Trigeminal Autonomic Cephalalgias (TACs)

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Summary Points

- 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.

Summary Points

- 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

Costa A, Ravaglia S, Sances G, et al. Cephalalgia 2003; 23(6): 407–413

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

Lovely TJ, Kotsiakis X, Jannetta PJ. Headache 1998; 38(8): 590–594

Rhythmicity

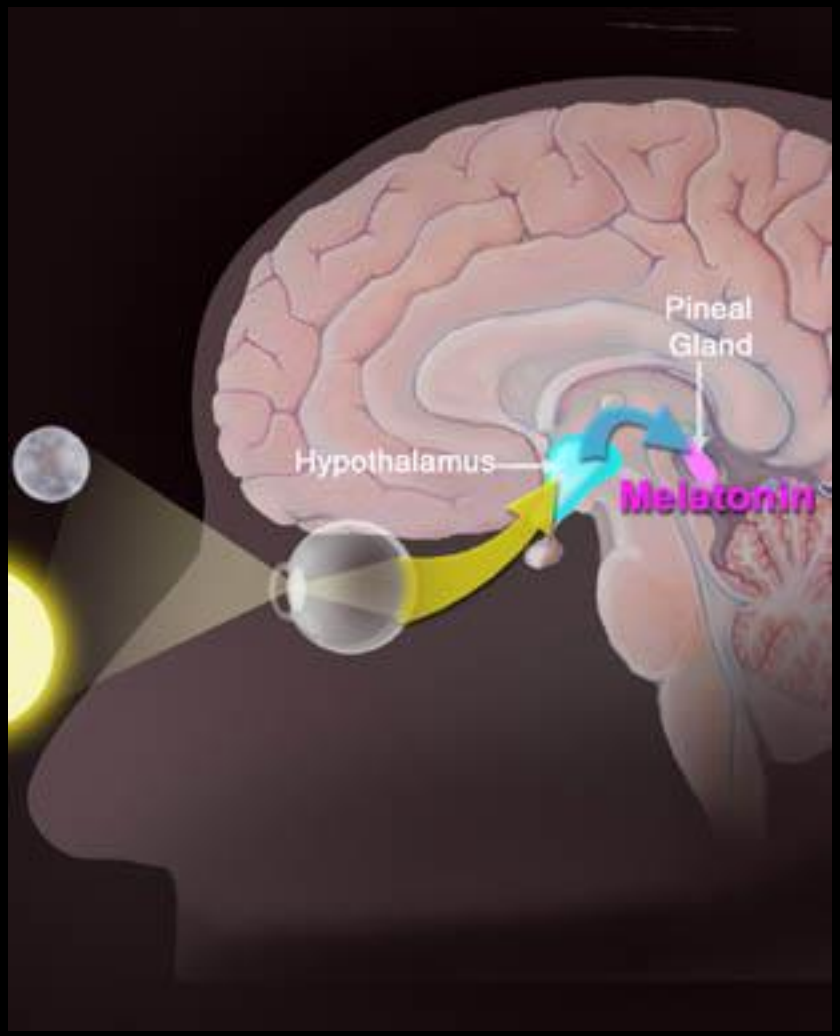
- The periodicity and sleep association in TACs suggests involvement of central sites involved in the control of the human ‘biological clock’
- Located in the suprachiasmatic nucleus, situated in the anterior part of the hypothalamus dorsal and above the optic chiasm

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 peroids

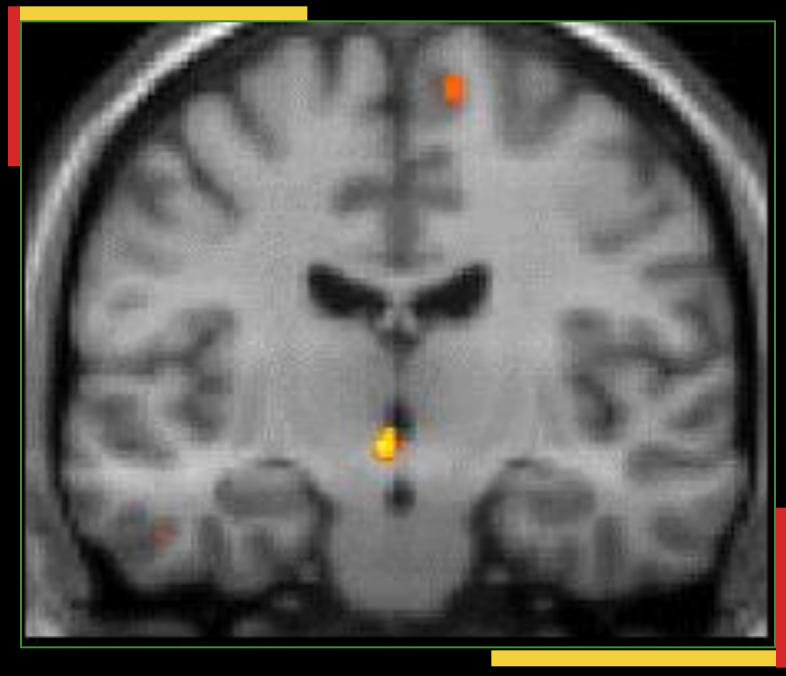
May A. Lancet 2005.

