Trigeminal Autonomic Cephalalgias
Rashmi Halker Singh, MD FAHS
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Disclosures
• Honoraria from Allergan and Amgen for advisory board, Current Neurology and Neuroscience Reports for editing Headache section

Objectives
• Identify the diagnostic criteria, clinical features, and pathogenesis of cluster headache, chronic paroxysmal hemicrania, SUNCT, and hemicrania continua
• Develop evidence-based approach to the treatment of these headache disorders
The TACs: ICHD-3 classification

- Overview
- Cluster Headache
- Paroxysmal Hemicrania
- SUNCT/SUNA
- Hemicrania Continua

The TACs: Autonomic Symptoms

- Cardinal feature of the TACs

- Caused by cranial parasympathetic activation triggered by nociceptive trigeminal activation

- Can be seen with any nociceptive input to V1 – can also be seen with migraine

The TACs: Posterior Hypothalamic Activation
TAC vs Migraine

<table>
<thead>
<tr>
<th>TAC</th>
<th>Migraine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autonomic Symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>• Prominent</td>
<td>• Bilateral</td>
</tr>
<tr>
<td>• Lateralized to side of pain</td>
<td>• Mild</td>
</tr>
<tr>
<td>• Consistent symptoms with every attack</td>
<td>• Do not always parallel the severity of the attacks</td>
</tr>
<tr>
<td><strong>Photophobia/Phonophobia</strong></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral to the side of pain</td>
<td>Bilateral even when pain is lateralized</td>
</tr>
</tbody>
</table>

Pituitary Tumors and TACs

- Increased prevalence of TACs in patients with pituitary tumors and headache
  - 86 patients with headache and pituitary tumor
  - SUNCT (5%) and cluster headache (4%)
- 40 cases of symptomatic TACs in the literature
  - Pituitary tumors (16)
    - 7/10 SUNCT; 2/3 PH; 7/27 cluster
- MRI brain imaging with pituitary views & pituitary function tests are an important part of the evaluation in all patients with TACs.

Cittadini and Matharu. The Neurologist, 2009

Cluster Headache Phenotype

- Visual Analogue Score
- Pain intensity
- Time to peak
- Duration
- Side-locked
- 24-hour attack frequency
- Nocturnal predilection
- Autonomic features
- Agitation, pacing
- "Migrainous" symptoms may occur
Cluster Headache
ICHD-3 Diagnostic Criteria

A. At least 5 attacks

B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes if untreated

C. Either or both of the following:
   a) Headache is accompanied by at least one of the following, ipsilateral to the side of the pain:
      i) Conjunctival injection and/or lacrimation
      ii) Nasal congestion and/or rhinorrhoea
      iii) Eyelid oedema
      iv) Forehead and facial sweating
      v) Miosis and/or ptosis
   b) A sense of restlessness or agitation

D. Attacks have a frequency from one every other day to 8 per day

E. Not attributed to another disorder

Cephalalgia 2018

Cluster Headache
ICHD-3 Diagnostic Criteria

• Episodic Cluster Headache
   – Attacks fulfilling criteria for cluster headache
   – At least 2 cluster periods lasting 7-365 days separated by pain-free remission periods of at least 3 months

• Chronic Cluster Headache
   – Attacks fulfilling criteria for cluster headache
   – Occurring without a remission period, or remission periods lasting < 3 months

Cluster Headache

27% only 1 cluster cycle

Episodic 80%
Chronic 20%
Cluster headache

**Epidemiology**

- **Prevalence**: 240/100,000
  - Multiple sclerosis: 177/100,000
- **Incidence**: 9.8/100,000
  - Multiple sclerosis: 7.5/100,000
- **Mean age of onset**: 31.5 years (27-37)
- **Male:Female ~ 3:1**


**Clinical Manifestations**

- **Attack profile**
  - Pain and associated cranial autonomic symptoms
- **Periodicity**
  - Circannual
  - Circadian

Pain Location

Raskin NH: Headache 2nd Ed p230
Location of Maximal Pain During Cluster Attacks in 180 Patients

