Trigeminal Autonomic Cephalalgias (TACs)

María-Carmen Wilson, MD
Director, Headache and Facial Pain Program
Ochsner, North Shore Region
Trigeminal autonomic cephalgias (TACs) are headaches/facial pains classified together based on:

- a suspected common pathophysiology involving the trigeminovascular system, the trigeminoparasympathetic reflex and centers controlling circadian rhythms;

- a similar clinical presentation of trigeminal pain, and autonomic activation.
There is much overlap in the diagnostic features of individual TACs.

In contrast, treatment response is relatively specific and aids in establishing a definitive diagnosis.
Secondary Etiology

TACs are often presentations of underlying pathology; all patients should be imaged.
Pathophysiology

- Trigeminal Pain
- Rythmicity
- Autonomic Signs
Trigeminal Pain

- Central component prevails
- Peripheral mechanisms do not explain:
  - gender predilections
  - unilaterality of the symptoms
  - sleep association
  - in cluster headache, the circadian rhythmicity of attacks
Trigeminovascular System

- Pain implicates activity of the trigeminal and upper cervical nerves
- Increased levels of calcitonin-gene-related peptide (CGRP), nitric oxide (NO) and vasoactive intestinal peptide (VIP) in the cranial circulation in TACs indicate activity of the trigeminal and parasympathetic nerves

Neuropathic Mechanisms

- Attacks of Paroxysmal hemicrania (10%) and SUNCT (trigeminal neuralgia-like triggers)
- Successful microvascular decompression in cluster headache suggests that neuropathic mechanisms may be involved

Lain AH, Caminero AB, Pareja JA. Cephalalgia 2000; 20(7): 671–673
Rhythmicity

The periodicity and sleep association in TACs suggests involvement of central sites involved in the control of the human ‘biological clock’

Located in the suprachiasmatic nucleus, situated in the anterior part of the hypothalamus dorsal and above the optic chiasm
PERIODICITY DYSFUNCTIONAL HYPOTHALAMIC PACEMAKER

- Altered secretory circadian rhythms of hypophyseal hormone systems (melatonin, testosterone, beta-endorphin, beta-lipotropin, cortisol, prolactin)
- Circannual and circadian rhythmicity
- Seasonal predilection of cluster periods

HYPOTHALAMUS – SUPRACHIASMATIC NUCLEUS
HYPOTHALAMUS ABNORMAL – FUNCTION AND STRUCTURE

Function

Structure

PAIN / AUTONOMIC SIGNS

- Trigeminovascular activation (CGRP)
- Cranial parasympathetic activation (VIP)
- Internal carotid artery dilation (cavernous)

May A. Lancet 2005
Trigeminal Autonomic Cephalgias (TACs)

With autonomic features

- Cluster
- The paroxysmal hemicranias
- SUNCT and SUNA
- Cluster-Tic
- CPH-Tic
- Hemicrania continua
Short-Lasting Headaches other than TACs

Without autonomic features (These are not TACs):

- Trigeminal neuralgia
- Idiopathic stabbing headaches
- Benign cough headaches
- Benign exertional headaches
- Headaches associated with sexual activity
- Hypnic headaches
FREQUENCY

- Trigeminal Neuralgia
- SUNCT/A
- Paroxysmal Hemicrania
- Cluster Headache
- Vascular Orofacial Pain
- Transformed Migraine

Frequency range:
- 1/2 d
- 1/d
- 8/d
- 40/d
- 200/d

Duration

Cluster headache (Archetypal TAC)

- Episodic (90%)
- Chronic (10%)
  - Cluster period lasts for more than one year without remission or remission lasts less than 14 days
- Related syndromes

ICHD-3.
EPIDEMIOLOGY

- Prevalence (0.1% – 0.4%)
- Predominantly male (4.3-1 male to female ratio)
- Mean age of onset (27 – 31 years)
- Rare before the age of 10 years

Sjaastad O. Cephalalgia. 2003
Fischera M. Cephalalgia 2008.
Positive family history in 5% - 20% of sufferers

1st-degree relatives have a 14X increased risk

Five identical twin pairs with 100% concordance

Autosomal dominant disorder in about 5% of cases

Loene M. Neurology 2001
Genetic Predisposition: Smoking

- Up to 85% cluster patients are chronic cigarette smokers.
- Quitting smoking has no effect on the disease.
- Smoking maybe a factor for the development of Cluster, genetic predisposition?

