Trigeminal Autonomic Cephalgias

IHS Master’s School in Brazil - Phase III
São Paulo
May 12, 2012

Alan M. Rapoport, M.D.

PRESIDENT ELECT
THE INTERNATIONAL HEADACHE SOCIETY

CLINICAL PROFESSOR OF NEUROLOGY
DAVID GEFFEN SCHOOL OF MEDICINE AT UCLA
LOS ANGELES, CALIFORNIA

FOUNDER AND DIRECTOR-EMERITUS
THE NEW ENGLAND CENTER FOR HEADACHE
STAMFORD, CT
Headache Classification

**Primary Headaches**
- Migraine
- Tension-type
- Trigeminal Autonomic Cephalgias
  - *Cluster headache*

**Secondary Headaches**
- Tumor, hemorrhage
- Meningitis, trauma
- ?Sinusitis, ? Cervical problem
- ?TMD
- Giant cell arteritis
- Other systemic disorders

Short-Lasting Headaches

_Last less than 4 hours_

Differentiated clinically by the presence or absence of _autonomic features_
Short-Lasting Headaches

Without autonomic features:

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

With autonomic features (TACs)

- **Cluster**
  - The paroxysmal hemicranias
  - SUNCT and SUNA
  - Cluster-Tic
  - CPH-Tic
  - (Hemicrania Continua) (Exacerbations are short-lasting with autonomic features)
Cluster Headache
Epidemiology

- Rare disorder affecting approximately 0.09 – 0.4% of the US population

- Sex ratio (M:F) (Manzoni, *Cephalalgia* 1998)
  - Prior to 1960  6.2:1
  - 1980-1987  3.0:1
  - 1990-1995  2.1:1
  - ICHD-II  3-4:1
The Trigeminovascular System of Moskowitz

Goadsby. NEJM 2000
Cluster Headache: Pathophysiology

- Not fully understood
- Pain distribution suggests activation of trigeminovascular pathways
- Associated autonomic signs implicate blood-flow changes within cavernous sinus or stimulation of the trigeminal autonomic pathway
- Temporal profile (circadian pattern) of attacks and seasonal (circannual pattern) suggest disruption of hypothalamic circadian rhythm (Kudrow)
- PET studies reveal increased metabolic activity in ipsilateral hypothalamic suprachiasmatic nucleus (May & Goadsby)
- Leone/Bussone: DBS in posterior hypothalamus successful in > 22 pts
Hypothalamic Dysfunction-Cluster and SUNCT

Pathogenesis of Pain: Autonomic Signs

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

Cluster Headache Definitions

- **Cluster Period** - Time during which attacks recur on a daily basis
- Typical period cycle lasts 4-8 weeks (range 2 weeks to 6 months)
- **Remission Period** - Time during which patient experiences no headaches - even if exposed to triggers
- Typical remission period lasts 6-12 months
3.1 Cluster headache

A. At least 5 attacks fulfilling criteria B-D
B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 min if untreated
C. Headache is accompanied by ≥1 of the following:
   1. ipsilateral conjunctival injection and/or lacrimation
   2. ipsilateral nasal congestion and/or rhinorrhoea
   3. ipsilateral eyelid oedema
   4. ipsilateral forehead and facial sweating
   5. ipsilateral miosis and/or ptosis
   6. a sense of restlessness or agitation
D. Attacks have a frequency from 1/2 d to 8/d
E. Not attributed to another disorder
Cluster Headache: Clinical Features

- Headaches are unilateral, rare side-shift
- Maximal pain is retro- and peri-orbital
- Pain may radiate into ipsilateral temple, jaw, V2 especially the upper teeth and neck
- Pain is excruciatingly severe, with tremendous pressure or “hot poker” being twirled
- Agitation with pacing or rocking activity; patients cannot stay still (now diagnostic)
- Called the “Suicide headache”
Location of Maximal Pain During Cluster Attacks in 180 Patients

- Ocular: 145 patients
- Temporal: 135 patients
- Frontal: 130 patients
- Maxillary: 90 patients
- Zygomatic: 80 patients
- Nasal: 60 patients
- Parietal: 50 patients
- Occipital: 40 patients
- Auricular: 30 patients
- Mandibular: 20 patients
- Cervical: 10 patients
- Scapular: 5 patients

*Raskin NH: Headache 2nd Ed p231*
Pain Location

- Raskin NH: Headache 2nd Ed p230
Cluster headache
Associated Clinical Features

- Motor restlessness (93%)
- Lacrimation (91%)
- Conjunctival injection (77%)
- Nasal congestion (75%)
- Ptosis or eyelid swelling (74%)
- Rhinorrhea (72%)
- Horner’s syndrome (30%)
- Nausea (50%)/Vomiting (23%)
- Photophobia (56%)
- Phonophobia (43%)
- Aura (14%)--mostly visual, 36% of these also had migraine