<table>
<thead>
<tr>
<th>Pain sites</th>
<th>Patients (no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular</td>
<td></td>
</tr>
<tr>
<td>Temporal</td>
<td></td>
</tr>
<tr>
<td>Frontal</td>
<td></td>
</tr>
<tr>
<td>Maxillary</td>
<td></td>
</tr>
<tr>
<td>Zygomatic</td>
<td></td>
</tr>
<tr>
<td>Nasal</td>
<td></td>
</tr>
<tr>
<td>Parietal</td>
<td></td>
</tr>
<tr>
<td>Occipital</td>
<td></td>
</tr>
<tr>
<td>Auricular</td>
<td></td>
</tr>
<tr>
<td>Mandibular</td>
<td></td>
</tr>
<tr>
<td>Cervical</td>
<td></td>
</tr>
<tr>
<td>Scapular</td>
<td></td>
</tr>
</tbody>
</table>

Cluster Headache
Comorbidities and Mimics

- Obstructive sleep apnea (58%)
  - 8-fold increased risk
  - 24X (BMI > 24)
  - 13X (Age >40)
- Tobacco (85%) and alcohol abuse
- Low testosterone
- Arterial dissection
- Sinusitis
- Glaucoma
- Cervical cord lesions
- Hypnic headache
- Intracranial lesions
  - Pituitary / parasellar

Circannual Periodicity
Attack and Remission Phases

Circadian Periodicity

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

Periodicity: Dysfunctional Hypothalamic Pacemaker

- Disordered circadian rhythms (melatonin, cortisol, etc)
- Circannual and circadian rhythmicity
- Seasonal predilection of cluster periods
- Functional imaging

Therapy of Cluster HA

Acute therapy → Preventive therapy

Transitional therapy

Avoid triggers: Alcohol, nitroglycerin, altitude, sildafenil
Guidelines; Effective

- Level A
  - Suboccipital steroid injections
- Level B
  - Cimamide ns (not used in US)
- Level C
  - Lithium 900mg daily
  - Verapamil 360mg daily
  - Warfarin to INR 1.5-1.9
  - Melatonin 10mg daily
- Level U
  - Frovatriptan 5mg daily
  - Capsaicin IN
  - Nitrate tolerance
  - Prednisone 20mg QOD

Guidelines; Ineffective

- Level B
  - Sodium Valproate 1000-2000mg
  - Sumatriptan 100mg tid
  - DBS in refractory CCH
- Level C
  - Cimetidine/chlorpheniramine 800-2000/16-20
  - Misoprostol 300 micrograms
  - Hyperbaric Oxygen 100%
  - Candasartan 32mg
Clinical Practice

- Corticosteroids at cycle onset
- High dose verapamil (240-720 mg/day)
- Lithium (600-1200 mg)
- Gabapentin (1800mg)
- Methysergide
- Divalproex sodium
- Topiramate
- Devices (VNS)

Acute Treatment of Cluster Headache; Guidelines

- Level A
  - Oxygen
  - Sumatriptan 6mg SQ
  - Zolmitriptan 5mg NS
- Level B
  - SPG stimulation in CCH
  - Sumatriptan 20mg NS
  - Zolmitriptan 5mg and 10mg oral
- Level C
  - Cocaine/Lidocaine NS
  - Octreotide SQ

Chronic Paroxysmal Hemicrania
Headache Phenotype

- 24-hour attack frequency: >5
- Side-locked
- Duration: 2-30 mins

ICHD-3. Cephalalgia 2018
Paroxysmal Hemicrania
ICHDS-3 Diagnostic Criteria

A. At least 20 attacks fulfilling B-E
B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 2-30 minutes
C. Either or both of the following
   1. At least one of the following, ipsilateral to the pain:
      A. Conjunctival injection and/or lacrimation
      B. Nasal congestion and/or rhinorrhea
      C. Eyelid oedema
      D. Forehead and facial sweating
      E. Miosis and/or ptosis
   2. A sense of restlessness or agitation
D. Occurring with a frequency >5 per day
E. Attacks are prevented absolutely by therapeutic doses of indomethacin
F. Not attributed to another disorder

Cephalalgia 2018

PH: Indomethacin

• ICHD-3: “In an adult, oral indomethacin should be used initially at a dose of at least 150 mg daily and increased if necessary up to 225 mg daily. The dose by injection is 100-200 mg. Smaller maintenance doses are often employed.”