Rozen T. Headache 2005
ATTACK PROFILE

- Unilateral orbital/supraorbital/temporal severe pain intensity
- Rapid onset (5 – 15 min) / short duration (45 – 90 min) range 15-180)
- “Agitated” patient (pacing / restless)
- ‘Migrainous’ symptoms (nausea, photophobia, phonophobia, aura)
- Restlessness (in contrast to migraineurs)

May A. Lancet 2005
AUTONOMIC FEATURES: Parasympathetic Activity/Sympathetic Impairment

- Conjunctival injection
- Lacrimation
- Nasal congestion / rhinorrhea
- Partial Horner’s syndrome
- Facial flushing / sweating
- Edema

Drummond PD. Cephalalgia 2006
Pain Location

Cluster Headache
Paroxysmal Hemicrania
SUNCT
Hemicrania Continua
Migraine

- Neck
- Shoulder, neck, arm

CIRCCANNUAL PERIODICITY

January

February

March

June

July

August

May A. Lancet 2005
CIRCADIAN PERIODICITY

1-3 attacks daily (up to 8 attacks/day)

Peak time periods

AM
PM
PM
REM sleep

May A. Cephalalgia. 2005
ASSOCIATED FEATURES

- High alcohol / tobacco usage
- Leonine facies (heavy facial features)?
- Peau d’orange skin?
- Hazel-colored eyes?
- Duodenal ulceration?
- Type A personality?
Requiring ALL of the following:

- At least 5 attacks
- Location in the orbital/supraorbital/temporal region
- Duration: 15-180 minutes (untreated)
- During part (but less than half) of the time course attacks maybe less severe and/or shorter duration
Either or both of the following:

- At least one of the following
  - Conjunctival injection and/or lacrimation
  - Nasal congestion and/or rhinorrhea
  - Eyelid edema
  - Forehead and facial sweating
  - Sensation of fullness in the ear
  - Miosis and/or ptosis

- A sense of restlessness or agitation
ICHD-3

- Attacks have a frequency between 1 every other day and 8 per day for more than half of the time when the disorder is active
- No better accounted for by another ICHD-3 diagnosis
Diagnostic Criteria for Episodic Cluster

- Attacks fulfilling criteria for cluster headache and occurring in bouts (cluster periods)
- At least 2 cluster periods lasting from 7 days to 1 year (when untreated)
- Separated by pain-free remission periods of one month or more
Diagnostic Criteria for Chronic Cluster

- Attacks fulfilling criteria for cluster headache
- Attacks occurring without a remission period, or with remissions lasting less than one month, for at least one year
“SYMPTOMATIC” CLUSTER HEADACHE
Secondary Cluster Headache

- Intracranial large artery aneurysms
- Meningiomas
- AVMs
- Pituitary macroadenomas
- Recurrent nasopharyngeal carcinoma
- Aspergilloma in sphenoid sinus
- Benign posterior fossa tumor
- Lymphomas
# Cluster Headache: Differential Diagnosis

<table>
<thead>
<tr>
<th>Feature</th>
<th>Cluster</th>
<th>CPH</th>
<th>EPH</th>
<th>SUNCT</th>
<th>Stabbing headache</th>
<th>Trigeminal neuralgia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M:F)</td>
<td>4:1</td>
<td>1:3</td>
<td>1:1</td>
<td>2.3:1</td>
<td>F&gt;M</td>
<td>F&gt;M</td>
</tr>
<tr>
<td>Attack Duration</td>
<td>15-180 min</td>
<td>2-45 min</td>
<td>1-30 min</td>
<td>5-250 s</td>
<td>&lt;1s</td>
<td>&lt;1s</td>
</tr>
<tr>
<td>Attack Frequency</td>
<td>1-8/day</td>
<td>1-40/day</td>
<td>3-30/day</td>
<td>1/day-30/hr</td>
<td>Few-many</td>
<td>Few-many</td>
</tr>
<tr>
<td>Autonomic Features</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Alcohol PPT</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Indomethacin Effect</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

ACUTE TREATMENT

High efficacy
- $O_2$
- Sumatriptan subcutaneous (6 mg)
- IV/IM/SQ dihydroergotamine mesylate 0.5 – 1.0 mg

Limited efficacy
- Zolmitriptan NS 10 mg
- Ergotamine 1 – 2 mg oral or suppository
- Intranasal lidocaine

Law S. Cockrane database 2013..
OXYGEN

- 100% O₂ 7 – 12 liters / min for 15 minutes
- Efficacy 70% at 15 minutes
- Most effective when headache at maximum intensity
- May delay rather than completely abort attack
- Main limitation is accessibility

Fogan L. Arch Neurol. 1985
Ekbom K, Cephalalgia 1995
Petersen AS, Cephalalgia 2014.
SUMATRIPTAN SUBCUTANEOUS

- Effective in 90% of patients for 90% of their attacks for *both* acute and chronic cluster
- Efficacy within 15 minutes in 50% - 75%
- No tachyphylaxis
- Attack frequency not increased with prolonged use
- Not effective for cluster prophylaxis