Kudrow Cluster headache 1980
Cluster Headache
Comorbidities and Mimics

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

The Case of John, the Executive

- John is a 40 yo executive and in the last 5 years he has had 3 episodes of left sided headache for weeks at a time.
- Each series of headaches start in March and continue daily for 4-6 weeks. Every day he gets 2 headaches, one at 2 am and one at 6 pm.
- They are over the left eyebrow, 10/10 intensity, pressure, excruciating steady pains.
- Left eye turns red and tears and the eyelid droops.
- Duration: 1 hour.
- Triggers: napping, 2 caipirinhas (in a cluster period).
- Treatment: Nothing has helped (propranolol, divalproex sodium, amitriptyline, opiates).
- Behavior: agitated, rocking, moving.
- In between attacks he is pain free.
The Case of John the Executive

Examination:

- He is tall and thin with a furrowed brow
- During an attack he bends forwards and rocks
- Left eye red and tearing with small pupil and ptosis
- MRI with gadolinium normal

- Diagnosis ?
- Treatment ?
The Case of John the Executive

Treatment

- Start verapamil 240 mg tid and increase to 480 mg tid after checking EKG
- Rent a D cylinder oxygen tank for the bedroom.
- Use in the sitting position bending forwards
- Sumavel Dose Pro (sumatriptan 6 mg sc)
- Consider zolmitriptan 5 mg nasal spray
Cluster Headache in the US - Rozen

- A survey of 187 questions placed on a website for 3 months in 2008
- 1134 completed, 816 males, 318 females
- 5 year delay in diagnosis
- At initial examination only 21% had correct diagnosis
- 55% had suicidal ideation
- Eye color brown and blue, not hazel
- Mostly right sided
- Most attacks occur between early evening and morning

Rosen TD, Fishman RS. Cluster Headache in the USA. Headache 2012;52:99-113
Cluster Headache in the US

- Peak onset between midnight and 3 am
- Triggers: beer > weather changes > smells
- Low prevalence of peptic ulcer, cardiac and cerebro-vascular diseases
- High prevalence of smoking
- High prevalence of restless legs syndrome
- Disabling: - 20% have lost a job
  - 8% are out of work or on disability

Rosen TD, Fishman RS. Cluster Headache in the USA. Headache 2012;52:99-113
Trigeminal Autonomic Cephalalgias

Cluster Headache

- Autonomic features
- Agitation, pacing
- ‘Migrainous symptoms may occur

Visual Analogue Score

Pain intensity

Time to peak

Duration

24-hour attack frequency

Side-locked

Nocturnal predilection
Trigeminal Autonomic Cephalalgias

**Paroxysmal Hemicrania**

- Pain intensity
- Visual Analogue Score
- Duration: mean 17 mins
- 24-hour attack frequency: mean 11

Cittadini et al. *Neurology* 2007
Trigeminal Autonomic Cephalalgias

**SUNCT**

![Graph showing pain intensity over time with visual analogue score](image)

- **Visual Analogue Score**
  - 00:00
  - 06:00
  - 12:00
  - 18:00
  - 24:00

- **Pain intensity**
  - 30-200 attacks per day

- **60 seconds**
Cluster Headache: Differential Diagnosis

- **Primary Headache Disorders:**
  - The paroxysmal hemicranias
  - SUNCT syndrome
  - Hemicrania continua
  - Hypnic headache

- **Secondary Headache Disorders**
  - AVMs
  - Aneurysms
  - Tumors (cervical, sphenoid, maxillary, pituitary)
  - Giant cell arteritis
  - Dissection
  - Venous sinus occlusion
### RELATED SYNDROMES

#### “Trigeminal-autonomic cephalgias”

<table>
<thead>
<tr>
<th></th>
<th>CPH</th>
<th>EPH</th>
<th>SUNCT</th>
<th>Cluster</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: F:M</td>
<td>3:1</td>
<td>1:1</td>
<td>1:2.3</td>
<td>1:4</td>
</tr>
<tr>
<td>Attacks/day</td>
<td>1-40</td>
<td>3-30</td>
<td>1/d-30/hr</td>
<td>0-8</td>
</tr>
<tr>
<td>Attack duration</td>
<td>2-45 min</td>
<td>1-30 min</td>
<td>15-200 s</td>
<td>15-180 min</td>
</tr>
<tr>
<td>Indomethacin response</td>
<td>++</td>
<td>++</td>
<td>No</td>
<td>+/-</td>
</tr>
</tbody>
</table>

Cluster Headache: Acute Treatment Options

- 100% oxygen inhalation at 7-10L/min. (up to 15L/min if refractory) (Todd Rozen)
- 12L/min DB, PC vs air (Goadsby)
- Sumatriptan 6 mg sc at headache onset
- DHE 45 0.5-1.0 mg SC,IM,IV
- Zolmitriptan 5 or 10 mg nasal spray (Rapoport)
- Ergotamine tartrate SL,PO or PR
- Lidocaine 4-6% nasal drops at headache onset and 14 min later
- Methylphenidate 5 mg prn headache?
- Olanzapine?
A meta-analysis of two double-blind, placebo-controlled, randomised, three-attack crossover studies shows that zolmitriptan nasal spray 5 mg and 10 mg is significantly more effective than placebo in the acute treatment of cluster headache.

