# **Trigeminal Autonomic Cephalgias**

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#### **PRESIDENT ELECT** THE INTERNATIONAL HEADACHE SOCIETY

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## 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

Primary Headache 90%

ICHD -II Cephalalgia 2004; 24 (Suppl 1):1-160.

# 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 shortlasting 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



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





May A et al. Lancet. 1998; Nat Med. 1999; Neurology. 2000.

# Pathogenesis of Pain: Autonomic Signs



Trigeminovascular activation (CGRP)

Parasympathetic activation (VIP)

Internal carotid artery dilation (cavernous)

Edvinsson L, Goadsby PJ. Eur J Neurol. 1998.

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



Raskin NH: Headache 2<sup>nd</sup> Ed p231

# **Pain Location**



## 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

•Bahra A, et al. Neurology 2002 •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, excrutiating 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 survery 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

# Cluster Headache in the US

- Peak onset between midnight and 3 am
- Triggers: beer>weather changes>smells
- Low prevalence of peptic ulcer, cardiac and cerebrovascular 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

### **Trigeminal Autonomic Cephalalgias** *Cluster Headache*



### **Trigeminal Autonomic Cephalalgias** *Paroxysmal Hemicrania*



### Trigeminal Autonomic Cephalalgias SUNCT



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"

	СРН	EPH	SUNCT	Cluster
Sex: F:M	3:1	1:1	1:2.3	1:4
Attacks/day	1-40	3-30	1/d-30/hr	0-8
Attack duration	2-45 min	1-30 min	15-200 s	15-180 min
Indomethacin response	++	++	Νο	+/-

•Goadsby PJ, Lipton RB. Brain. 1997.

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 ?

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

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

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.

Hedlund C, **Rapoport A**, Dodick D, Goadsby P. "Zolmitriptan Nasal Spray in the Acute Treatment of Cluster Headache: A Meta-Analysis of Two Studies." *Headache* 2009;49:1315-1323

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

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



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

After Dodick DW et al. Cephalalgia. 2000.

### 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-l evidence available

## **Transitional Treatment Occipital Nerve Block**





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

Ambrosini et al. Pain 2005;118:92-96

Cluster Headache: Preventive Therapies

- Verapamil 120-480 mg/day (or higher)
- Methysergide (not available in the U.S.)
- Methylergonovine (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			
Therapy	Cluster headache	Paroxysmal hemicrania	SUNCT syndrome	
Acute	100% O <sub>2</sub> , 12 l/min (A)	None	None	
	Suma 6 mg s.c. (A)			
	Suma 20 mg nasal (A)			
	Zolmi 10 mg nasal (A)			
	Zolmitriptan 10 mg oral (B)			
	Lidocaine nasal (B)			
	Octreotide (B)			

effective. (suma=sumatriptan; zolmi=zolmitriptan)

•EFNS Guidelines. May A et al, Eur J Neurol 2006;13 (10):1066–1077

## **Trigeminal Autonomic Cephalgias Evidence-Based Treatment**

	Treatment of choice				
Therapy	Cluster headache	Paroxysmal hemicrania	SUNCT syndrome		
Preventive	Verapamil (A)	Indomethacin (A)	Topiramate (B) *		
	Corticosteroids (A) (PO/ONB)*	Verapamil (C)	Lamotrigine (C)		
	Lithium carbonate (B)	NSAIDs (C)	Gabapentin (C) *		
	Methysergide (B)				
	Topiramate (B)				
	Ergotamine tartrate (B)				
	Valproic acid (C)				
	Melatonin (C)				
	Gabapentin (C) *				
A denotes effective, B denotes probably effective, C denotes possibly effective.					

•EFNS Guidelines. May A et al, Eur J Neurol 2006;13 (10):1066–1077

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)

### **Preoperative condition**

### **Post-operative condition** (4 months)





Stimulator switched off: the attacks reappear. When it is switched on again attacks disappear



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

## Case Presentation SUNCT SYNDROME (3.3)

Case of Drs. D' Andrea and D' Amico from Advanced Therapy of Headache II, 2006

- "A 66-year-old woman presented with a one-year history of headache. The headaches were shortlasting (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."

## Case Presentation SUNCT SYNDROME (3.3)

Case of Drs. D' Andrea and D' Amico from Advanced Therapy of Headache II, 2006

- "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."

## Case Presentation SUNCT SYNDROME (3.3)

Case of Drs. D' Andrea and D' Amico from Advanced Therapy of Headache II, 2006

- "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 5<sup>th</sup> nerve
- 1 of 4 occipital nerve blocks helpful

# HISTORY

### PAST HISTORY

- Past medical history includes cardiac arrythmia 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