Trigeminal Autonomic Cephalalgias (TACs)

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Objectives

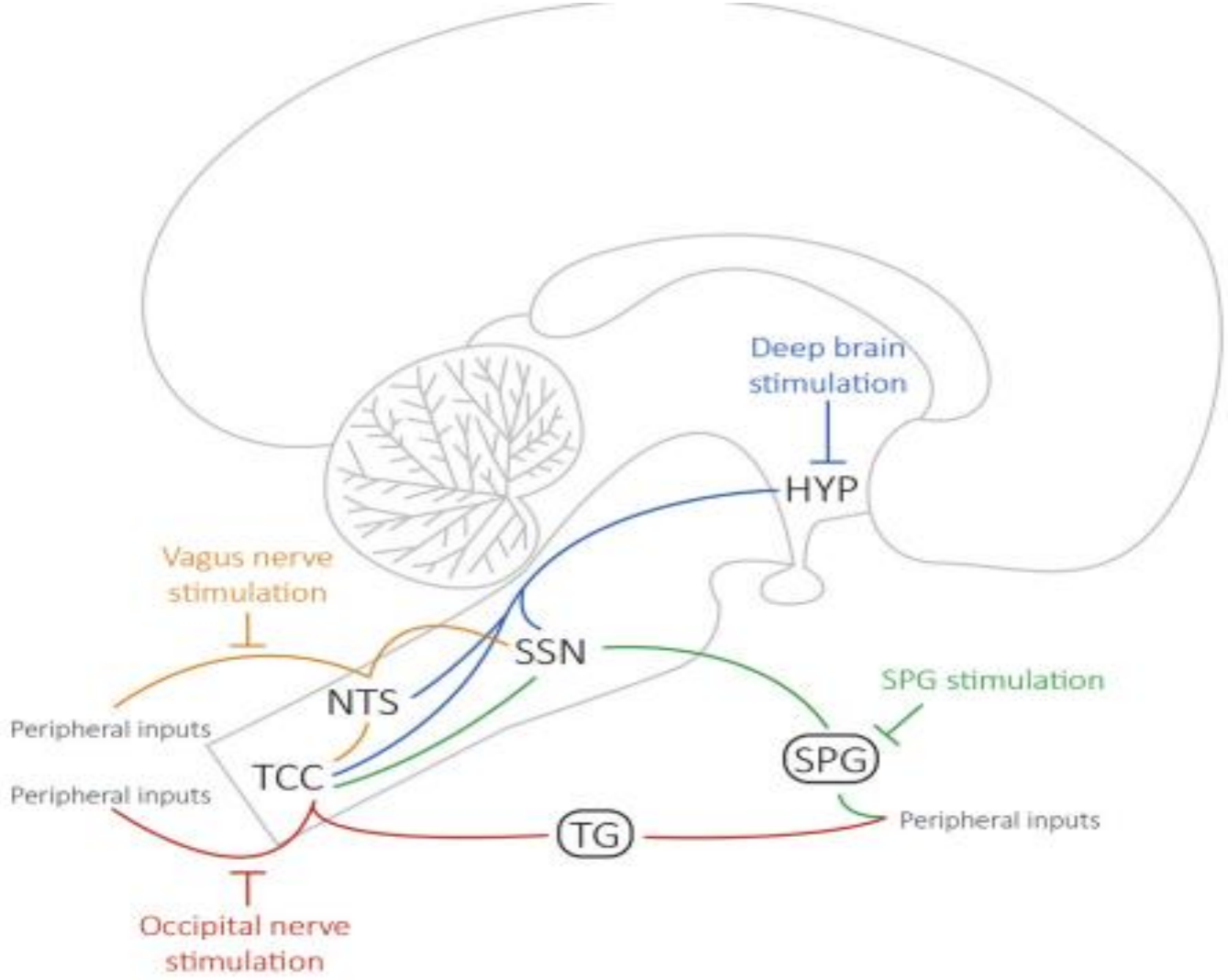
- Identify the diagnostic criteria, clinical features, pathogenesis, and treatment options for:
  - Cluster headache
  - Paroxysmal hemicrania
  - SUNCT/SUNA
  - Hemicrania continua