—both doses were significantly better than placebo in providing a headache response at 30 minutes, the primary end point of the two studies.

The superiority of zolmitriptan over placebo was apparent in patients with both chronic and episodic cluster headache.

Zolmitriptan nasal spray was well tolerated in patients with cluster headache.

Zolmitriptan nasal spray in the acute treatment of cluster headache: a meta-analysis of two double-blind, placebo-controlled, randomised, cross-over studies

Cecilia Hedlund, Alan M. Rapoport, Peter J. Goadsby

![Graph showing the effectiveness of Zolmitriptan nasal spray in treating cluster headache compared to placebo. The graph displays the percentage of patients responding at various time points (10 min, 15 min, 20 min, 30 min) for Placebo, ZOMIG Nasal Spray 5 mg, and ZOMIG Nasal Spray 10 mg.]
Cluster Headache: Preventive Therapy Options

- Used to shorten attack duration and frequency
- Continue for 2 weeks longer than typical cycle, then gradually taper
- **BRIDGE THERAPY:** Concurrent use of corticosteroids over 1-2 weeks (previously longer), ergots or triptans and GON block
Cluster Headache Prevention

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

**Maintenance**
- Verapamil **  
  (240 mg to 720 mg/day)
- Methysergide  
  (2 mg tid; up to 12 mg daily)
- Methylergonovine (0.2 mg tid; up to 1.2 mg daily)
- Lithium carbonate  
  (150 mg to 300 mg tid)

**Class-I evidence available**

Transitional Treatment
Occipital Nerve Block

- Placebo (10)
- ONB (13)

- Short-term response:
  - Placebo: 0%
  - ONB: P=0.0001

- Long-term response:
  - Placebo: 0%
  - ONB: P=0.0026

- Short-term response: Attack free within 72 h and sustained for 1 week
- Long-term response: Attack free within 72 h and sustained for 1 month

Cluster Headache: Preventive Therapies

- Verapamil 120-480 mg/day (or higher)
- Methysergide (not available in the U.S.)
- Methyl ergonovine (Methergine) 0.2-0.4 mg tid
- Lithium carbonate 300-900 mg/day (300 bid)
- Sodium valproate 250-1500 mg/day (Kuritzky)
- Gabapentin 1800-3000 mg/day
- Indomethacin 75-250 mg/day
- Topiramate (50 to 300 mg) ?
- Melatonin ?
- Methylphenidate 5-15 mg/day ?
- Ergotamine tartrate up to 4 mg/day
  – HS to prevent nocturnal attacks (KUDROW)
# Trigeminal Autonomic Cephalgias: Evidence-Based Treatment

## Treatment of choice

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Cluster headache</th>
<th>Paroxysmal hemicrania</th>
<th>SUNCT syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>100% $O_2$, 12 l/min (A)</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Suma 6 mg s.c. (A)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Suma 20 mg nasal (A)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Zolmi 10 mg nasal (A)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Zolmitriptan 10 mg oral (B)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lidocaine nasal (B)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Octreotide (B)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A denotes effective, B denotes probably effective, C denotes possibly effective. (suma=sumatriptan; zolmi=zolmitriptan)

## Trigeminal Autonomic Cephalgias Evidence-Based Treatment

### Therapy

<table>
<thead>
<tr>
<th></th>
<th>Cluster headache</th>
<th>Paroxysmal hemicrania</th>
<th>SUNCT syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preventive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verapamil (A)</td>
<td>Indomethacin (A)</td>
<td>Topiramate (B) *</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids (A)</td>
<td>Verapamil (C)</td>
<td>Lamotrigine (C)</td>
<td></td>
</tr>
<tr>
<td>(PO/ONB)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lithium carbonate (B)</td>
<td>NSAIDs (C)</td>
<td>Gabapentin (C) *</td>
<td></td>
</tr>
<tr>
<td>Methysergide (B)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topiramate (B)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ergotamine tartrate (B)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproic acid (C)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melatonin (C)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin (C) *</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A denotes effective, B denotes probably effective, C denotes possibly effective.

