**
 - **occipital nerve stimulation (prelim)**
 - **hypothalamic stimulation**
 - sumatriptan (20%)

E. Short-lasting unilateral neuralgiform headache attacks (SUNCT and SUNA)

Short-lasting Unilateral Neuralgiform Headache Attacks IHS 2013 Criteria

- At least 20 attacks fulfilling criteria below
- Moderate or severe unilateral head pain, with orbital, supraorbital, temporal and/or other trigeminal distribution, lasting 1-600 s and occurring as single stabs, series of stabs or in a saw-tooth pattern
- ≥ 1 of the following ipsilateral cranial autonomic symptoms or signs: 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
- Frequency $\geq 1/d$ for $>$ half the time when active
- Not better accounted for by another diagnosis

Two subtypes of short-lasting unilateral neuralgiform headache attacks

- Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)
- Short lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA)
- SUNCT may be a subform of SUNA, although this requires further study
- This review will focus on SUNCT

SUNCT criteria

- Attacks fulfilling criteria for short-lasting unilateral neuralgiform headache attacks
- Both of conjunctival injection and lacrimation (tearing)

Episodic SUNCT

- Attacks fulfilling criteria for SUNCT and occurring in bouts
- ≥ 2 bouts lasting 7 days to 1 year and separated by pain-free remission periods of ≥ 1 month

Chronic SUNCT

- Attacks fulfilling criteria for SUNCT, and criterion below
- Occurring without a remission period, or with remissions lasting < 1 month, for ≥ 1 year

SUNA criteria

- Attacks fulfilling criteria for short-lasting unilateral neuralgiform headache attacks
- Only one or neither of conjunctival injection and lacrimation (tearing)

Episodic SUNA

- Attacks fulfilling criteria for SUNA and occurring in bouts
- ≥ 2 bouts lasting 7 days to 1 year and separated by pain-free remission periods of ≥ 1 month

Chronic SUNA

- Attacks fulfilling criteria for SUNA, and criterion below
- Occurring without a remission period, or with remissions lasting < 1 month, for ≥ 1 year

SUNCT background

- 1978 First case reported by Sjaastad et al
- 1989 Term coined and detailed description given by Sjaastad et al
- 2004 IHS gives diagnostic criteria

SUNCT epidemiology

- Rare
- M:F 2:1
- Mean age at onset 48, range 19-75

SUNCT clinical features

- Minority (20%) have side-alternating attacks
- Eye, retro-orbital, forehead, nose, temple, cheek
- Single stabs, groups of stabs, or saw tooth pattern of stabs
- Less often described as electric shock, sharp, shooting, burn, throb
- Prominent ipsilateral conjunctival injection and tearing
- 62% of SUNCT patients agitated during attack
- 37% photophobia, 26% unilateral photophobia, 30% phonophobia, 9% unilateral phonophobia
- Mean duration:
 - Single stab 58 sec; Stab groups 396 sec; Saw tooth 1160 sec
- One patient had saw tooth attack duration of 200 min
- 20/43 patients had interictal background pain (5 of those were overusing analgesics)
- Mean attack frequency 59/day (range 2-600/day; some could not quantify)

SUNCT periodicity and chronicity

- 30% with primary episodic SUNCT
 - Bouts lasted for a mean of 7.5 weeks (range 1-30 weeks)
 - Average remission time 52 weeks (range 3-364 weeks)
- 40% with primary chronic SUNCT
- 23% with secondary chronic SUNCT
- Only 7% report predominantly nocturnal attacks (unlike 73% in cluster headache)

SUNCT triggers

- Most have triggered and spontaneous attacks
- Touch face
- Chew, wind, wash face, brush teeth, move, talk
- No alcohol trigger in SUNCT group
- 95% of SUNCT patients have no refractory period
- Calcium channel blockers?

Abnormal exam

- 5/43 SUNCT patients had reduced pinprick sensation in V1 or V2 without structural cause on neuroimaging
 - Beware!
- 1/43 with Horner's syndrome

SUNCT unusual

- Bilateral or side-alternating attacks
- Very frequent attacks for 1-3 days (status)
- Blepharospasm
- Rotatory neck movements can abort
- Side-alternating attacks of throat pain with prominent conjunctival injection and tearing
- Sensory aura
- Resolution after contralateral MCA infarction

Secondary SUNCT

- Cerebellopontine angle AVM
- Venous angioma in region of brainstem and right cerebellar hemisphere
- Brainstem cavernous hemangioma
- Brainstem infarct
- Posterior fossa pilocytic astrocytoma
- NF2 with bilateral acoustic neuromas and pontomedullary compression
- Posterior fossa lesion in AIDS patient
- Basilar impression
- Craniosynostosis causing foreshortened posterior fossa
- Trigeminal nerve compression by vascular loop
- Multiple sclerosis, Neuromyelitis optica (cord and brainstem involvement)
- EBV-associated post-transplant leiomyosarcoma of the cavernous sinus
- Pituitary tumors: Acromegaly; Prolactinoma (with or without cavernous sinus invasion; may have dopamine agonist-induced attacks)
- Lacrimal gland retention cyst or cholesterol cyst
- Metastatic intraorbital carcinoid
- Ocular trauma