The TACs: Autonomic Symptoms

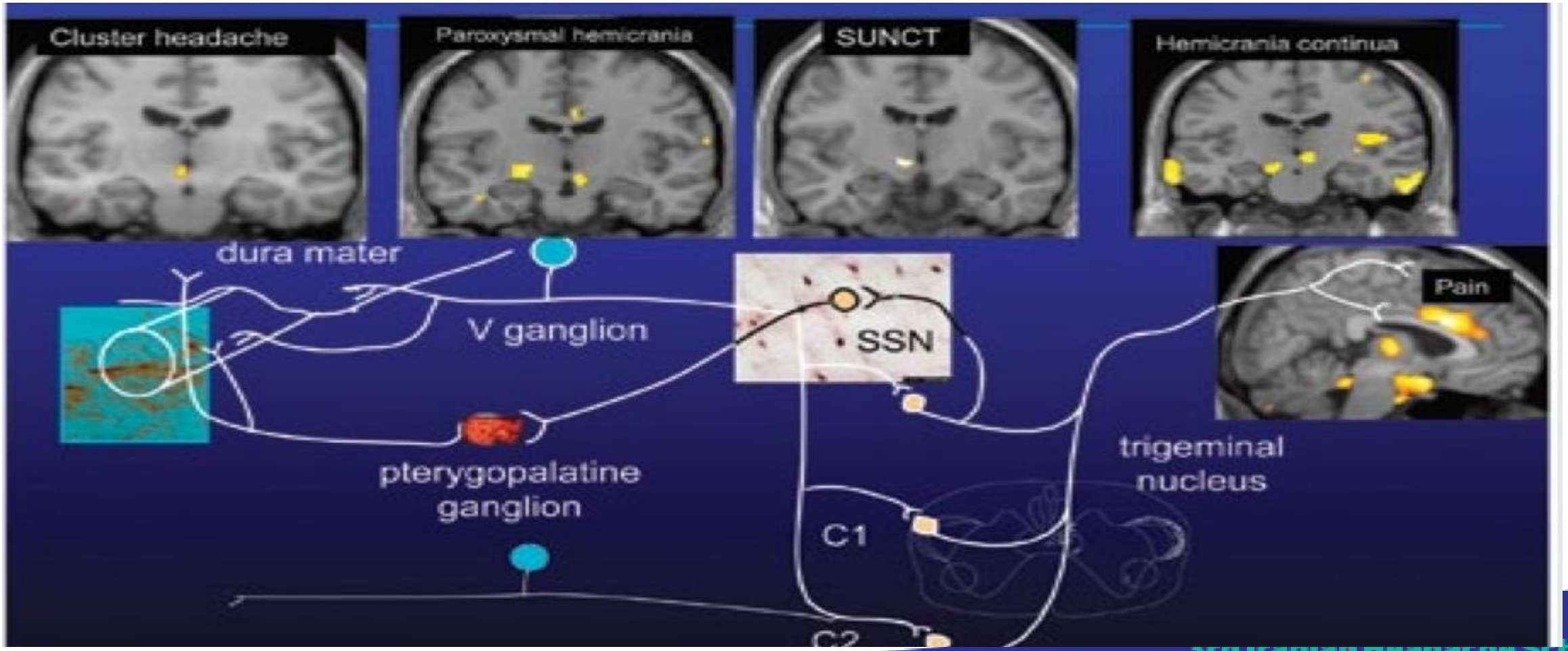
- Cardinal feature of the TACs
- Caused by cranial *parasympathetic activation* triggered by nociceptive trigeminal activation
- Can be seen with any nociceptive input to V1
  - can also be seen with migraine

PATHOPHYSIOLOGY OF THE TRIGEMINAL AUTONOMIC CEPHALALGIAS

- The TACs are thought to involve at least 3 brain systems: the trigeminovascular system, the autonomic system, and the hypothalamus.
- There is emerging evidence that the vagus nerve may also be important. Most research has focused on cluster headache but there is preliminary data for the other TACs as well.



The TACs: Posterior Hypothalamic Activation



Goadsby PJ. *Continuum 2012*.

The Trigeminovascular System

- Anatomy: the ophthalmic branch of the trigeminal nerve receives inputs from the forehead, eye, dura, and large cranial vessels. The trigeminal nerve then connects to the trigeminocervical complex, specifically the most inferior portion of the trigeminal nucleus (the trigeminal nucleus caudalis) and the dorsal horns of the upper cervical spine. From here the system becomes more distributed, but includes connections to the pain neuromatrix, a collection of cortical and subcortical areas involved in pain processing.

- Molecular signaling: pain signaling molecules of the trigeminovascular system include calcitonin gene–related peptide (CGRP), substance P, pituitary adenylate cyclase-activating peptide-38 (PACAP-38), and neurokinin-A.
- Increases in CGRP and preliminary data of increases in PACAP-389 have been observed during a cluster headache attack, and galcanezumab, a monoclonal CGRP antibody, is an effective treatment of cluster headache.