---

Cluster Headache: Treatment Resistant Patients

- Occipital nerve blocks including steroids
- Hospitalization for IV DHE
- Histamine desensitization
- Occipital Nerve Stimulation
- Surgery
Cluster Headache: Surgical Options

- Radiofrequency thermocoagulation of trigeminal ganglion is procedure of choice
- Microvascular decompression of trigeminal nerve (Janetta Procedure)
- Gamma knife lesioning root entry zone (Wolf)
- DBS of the posterior ipsilateral hypothalamus, as done at Istituto Neurologico Besta in Milano (Leone/Bussone/Franzini/Brogi)
Stimulator switched off: the attacks reappear. When it is switched on again attacks disappear.

Repeat MRI at 7 months showed electrode had not moved from original position.

Leone M et al, NEJM 2001; 345 (19): 1428-1429
Welcome to BOSTON

IHC 2013

June 27-30, 2013

American Headache Society

(2015 – Europe )
SUNCT SYNDROME
“A 66-year-old woman presented with a one-year history of headache. The headaches were short-lasting (5 to 120 seconds) episodes of moderate or severe throbbing or stabbing pain in the left retro-orbital region. They were always accompanied by intense ipsilateral tearing, conjunctival injection and nasal obstruction.

No photophobia, phonophobia or nausea was present. In the first six months after onset, the attacks were sporadic, occurring no more than four to five times a month. Subsequently they became much more frequent.”
“When she first came to our observation, she had been experiencing 10 to 30 attacks a day for 40 days. Sometimes 5-10 episodes occurred in series, with minimal pauses between them. Most occurred in the morning and afternoon.

However rare attacks would wake the patient during the night. In her most recent visits the patient reported that many attacks seemed to be provoked by stretching the neck or chewing vigorously.”
“Recent data suggest that lamotrigine is often effective, and, in the absence of more effective treatments may be considered the current first choice drug. Gabapentin and topiramate may be second choice options.

Five open label studies have been published in which 11 patients were successfully treated: eight with complete remission and 3 with significant improvement (to their complete satisfaction).

The doses used ranged from 125 to 200 mg/day. Side effects, the most common of which is skin rash, are generally avoided by starting
THE ATTORNEY IN PAIN
The Attorney in Pain

JH is a 56 year old male attorney
Intense HA in V1 and V2 on left side
Began January, 2006 after basketball injury
Initially 10 min pains in left cheek
Became 1-2 hr pains in left forehead and behind left eye
4 attacks throughout day
  - Can awaken him at night
  - No autonomic symptoms
  - Wife says he gets agitated
PREVIOUS TREATMENT

- Seen GPs, Neurologists and HA specialists
- Preventive Meds
  - Verapamil
  - Topiramate
  - Gabapentin
  - Methysergide
  - Lithium
- 2 x gangliorhizolysis operations on left 5th nerve
- 1 of 4 occipital nerve blocks helpful
HISTORY

PAST HISTORY
- Past medical history includes cardiac arrhythmia treated with ablation, uric acid kidney stones and Rosacea.
- Surgical history includes multiple joint operations and back surgery for herniated disc.

FAMILY HISTORY
- Family history includes possible migraine in his mother
MEDICATIONS

- Verapamil 80 mg 5 pills/day
- Frovatriptan 2.5 mg hs
- Zolmitriptan 5 mg nasal spray prn
- Sumatriptan 6 mg sc injections
- Oxygen 7L/min
EXAMINATION

- Complete neurological exam is normal except for the following findings:
  - Left pupil is 3.5 mm - constantly
  - Right pupil is 3 mm and they both respond well to light. No ptosis.
  - His eyes hurt when he moves them when he has a headache
  - Left foot plantar flexion weakness following disc surgery
EVALUATION

- Routine blood work normal
- Multiple CT and MRI scans with good views around the pituitary are normal.
- MRI looking for a vascular loop in the area of the left trigeminal nerve was negative (often seen in trigeminal neuralgia).
What is His Diagnosis?
IMPRESSION

- Chronic cluster headache, left, V1 and V2
- Rule out secondary causes of pain involving the left V1 and V2.
  - atypical syndrome due to larger left pupil
  - lack of autonomic symptoms
TREATMENT PLAN

- Suggest an MRI with GAD plus either an MRA or CTA with thin cuts through the cavernous sinus and 3rd nerve and pituitary area
- Rule out compression via a vascular loop
- Increase verapamil slowly to 80 mg 8 tablets/day
- Stop frovatriptan and zolmitriptan
- Increase oxygen to 15 Liters per minute
- Start ergotamine tartrate tablets bid
- Consider clomiphene
- Consider a prednisone taper, GON stimulation and DBS.
LEARNING POINTS

- This is atypical for cluster: age of onset older, no autonomic signs, left pupil larger, lack of response to medication
- Cluster must be differentiated from trigeminal neuralgia and pituitary tumor
- Migraine must be differentiated from cluster headache