Cluster Headache

OBJECTIVES
- Describe the clinical features and diagnosis of cluster headache
- Discuss the pathogenesis of cluster pain and autonomic features
- Review acute and preventive therapy
- Overview of new treatment horizons for refractory chronic cluster

IHS CLASSIFICATION
- Cluster headache
  - Episodic type (80%)
  - Chronic type (20%)
    (Cluster period lasts for more than one year without remission or remission lasts less than 14 days)

Cluster Periods

AGE OF ONSET
- 80% with first attack (2nd-4th decades)
- Mean age of onset 31.5 years (27-37 yrs)
- Range
  - Youngest – 1 yr old
  - Oldest – 80+ yrs

CIRCADIAN PERIODICITY
- Cluster Attacks
  - 1 to 3 attacks daily (up to 8 attacks/day)
  - Peak time periods

CIRCANNUAL PERIODICITY
- Cluster Periods
  - Kudrow L. Cephalalgia. 1987
  - Waldenlind E. Cluster Headache and Related Conditions. 1999

REM sleep; Obstructive sleep apnea

ATTACK PROFILE

- Unilateral orbital / temporal severe pain
- Rapid onset (5 – 15 min)
- Short duration (45 – 90 min)
- Agitation/restlessness (90%)
- Autonomic features
- "Migrainous" symptoms: nausea, photophobia, phonophobia, aura

CRANIAL AUTONOMIC SYMPTOMS

- Lacrimation (90%)
- Conjunctival injection (75%)
- Nasal stuffiness, rhinorrhea (75%)
- Ptosis, eyelid edema (75%)

DISTINGUISHING CLUSTER FROM OTHER TRIGEMINAL AUTONOMIC CEPHALGIAS

<table>
<thead>
<tr>
<th>Feature</th>
<th>Cluster</th>
<th>PH</th>
<th>SUNCT</th>
<th>HC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M:F)</td>
<td>3:1</td>
<td>1:3</td>
<td>3:1</td>
<td>1:2</td>
</tr>
<tr>
<td>Attack duration</td>
<td>60 min</td>
<td>15 min</td>
<td>5-250 s</td>
<td>mins-days</td>
</tr>
<tr>
<td>Attack frequency</td>
<td>1-3/day</td>
<td>5/day</td>
<td>1/day-30/hr</td>
<td>variable</td>
</tr>
<tr>
<td>Autonomic features</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Indocin effect</td>
<td>+/-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

SUNCT = short-lasting unilateral neuralgiform pain with conjunctival injection and tearing syndrome; PH = paroxysmal hemicrania; HC = hemicrania continua

PATHOGENESIS OF PAIN: AUTONOMIC SIGNS

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

PERIODICITY: THE RESULT OF DYSFUNCTIONAL HYPOTHALAMUS

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

HYPOTHALAMIC DYSFUNCTION-CLUSTER AND SUNCT

- H-Spectroscopy demonstrates decreased NAA/Cr ratio in ipsilateral posterior hypothalamus suggesting neuronal loss/dysfunction


CLUSTER HEADACHE PATHOGENESIS

- Trigger: nitroglycerin, alcohol, photoperiod stress, sleep-wake cycle alteration.

<table>
<thead>
<tr>
<th>Brain Areas</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothalamus</td>
<td>SSN</td>
</tr>
<tr>
<td>Trigeminal ganglion</td>
<td>Pterygopalatine ganglion (parasympathetic)</td>
</tr>
<tr>
<td>Superior cervical ganglion</td>
<td></td>
</tr>
</tbody>
</table>

TREATMENT

Medical Treatment

- Acute Therapy
- Preventive Therapy

ACUTE TREATMENT

- High efficacy
  - O₂
  - Sumatriptan subcutaneous (6 mg)
  - Sumatriptan nasal spray (20 mg)
  - Zolmitriptan (10 mg oral)
  - IV/IM/SC dihydroergotamine mesylate 0.5mg – 1.0 mg
  - Octreotide subcutaneous (100 mg)

- Limited efficacy
  - Ergotamine 1 mg – 2 mg oral or suppository
  - DHE nasal spray
  - Intranasal lidocaine


OXYGEN

- 100% O₂: 7 – 10 liters / min for 15 to 20 minutes
- Efficacy 70% at 15 minutes
- Most effective when headache is at maximum intensity
- May delay rather than abort attack
- Main limitation is lack of accessibility and inconvenience