HYPOTHALAMUS – SUPRACHIASMATIC NUCLEUS

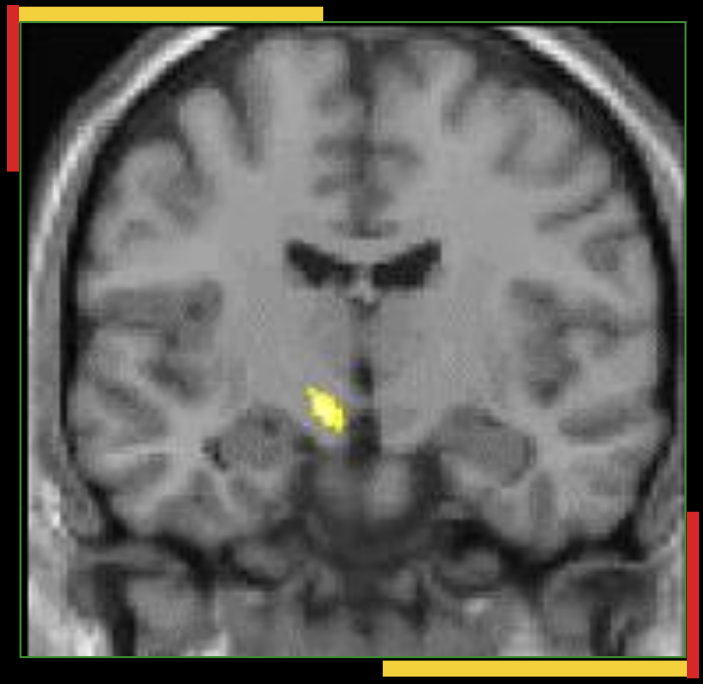


HYPOTHALAMUS ABNORMAL – FUNCTION AND STRUCTURE

Function



Structure



May A et al. *Lancet*. 1998; *Nat Med*. 1999

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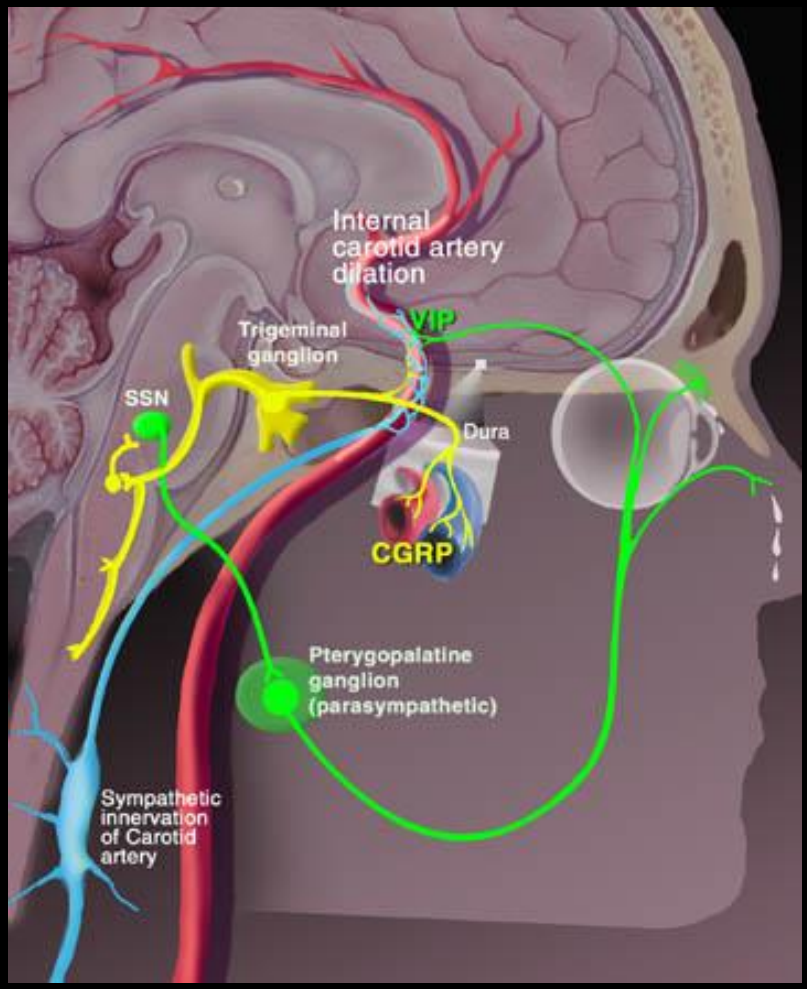
PAIN / AUTONOMIC SIGNS

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



May A. Lancet 2005

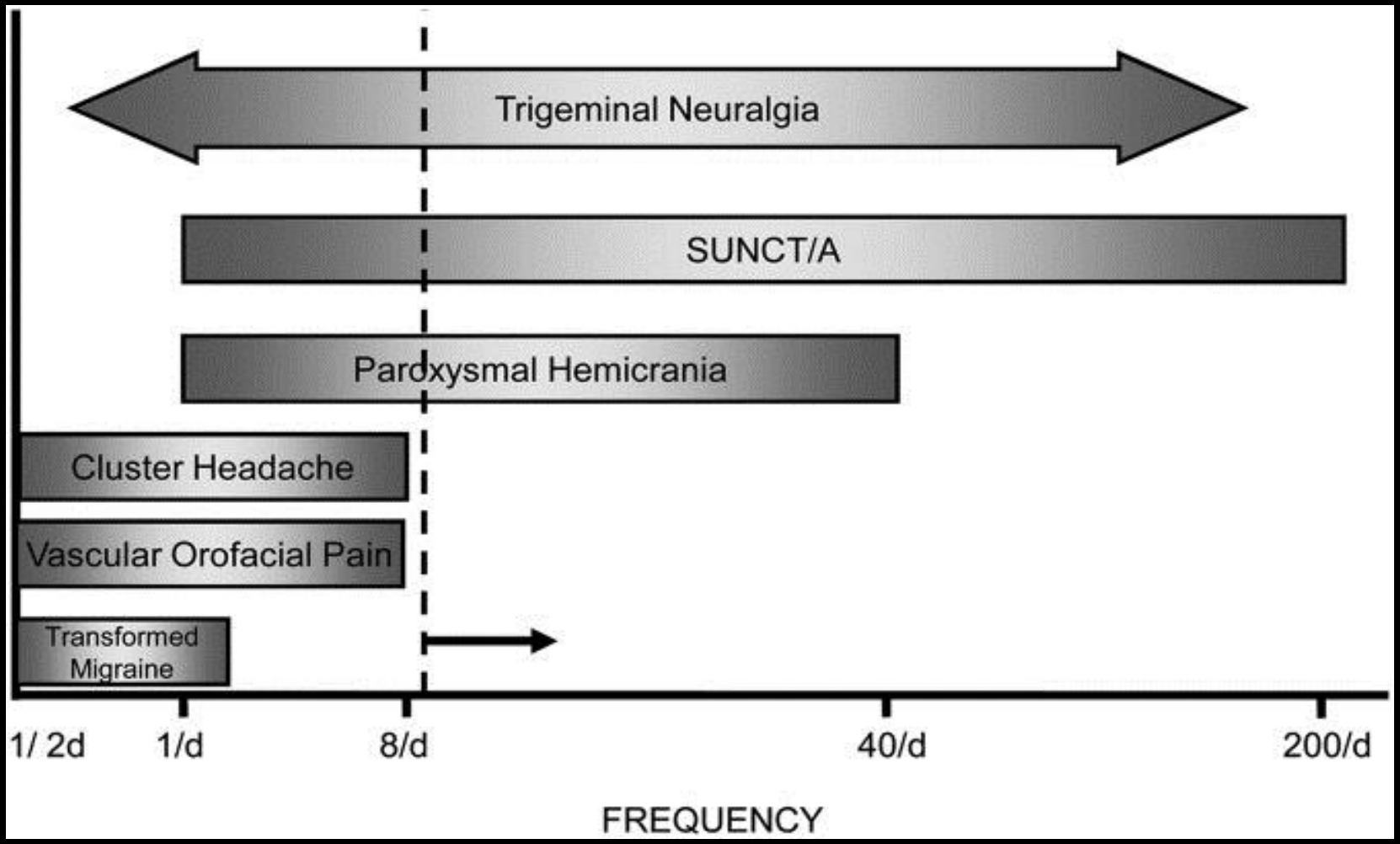
Trigeminal Autonomic Cephalgias (TACs)