Tip

- Given the propensity for pituitary and peripituitary gland disease to present as a phenotypic TAC, would do MRI with pituitary views as part of TAC w/u
 - If SUNCT is most likely, add posterior fossa cuts to look for vessel compressing trigeminal nerve

SUNCT vs. trigeminal neuralgia

Feature	SUNCT	Trigeminal neuralgia
Gender (M:F)	2:1	1:2
Pain location	V1	V2/3
Duration	1 min	Few seconds
Autonomic features	Prominent	Mild lacrimation
Refractory period	Absent	Present
Carbamazepine effect	Partial effect	+

SUNCT treatment

- **Lamotrigine (50-400 mg/day)**
- Topiramate (75-400 mg/day)
- Gabapentin (600-3600 mg/day)
- Carbamazepine (200-1200 mg/day)
- Oxcarbazepine (600 mg/day)
- Clomiphene citrate (100 mg/day)

- Verapamil (240-960 mg/day)
- Zonisamide (300 mg/day)
- Periorbital onabotulinumtoxinA
- Corticosteroids PO
- Methylprednisolone 1 g IV X 3 days
- IV lidocaine (Start 1 mg/min, increase to max 3.3 mg/kg/h, need cardiac monitoring)
- Phenytoin 250 mg IV (2 hour reduction of frequency and intensity)
- SC sumatriptan (relief for 3-5 hours)
- Indomethacin no significant effect
- Successful procedures:
 - **Occipital nerve stimulation (bilateral)**
 - **Microvascular decompression**
 - Trigeminal ganglion compression
 - Glycerol rhizotomy
 - Gamma knife radiosurgery (trigeminal nerve and sphenopalatine ganglion)
 - Opioid blockade of superior cervical ganglion
 - Occipital nerve block
 - Hypothalamic stimulation
 - Small # of patients cured after surgical removal of their pituitary microadenomas

Lambru and Matharu Neurol Sci 2013 proposed algorithm for medical treatment of SUNCT/SUNA

	Medication and dose (max dose reported to be effective)
1 st line treatment	Lamotrigine (up to 600 mg/day)
2 nd line treatments	Oxcarbazepine (up to 2,400 mg/day)
	Topiramate (up to 700 mg/day)
	Duloxetine (30–120 mg/day)
3 rd line treatments	Carbamazepine (up to 1,600 mg/day)
	Gabapentin (up to 3,600 mg/day)
	Pregabalin (up to 600 mg/day)
	Mexiletine (up to 1,200 mg/day)
	Lidocaine patches (5 %)
Transitional treatments	IV lidocaine (1.3–3.3 mg/kg/h for 7–10 days)
	Greater occipital nerve injection (methylprednisolone 80 mg + 2 ml of 2 % lidocaine)
	Oral/IV corticosteroids

F. Pathophysiology of the TACs

- The trigeminal-autonomic reflex can account for many of the features of cluster headache, PH, SUNCT, and the painful exacerbations of HC
- The trigeminal-autonomic reflex pathway involves trigeminal afferents, brainstem connections between the trigeminal nucleus caudalis and the superior salivatory nucleus, and subsequent cranial parasympathetic outflow from the superior salivary nucleus through the seventh nerve
- Trigeminal activation would lead to pain in the distribution of the trigeminal nerve, and would also stimulate facial nerve parasympathetic outflow
- The extension of the trigeminal nucleus caudalis to C1/C2 could explain the extra-trigeminal (i.e. occipital) pain seen in the TACs
- In humans, stimulation of the trigeminal ganglion causes release of calcitonin gene-related peptide (CGRP) as well as vasoactive intestinal polypeptide (VIP)
- VIP is released from parasympathetic nerves
- Both of these peptides are elevated during attacks of PH and cluster headache, and both return to normal after successful treatment
- The hypothalamus may modulate signalling through the trigeminocervical complex, and regulate the trigeminal-autonomic reflex
- This seems intuitive in cluster headache, given the circadian nature of attacks

- The hypothalamus is known to have a modulatory role on the nociceptive and autonomic pathways, and there are direct hypothalamic-trigeminal connections
- Functional neuroimaging of the TACS has revealed the following
 - Hypothalamic activation in SUNCT and cluster headache
 - In addition, pontomedullary junction activation in SUNCT
 - Hypothalamic and midbrain activation in PH
 - Hypothalamic, midbrain, dorsal rostral pons, and pontomedullary junction activation in HC

G. Summary

- TACs are characterized by pain in a trigeminal nerve distribution, associated with ipsilateral cranial autonomic features
- Cluster headache
 - For diagnosis remember rule of 1-2s
 - Gold standard acute treatments=sumatriptan SC and oxygen
 - Gold standard transitional preventives=prednisone PO or occipital nerve block
 - Gold standard maintenance preventive=verapamil
- As concerns cluster, PH, and SUNCT: As the names get longer, the attack duration gets shorter and the attack frequency increases
- HC likely underdiagnosed
- HC and PH completely respond to indomethacin
- SUNCT/SUNA: start with lamotrigine preventively

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