OXYGEN INHALATION FOR EPISODIC AND CHRONIC CLUSTER

<table>
<thead>
<tr>
<th>Sex and type of cluster</th>
<th>N</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episodic</td>
<td>26</td>
<td>21</td>
<td>80.8</td>
</tr>
<tr>
<td>Chronic</td>
<td>19</td>
<td>13</td>
<td>68.4</td>
</tr>
<tr>
<td>Subtotal</td>
<td>45</td>
<td>34</td>
<td>75.6</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episodic</td>
<td>7</td>
<td>5</td>
<td>71.4</td>
</tr>
<tr>
<td>Chronic</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subtotal</td>
<td>7</td>
<td>5</td>
<td>71.4</td>
</tr>
<tr>
<td>Total</td>
<td>52</td>
<td>39</td>
<td>75.0</td>
</tr>
</tbody>
</table>


15-MINUTE RESPONSE HEADACHE–SUMATRIPTAN SC (6 MG) VS PLACEBO


- Sumatriptan 6 mg sc
- Placebo

*p<0.001 vs. placebo

Study 1: N=39
Study 2: N=134
**30-MIN RESPONSE HEADACHE—SUMATRIPTAN NASAL SPRAY (20 MG) VS PLACEBO**

- **Sumatriptan 20 mg**
- **Placebo**

<table>
<thead>
<tr>
<th>Headache Response</th>
<th>Pain Free</th>
</tr>
</thead>
<tbody>
<tr>
<td>57</td>
<td>26</td>
</tr>
<tr>
<td>47</td>
<td>18</td>
</tr>
</tbody>
</table>

p = 0.002


**SUMATRIPTAN SUBCUTANEOUS**

- No tachyphylaxis with repeated use
- Attack frequency not increased with prolonged use
- Not effective for preemptive or preventive treatment
- Overall and median time to pain relief longer in patient with chronic cluster headache


**ZOMITRIPTAN ORAL TABLET (10 MG) VS PLACEBO IN EPISODIC CLUSTER**

- **Zolmitriptan 5 mg**
- **Zolmitriptan 10 mg**
- **Placebo**

<table>
<thead>
<tr>
<th>Headache Response</th>
<th>Pain Free</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>40</td>
</tr>
<tr>
<td>47</td>
<td>18</td>
</tr>
</tbody>
</table>

p = 0.002


**CLUSTER HEADACHE PREVENTION**

**Transitional**
- Prednisone
  - (60 mg daily for 3 days, then 10 mg decrements every 3 days)

**Maintenance**
- Verapamil **
  - (240 mg to 720 mg/day)
- Methysergide
  - (2 mg tid; up to 12 mg daily)
- Lithium carbonate
  - (150 mg to 300 mg tid)
- Occipital Nerve Block **

**Class-I evidence available**


**VERAPAMIL FOR EPISODIC CLUSTER HEADACHE**

- **Verapamil 120 mg tid**
- **Placebo**

<table>
<thead>
<tr>
<th>Attacks per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run in 5 days</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>15</td>
</tr>
<tr>
<td>15</td>
</tr>
<tr>
<td>15</td>
</tr>
</tbody>
</table>

* p < 0.001 vs placebo


**CLUSTER HEADACHE OTHER PREVENTIVE OPTIONS**

- Melatonin (10 mg HS)
- Topiramate (50 mg to 200 mg/day)
- Gabapentin (900 mg to 2400 mg/day)
- Divalproex sodium (500 mg to 3000 mg/day)
- Occipital Nerve Block
  - (92% response rate > > 50% reduction in attack frequency; 70% remission Rate by 4 weeks)

REFRACTORY CLUSTER HEADACHE

- Combination therapy
- Hospitalization / headache specialist (repetitive IV DHE; IV methylprednisolone)
- Surgery

Dodick DW, Campbell JK. Wolff's Headache And Other Head Pain. 2001.

INDICATIONS FOR SURGERY

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

Dodick DW, Campbell JK. Wolff's Headache And Other Head Pain. 2001.

SURGICAL PROCEDURES FOR CLUSTER HEADACHES

- Sensory trigeminal pathway procedures
  - Radiofrequency or glycerol rhizotomy
  - Gamma knife radiosurgery
  - Trigeminal root section
- Autonomic (parasympathetic) pathway procedures
- Hypothalamic stimulation
- Occipital nerve stimulation


NEW TREATMENT HORIZON

Deep Brain and Occipital Nerve Stimulation

12 patients with refractory chronic cluster headache
Stimulating electrode implanted into periventricular hypothalamus ipsilateral to pain
Occipital nerve stimulation may be promising less invasive modality

Leone M et al. Cephalalgia 2003