- ***With autonomic features***
  - Cluster
  - The paroxysmal hemicranias
  - SUNCT and SUNA
  - Cluster-Tic
  - CPH-Tic
  - Hemicrania continua

Short-Lasting Headaches other than TACs

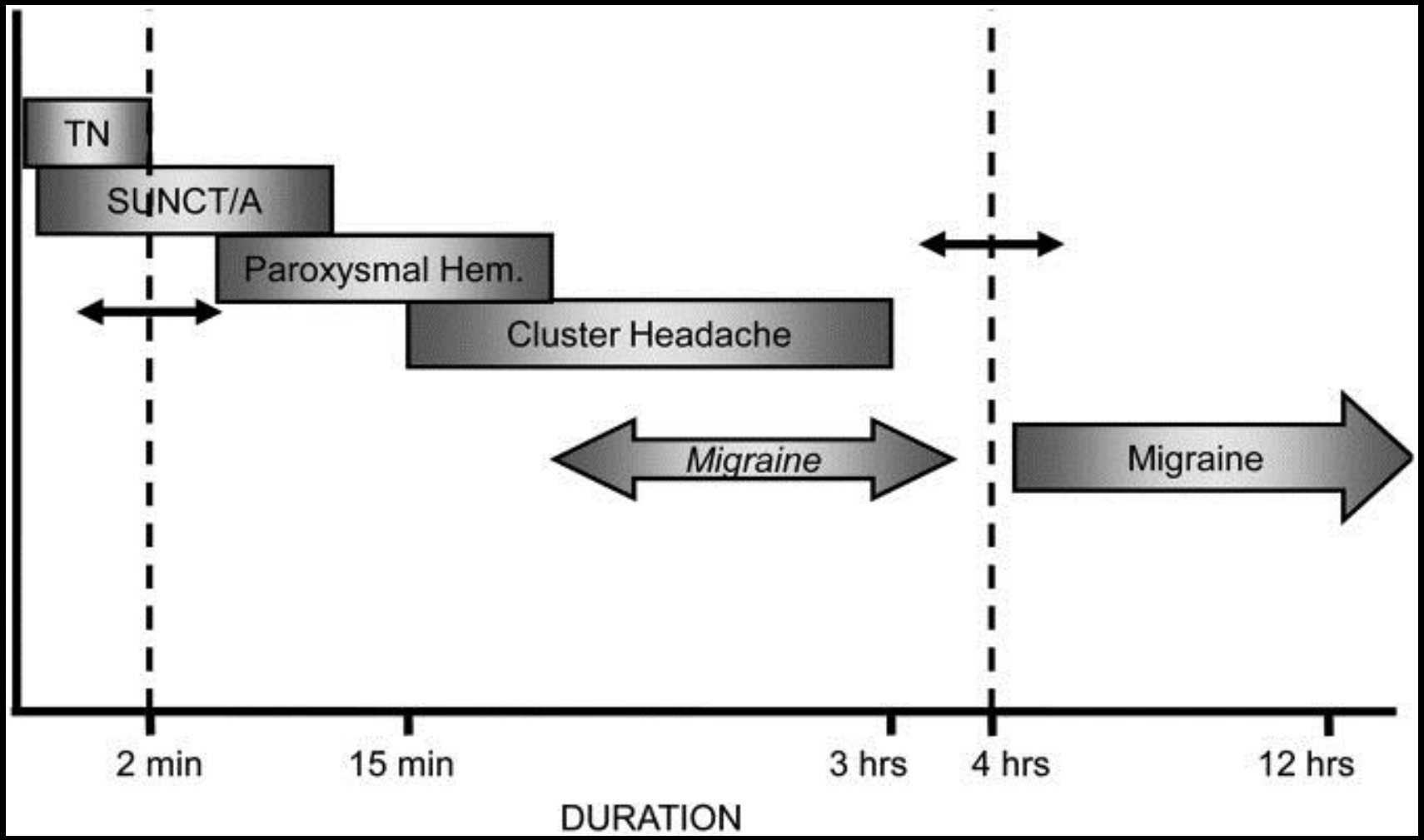
- ***Without autonomic features (These are not TACs):***
  - Trigeminal neuralgia
  - Idiopathic stabbing headaches
  - Benign cough headaches
  - Benign exertional headaches
  - Headaches associated with sexual activity
  - Hypnic headaches

FREQUENCY



Benoliel R. Trigeminal autonomic cephalgias. *British Journal of Pain*. 2012;6(3):106-123

Duration



Benoliel R. Trigeminal autonomic cephalgias. *British Journal of Pain*. 2012;6(3):106-123.

IHS CLASSIFICATION

- 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.