Cochrane, 2013
Control/Suppression Therapy

**Transitional**
- **Prednisone**
  (60 mg daily for 3 days, then 10 mg decrements every 3 days)
- **Ergotamine tartrate**
  (1 – 2 mg po / suppository daily)
- **DHE 45**
  (0.5 – 1.0 mg sc / im q 8 – 12 hrs)
- **Occipital nerve block**

**Maintenance**
- **Verapamil**
  (240 – 720 mg / day)
- **Methysergide**
  (unavailable)
  (2 mg tid; up to 12 mg daily)
- **Lithium carbonate**
  (150 – 300 mg tid)
- **Divalproex sodium**
  (500 – 2000 mg / day)
CLUSTER HEADACHE: OTHER OPTIONS

- Melatonin (10 mg HS)
- Topiramate (50 – 125 mg / day)
- Indomethacin (75 – 225 mg / day)

REFRACTORY CLUSTER HEADACHE

Combination therapy

- Lithium + Verapamil
- Valproate + Lithium
- Topiramate + Verapamil
Cluster Headache: Treatment Resistant Patients

- Hospitalization for IV DHE
- Histamine desensitization
- Occipital nerve blocks
- Surgery
In the Pipeline

- ClinicalTrial.gov. A study of LY2951742 in participants with episodic and chronic cluster headache (CGAL, CGAM)
- Injection every 30 days for 8 weeks
INDICATIONS FOR SURGERY/PROCEDURAL INTERVENTION

- Medically intractable
- Strictly unilateral cases
- Contraindications or intolerable side effects to medications
- Stable psychological and personality profiles including low addiction proneness
SURGICAL PROCEDURES FOR CLUSTER HEADACHES

Sensory trigeminal pathway procedures
- Radiofrequency or glycerol rhizotomy
- Gamma knife radiosurgery
- Trigeminal root section
- Other

Autonomic (parasympathetic) pathway procedures

Nesbitt, Neurology 2015
Schoenen, Cephalalgia 2013
Bendersky, Pain Prac 2015
For over 100 years, the sphenopalatine ganglion (SPG) has been a therapeutic target to treat primary headache disorders [Sluder, 1908].

Sluder first described the application of cocaine or alcohol to the SPG for the treatment of headaches.
Targeting the Sphenopalatine Ganglion (SPG)

- Ganglionectomy (Meyer et al. 1970)
- Percutaneous alcohol injection (Devoghel, 1981)
- Lidocaine or corticosteroid application (Costa et al. 2000; Felisati et al. 2006; Maizels and Geiger, 1999; Maizels et al. 1996; Yang and Oraee, 2006; Morelli et al. 2010; Kudrow et al. 1995)
Targeting the Sphenopalatine Ganglion (SPG)

- Cryosurgery (Cook, 1978)

- Stereotactic radiosurgery (Lad et al. 2007; Effendi et al. 2011)

- Radiofrequency (RF) lesioning (Narouze et al. 2009; Salar et al. 1987; Bayer et al. 2005; Shah and Racz, 2004; Sanders and Zuurmond, 1997)
Targeting the SPG

**Neurostimulation** *(Tepper et al. 2009; Ibarra, 2007; Ansarinia et al. 2010; Schoenen et al. 2013).*

Utilized as a reversible intervention that interrupts the trigeminal-autonomic reflex

Láinez MA. Ther Adv Neurol Disord. 2014
ONS, Different Headache Types

- **Trigeminal Autonomic Cephalalgias including Cluster**
  1. Clinical outcome data on 26 patients on case series
  2. 1/3 to 2/3 obtained 50% or more improvement

- **Hemicrania Continua**
  1. 9 patients to date on case series (9,7)
  2. 77% obtained 50% or more improvement

- **Migraine Headache**

- **Occipital Neuralgia, Occipital Deafferentation pain, SUNCT, Paroxismal Hemicrania, Cervicogenic headache**
ONS Complications

- Lead migration, typically within the first year, was the most common complication in all series, leading to frequent revisions. New reports suggest better outcome with paddle leads.

- Infection risk is low (7 cases reported in 150 implants).

- Battery malfunction, lead fracture, persistent surgical site pain, neck stiffness, shock-like sensations at the electrode site.
Non-invasive vagus nerve stimulation for PREVention and Acute treatment of chronic cluster headache (PREVA): A randomised controlled study.
Adjunctive prophylactic nVNS is a well-tolerated novel treatment for chronic CH, offering clinical benefits beyond those with SoC.
RX Paroxysmal Hemicrania

- Indomethacin 75-225 mg/day
- Other NSAIDs
- Verapamil
- Acetazolamide
RX Hemicrania Continua

- Indomethacine 25-300 mg/day
- Other NSAIDs
RX SUNCT

- Lamotrigine 100-300 mg/day
- Gabapentin 900-2700 mg/day
- Topiramate 50-200 mg/day
Questions?