PH: Episodic vs. Chronic

• Episodic Paroxysmal Hemicrania (35%)
  A. Attacks of PH occurring in bouts
  B. At least 2 bouts lasting 7-365 days, separated by pain-free periods lasting at least 3 months

• Chronic Paroxysmal Hemicrania (65%)
  A. Attacks meeting criteria for PH
  B. Occurring for > 1 year without remission periods or remission periods lasting < 3 months

Paroxysmal Hemicrania
Evidence-Based Treatment

- Acute: none
- Prophylactic:
  - Indomethacin (treatment of choice)
    - 25mg tid with meals or 75mg SR qday; 150mg often required
    - Dose can be lowered to find lowest effective dose
    - Intermittent discontinuation useful as remissions occur
- Other prophylactic options:
  - Verapamil
  - NSAIDs and COX-2 inhibitors
  - Topiramate
  - Occipital nerve block
  - Gabapentin
  - Acetazolamide
  - Sumatriptan SQ – can help some patients with longer attack duration

SUNCT/SUNA Headache Phenotype

Short-lasting Unilateral Neuralgiform headache attacks (SUNCT & SUNA): ICHD-3 Diagnostic Criteria

A. At least 20 attacks fulfilling B-D
B. Moderate-severe unilateral orbital, supraorbital, temporal and/or other trigeminal distribution head pain, lasting 1-600 seconds, and occurring as single stabs, series of stabs, or in a saw-tooth pattern
C. Headache is accompanied by at least one of the following, ipsilateral to the pain:
   1. Conjunctival injection and/or lacrimation
   2. Nasal congestion and/or rhinorhoea
   3. Eyelid oedema
   4. Forehead and facial sweating
   5. Miosis and/or ptosis
D. Attacks have a frequency at least 1 per day
E. Not attributed to another disorder
SUNCT vs SUNA: ICHD-3 criteria

- **SUNCT:**
  1. Meets criteria for short-lasting unilateral neuralgiform headache attacks
  2. Both of conjunctival injection and lacrimation (tearing)

- **SUNA:**
  1. Meets criteria for short-lasting unilateral neuralgiform headache attacks
  2. Only one or neither of conjunctival injection and lacrimation (tearing)

### SUNCT: Attack Phenotypes

![SUNCT Attack Phenotypes Diagram](Cohen_Cephalalgia_2006)

### Abnormal Examination and Imaging Findings in SUNCT

<table>
<thead>
<tr>
<th>SUNCT (10)</th>
<th>Abnormal examinations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lateral reduced sensation to pinprick 5 (12%)</td>
</tr>
<tr>
<td></td>
<td>Ipsilateral hypesthesia 1 (2%)</td>
</tr>
<tr>
<td></td>
<td>Ipsilateral changes post procedures 1 (2%)</td>
</tr>
<tr>
<td></td>
<td>Other neurological abnormalities 6 (14%)</td>
</tr>
<tr>
<td>Intracranial imaging</td>
<td>Total number imaged 37</td>
</tr>
<tr>
<td></td>
<td>Normal intracranial appearances 20 (54%)</td>
</tr>
<tr>
<td></td>
<td>Incidental findings 6 (16%)</td>
</tr>
<tr>
<td></td>
<td>Abnormal intracranial appearances:</td>
</tr>
<tr>
<td></td>
<td>Vascular loops 3 (8%)</td>
</tr>
<tr>
<td></td>
<td>Pathological white matter changes 2 (5%)</td>
</tr>
<tr>
<td></td>
<td>Pituitary lesions 3 (8%)</td>
</tr>
<tr>
<td></td>
<td>Space occupying lesions 2 (5%)</td>
</tr>
<tr>
<td></td>
<td>Unusual configuration in brainstem and lenticule in thalamus 1 (5%)</td>
</tr>
<tr>
<td></td>
<td>Total abnormal intracranial appearances 13 (29%)</td>
</tr>
</tbody>
</table>