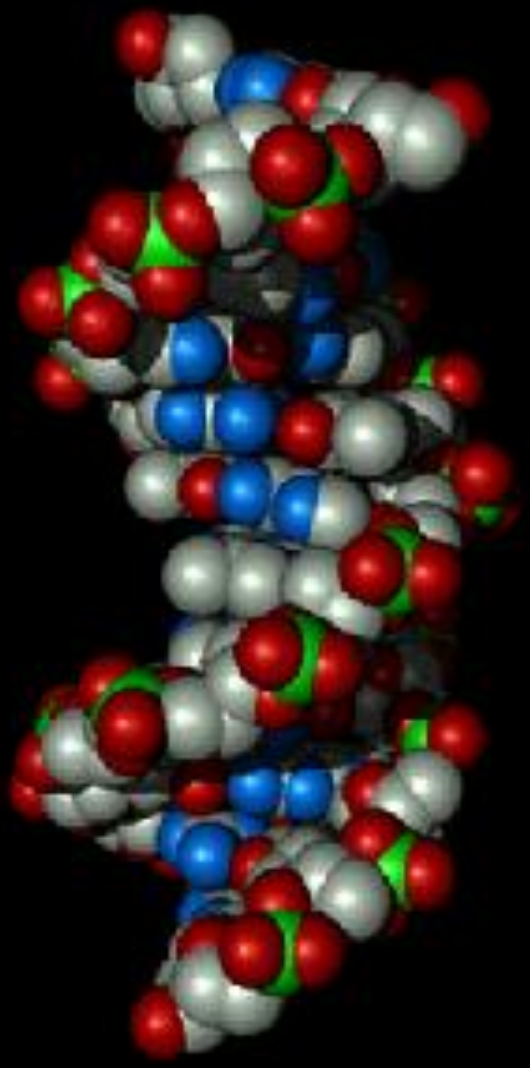
EPIDEMIOLOGY

- 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

Russell MB Lancet Neurology 2004.
Sjaastad O. *Cephalalgia*. 2003
Fischera M. Cephalalgia 2008.

GENETICS

- 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



Russel MB. *Cephalalgia*. 1997.
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

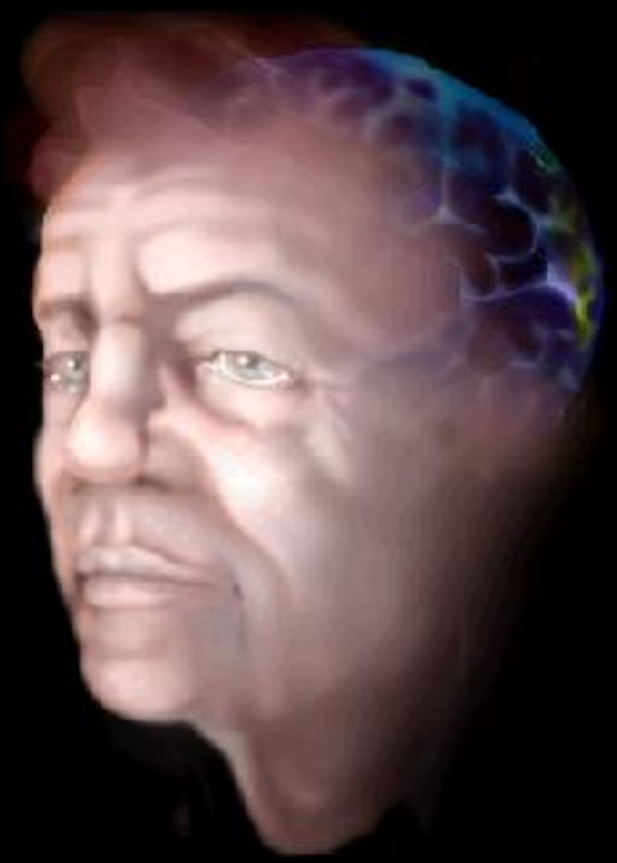
ATTACK PROFILE

- 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

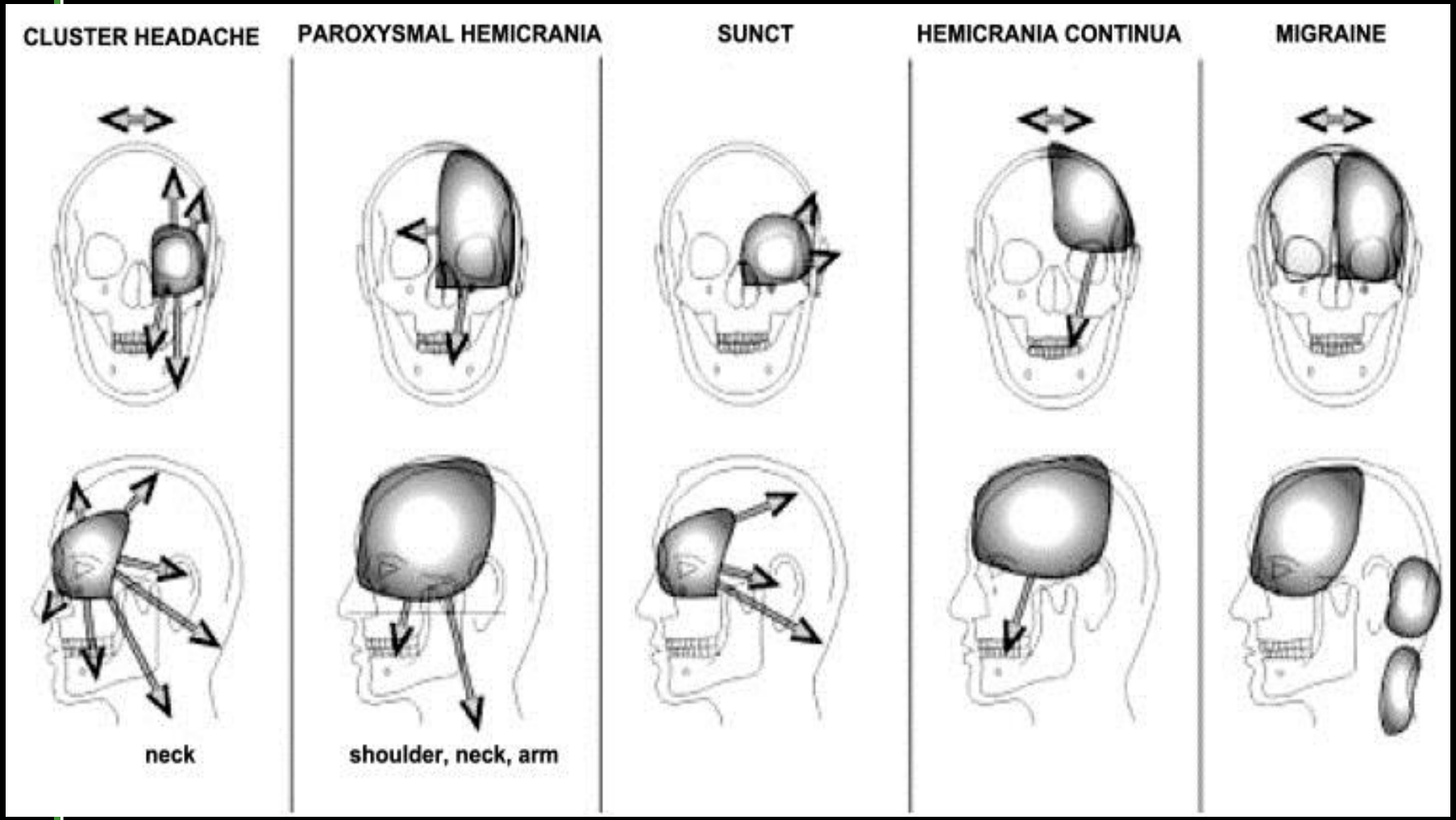
AUTONOMIC FEATURES: Parasympathetic Activity/Sympathetic Impairment

- Conjunctival injection
  lacrimation
- Nasal congestion / rhinorrhea
- Partial Horner's syndrome
- Facial flushing / sweating
  edema



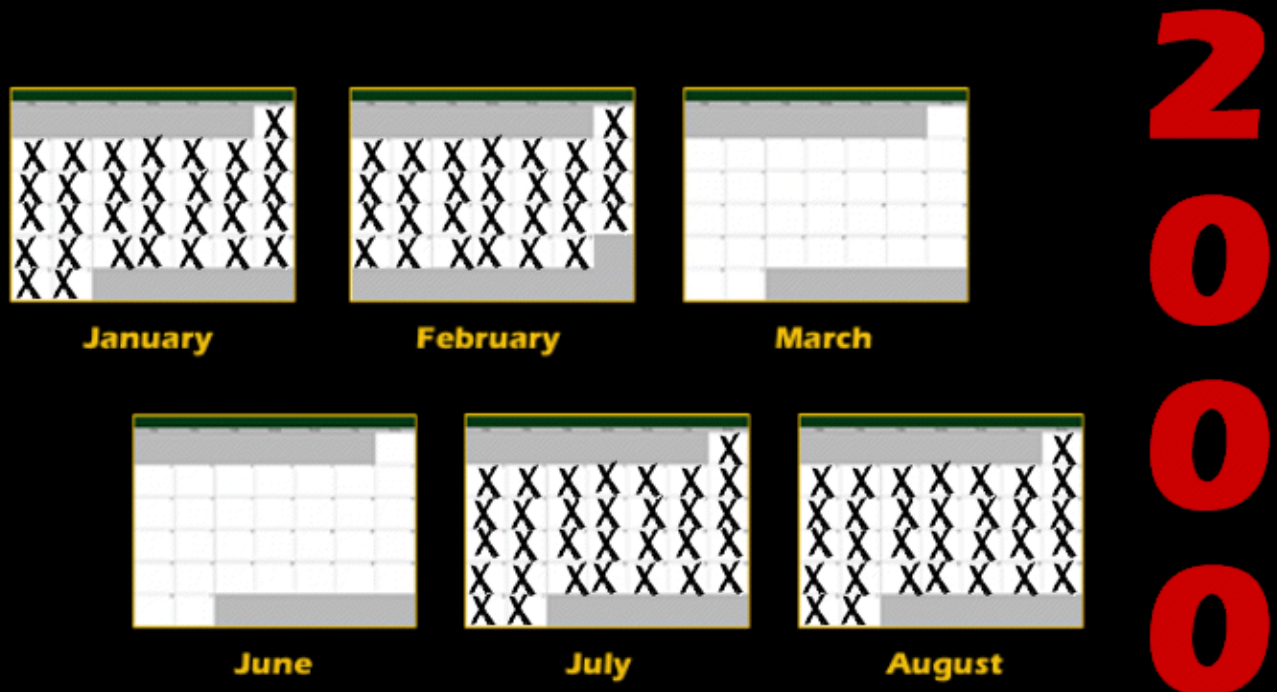
Drummond PD. Cephalalgia 2006

Pain Location



Benoliel R. Trigeminal autonomic cephalgias. *British Journal of Pain*. 2012;6(3):106-123

CIRCANNUAL PERIODICITY



May A. Lancet 2005

CIRCADIAN PERIODICITY

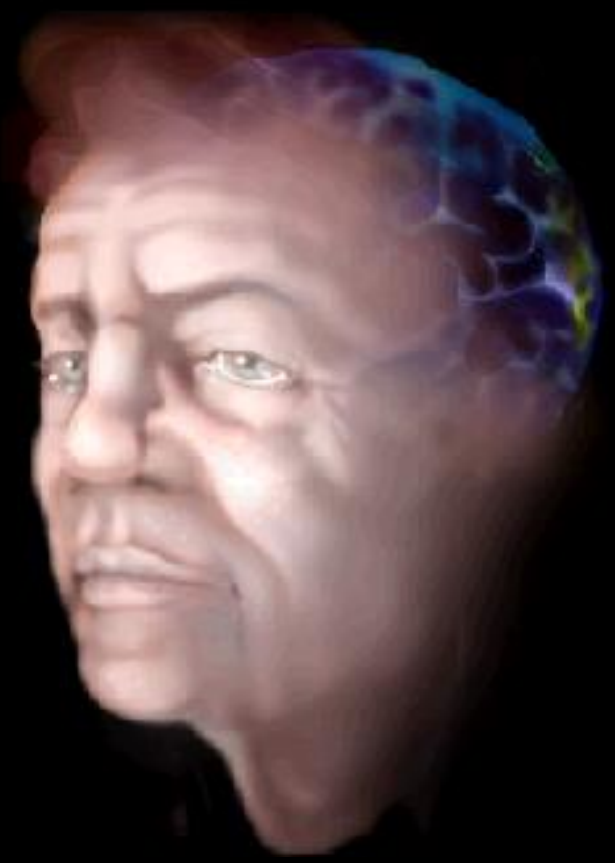
- 1-3 attacks daily (up to 8 attacks/day)
- Peak time periods

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?