*Cohen Cephalalgia 2006*
Prophylactic Treatments in SUNCT

<table>
<thead>
<tr>
<th></th>
<th># of Patients</th>
<th>Effective</th>
<th>Ineffective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen</td>
<td>10</td>
<td>0 (0%)</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>12</td>
<td>0 (0%)</td>
<td>12 (100%)</td>
</tr>
<tr>
<td>IV lidocaine</td>
<td>11</td>
<td>11 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>25</td>
<td>17 (68%)</td>
<td>8 (32%)</td>
</tr>
<tr>
<td>Topiramate</td>
<td>21</td>
<td>11 (52%)</td>
<td>10 (48%)</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>22</td>
<td>10 (45%)</td>
<td>12 (55%)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>36</td>
<td>14 (39%)</td>
<td>22 (61%)</td>
</tr>
<tr>
<td>Greater occipital nerve injection</td>
<td>8</td>
<td>5 (63%)</td>
<td>3 (37%)</td>
</tr>
</tbody>
</table>

SUNCT/SUNA vs Trigeminal Neuralgia

- **Location:**
  - V1 vs V2/V3

- **Refractory period:**
  - SUNCT/SUNA can be triggered without a refractory period
  - TN usually has a refractory period after each attack

- **Some patients have overlapping symptoms, and should be diagnosed with both**

Hemicrania Continua: ICHD-3 Diagnostic Criteria

A. Unilateral headache fulfilling B-D
B. Present for > 3 months, with exacerbations of moderate or greater intensity
C. Either or both of the following:
   A. At least one of the following, ipsilateral to the pain:
      A. Conjunctival injection and/or lacrimation
      B. Nasal congestion and/or rhinorrhea
      C. Eyelid oedema
      D. Forehead and facial sweating
      E. Miosis and/or ptosis
   B. A sense of restlessness or agitation, or aggravation of the pain by movement
D. Responds absolutely by therapeutic doses of indomethacin
E. Not attributed to another disorder
Hemicrania Continua: Pain Exacerbations

- Case series from Jefferson Medical Center – 34 patients
- Migrainous features
  - Nausea: 53%
  - Vomiting: 24%
  - Photophobia: 59%
  - Phonophobia: 59%
- Autonomic features (74% - at least one autonomic sx)
  - Lacrimation: 53%
  - Nasal congestion: 21%
  - Ptosis: 18%
- Other features
  - Jabs and jolts: 41%
- Other key features: eyelid edema, eyelid twitching, foreign body sensation in eye ipsilateral to headache

Rozen Neurol Clin 2009

Hemicrania Continua: Remitting vs Unremitting

- Hemicrania Continua, remitting subtype (12%)
  - Headache is not daily or continuous, but interrupted by remission periods of > 1 day without treatment
- Hemicrania Continua, unremitting subtype (88%)
  - Headache is daily and continuous for at least 1 year, without remission periods of at least 1 day

ICHD-3, Cephalalgia 2018

Hemicrania Continua: Treatment Options

- Indomethacin
  - ICHD-3: “should be used initially in an oral dose of at least 150 mg daily and increased if necessary up to 225 mg daily. Smaller maintenance doses are often employed.”
  - One suggestion for dosing: 25mg PO TID and increase every 5 days to 50mg-75mg TID, once remission achieved taper down to lowest effective dose
  - PPI for GI prophylaxis

- Non-indomethacin options:
  - Melatonin
  - Topiramate
  - Occipital nerve block
  - Gabapentin
### Trigeminal Autonomic Cephalgias

<table>
<thead>
<tr>
<th>Feature</th>
<th>PH</th>
<th>SUNCT</th>
<th>Cluster</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex F:M</td>
<td>2:1</td>
<td>1:2</td>
<td>1:3</td>
</tr>
<tr>
<td>Attack duration</td>
<td>~15 mins</td>
<td>~1 min</td>
<td>60 mins</td>
</tr>
<tr>
<td>Attack frequency</td>
<td>11</td>
<td>~30</td>
<td>1</td>
</tr>
<tr>
<td>Treatment of choice</td>
<td>Indomethacin</td>
<td>Lamotrigine</td>
<td>Verapamil</td>
</tr>
</tbody>
</table>

Thank you