ICHD-3

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

ICHD-3

- 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

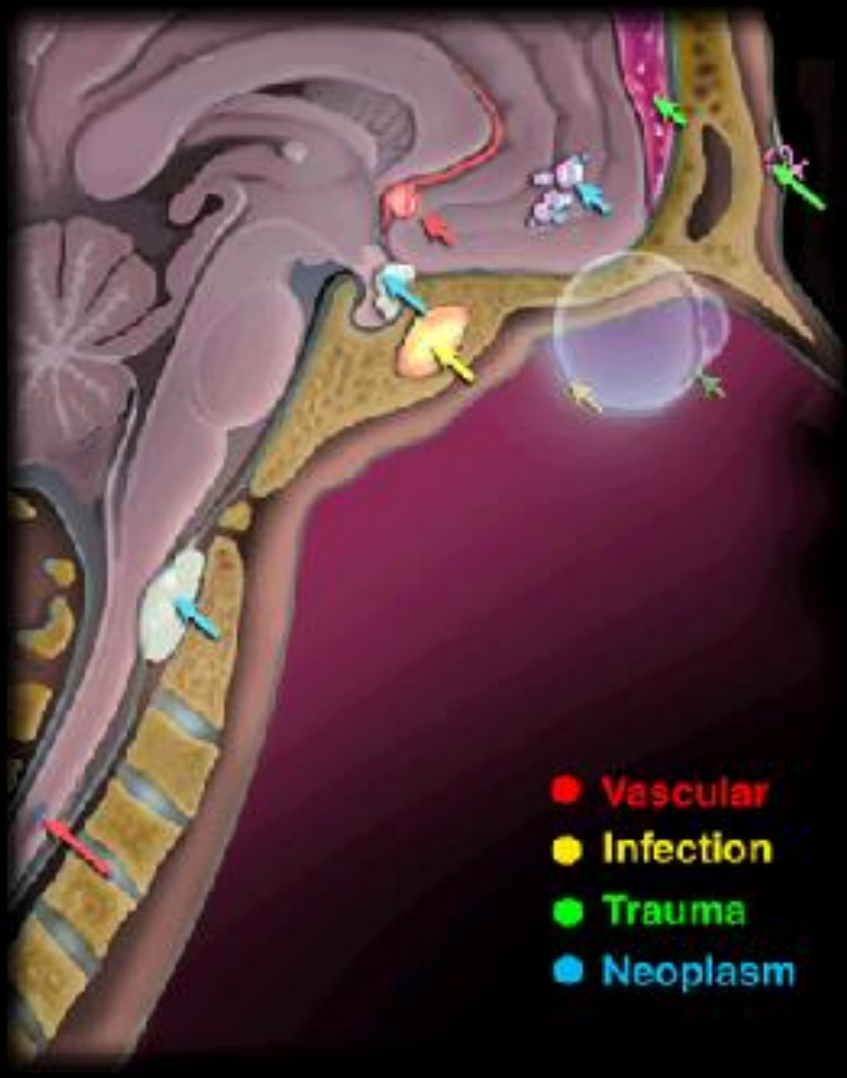
Diagnostic Criteria for Episodic Cluster

- 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
- Meninigiomas
- AVMs
- Pituitary macroadenomas
- Recurrent nasopharyngeal carcinoma
- Aspergilloma in sphenoid sinus
- Benign posterior fossa tumor
- Lymphomas

CLUSTER HEADACHE DIFFERENTIAL DIAGNOSIS

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

Goadsby PJ, Lipton RB. *Brain*. 1997.

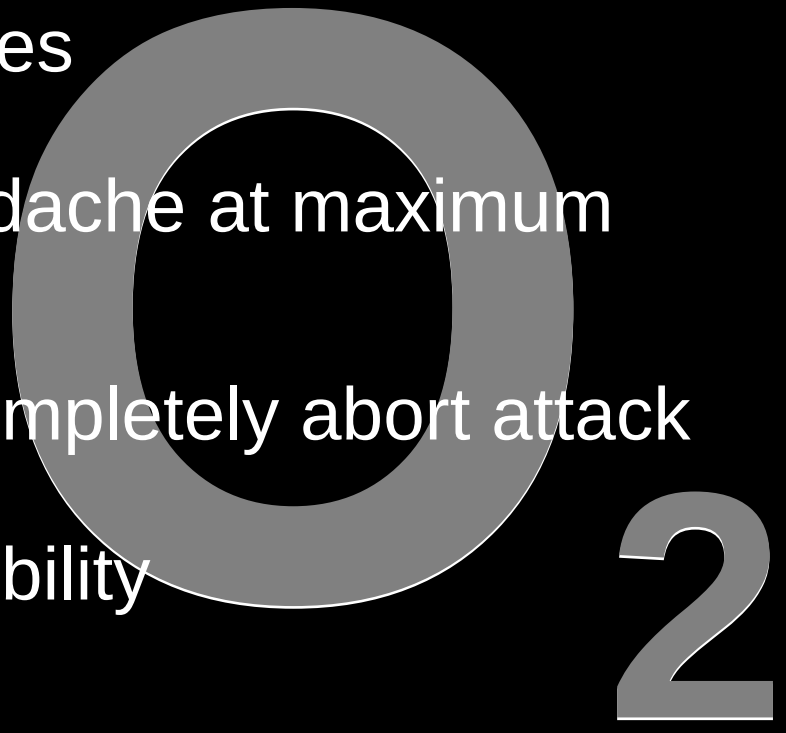
ACUTE TREATMENT

- 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..
Gooriah R. Ther Clin Risk Manag 2015.

OXYGEN

- 100% O_2 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

Gobel H et al. *Neurology*. 1998.
Ekbom K et al. *Cephalalgia*. 1995.
Cochrane, 2013

Control/Supression 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)

Leone M et al. *Cephalalgia*. 1996.
Wheeler SD, Carrazana EJ. *Neurology*. 1999.

REFRACTORY CLUSTER HEADACHE

- Combination therapy
  - Lithium + Verapamil
  - Valproate + Lithium
  - Topiramate + Verapamil

Cluster Headache: Treatment Resistant Patients

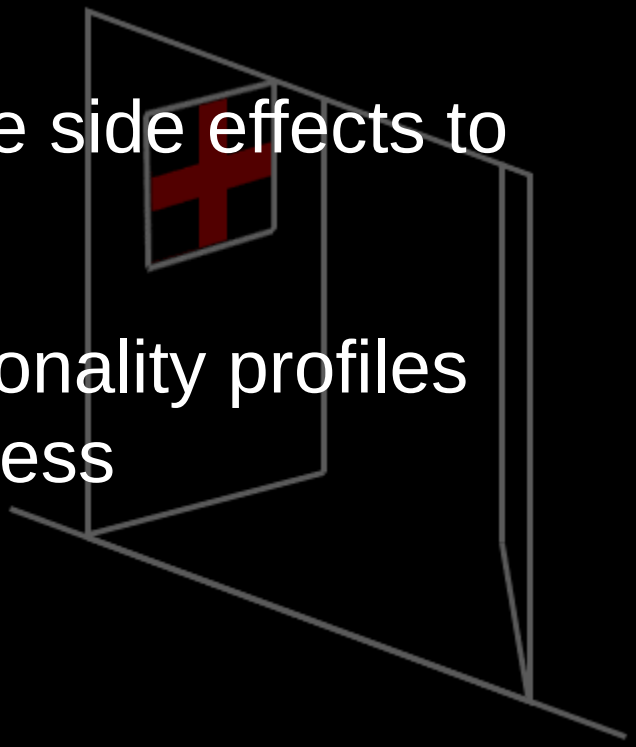
- Hospitalization for IV DHE
- Histamine desensitization
- Occipital nerve blocks
- Surgery

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

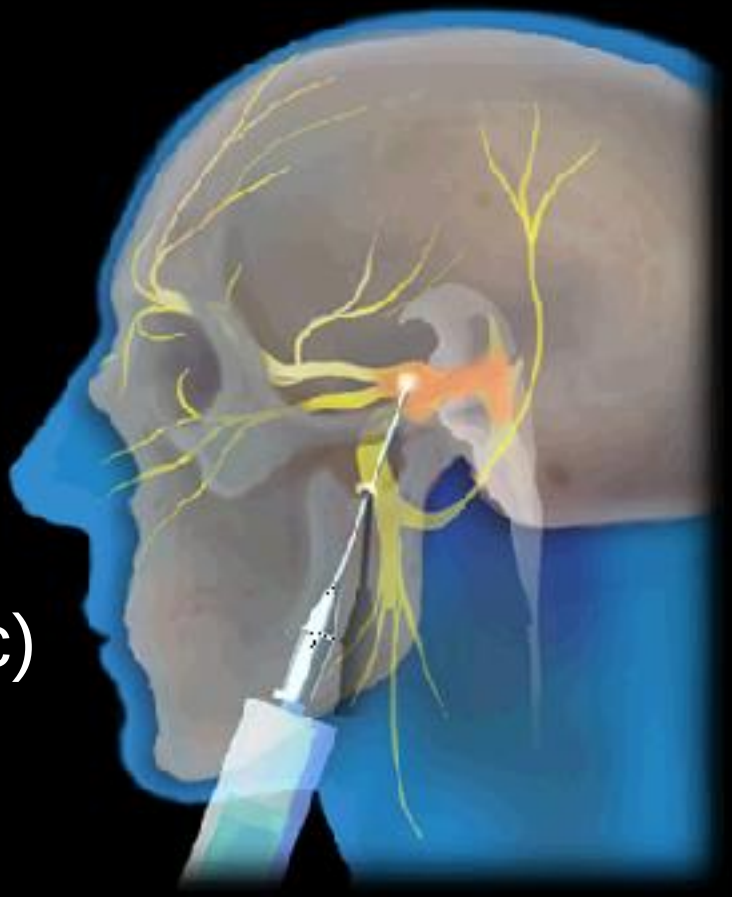
INDICATIONS FOR SURGERY/PROCEDURALINTERVENTION

- 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

Targeting the Sphenopalatine Ganglion (SPG)

- 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)

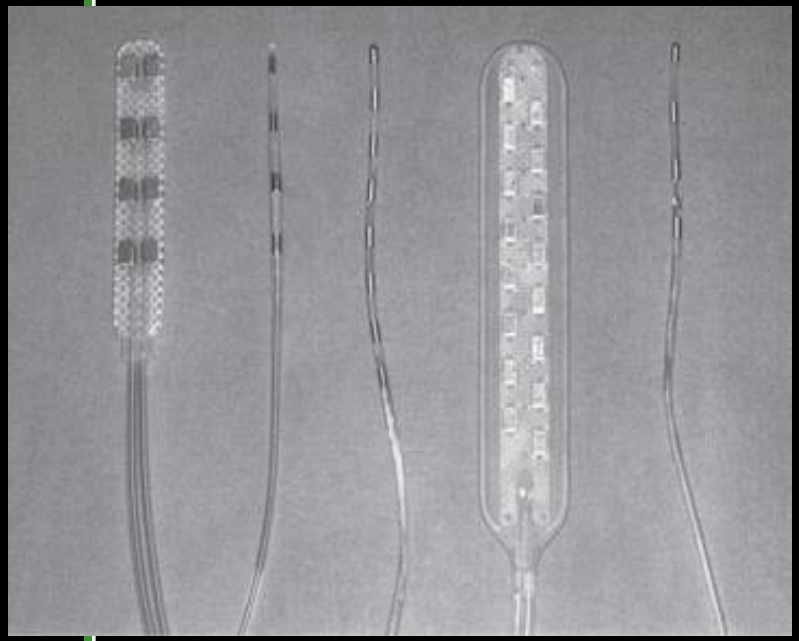
- Cryosurgery (Cook, 1978)
- Stereotactic radiosurgery (Lad *et al*. 2007; Effendi *et al*. 2011)
- Radiofrequency (RF) lesioning (Narouze *et al.* 2009; Salar *et al.* 1987; Bayer *et al.* 2005; Shah and Racz, 2004; Sanders and Zuurmond, 1997)

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 Equipment and Techniques



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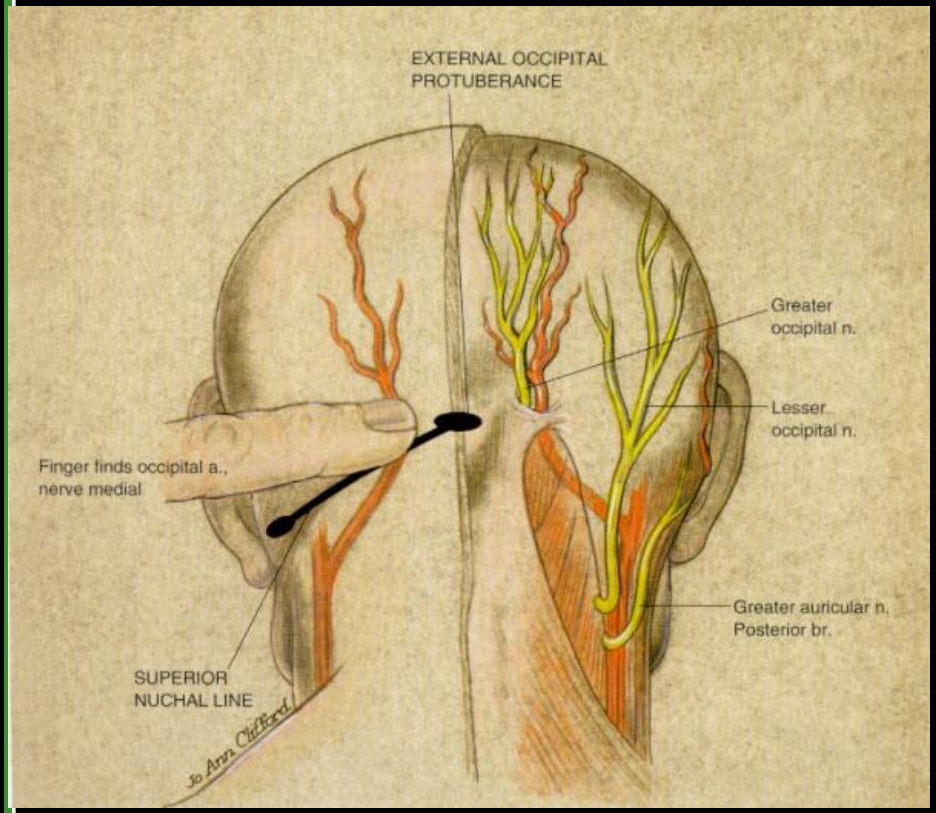

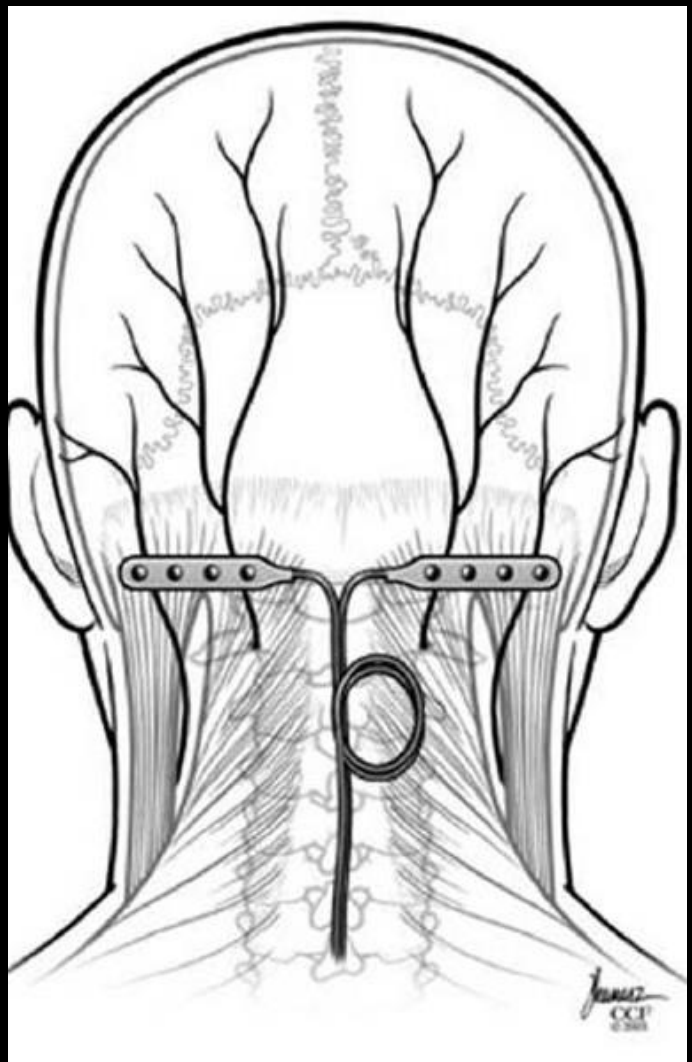

ONS, Different Headache Types

- 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 Stimulator

- Non-invasive vagus nerve stimulation for PREVention and Acute treatment of chronic cluster headache (PREVA): A randomised controlled study.

Non Invasive Vagus Nerve Stimulator

- Adjunctive prophylactic nVNS is a well-tolerated novel treatment for chronic CH, offering clinical benefits beyond those with SoC

Gaul C, Diener HC Cephalagia 2015

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?