The Autonomic System

- Anatomy: the superior salivatory nucleus, located in the pons, provides parasympathetic input to the sphenopalatine (or pterygopalatine) ganglion, which supplies the face including the lacrimal gland and paranasal sinuses.
- There is a strong connection between the trigeminovascular system and the autonomic system called the trigeminal autonomic reflex, with the afferent limb being the trigeminal nerve and the efferent limb being the facial/greater petrosal nerve. The trigeminal autonomic reflex is thought to be essential to the mechanism of cluster headache.

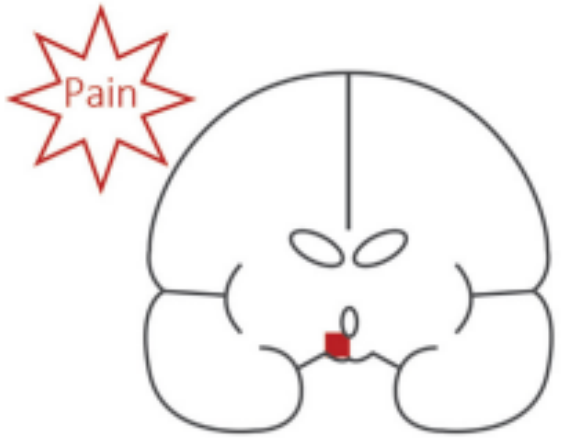
- Molecular signaling: signaling molecules of the autonomic system include vasoactive intestinal peptide (VIP) and PACAP-38. Increases in VIP have been observed during a cluster headache attack.

The Hypothalamus

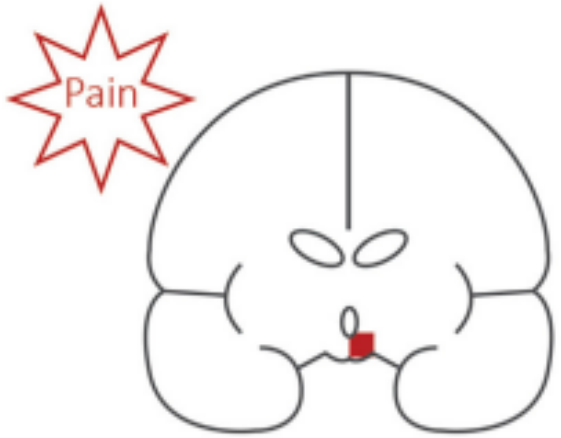
- Anatomy: the strongest evidence for hypothalamic involvement comes from functional imaging studies showing activation of the posterior hypothalamus in all TACs during an attack.
- Molecular signaling: molecules under direct or indirect hypothalamic control include pituitary hormones, VIP, orexin, corticosteroids, and melatonin. There are data for altered pituitary hormones in cluster headache, including prolactin, growth hormone,

Ipsilateral posterior hypothalamic stimulation

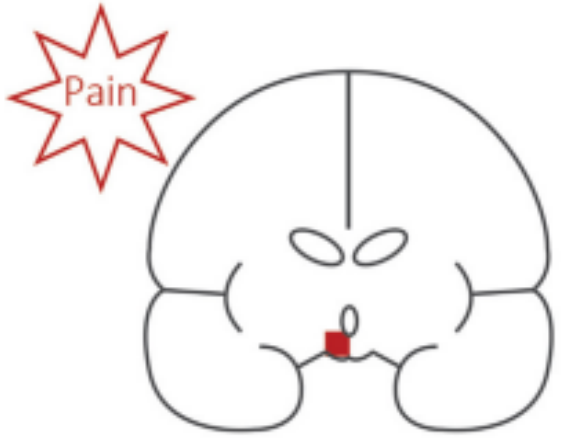
Contralateral posterior hypothalamic stimulation



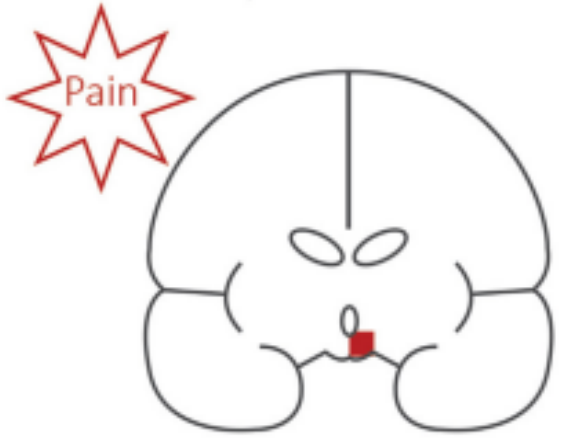
Cluster headache



Paroxysmal hemicrania



SUNCT



Hemicrania continua

TAC vs Migraine

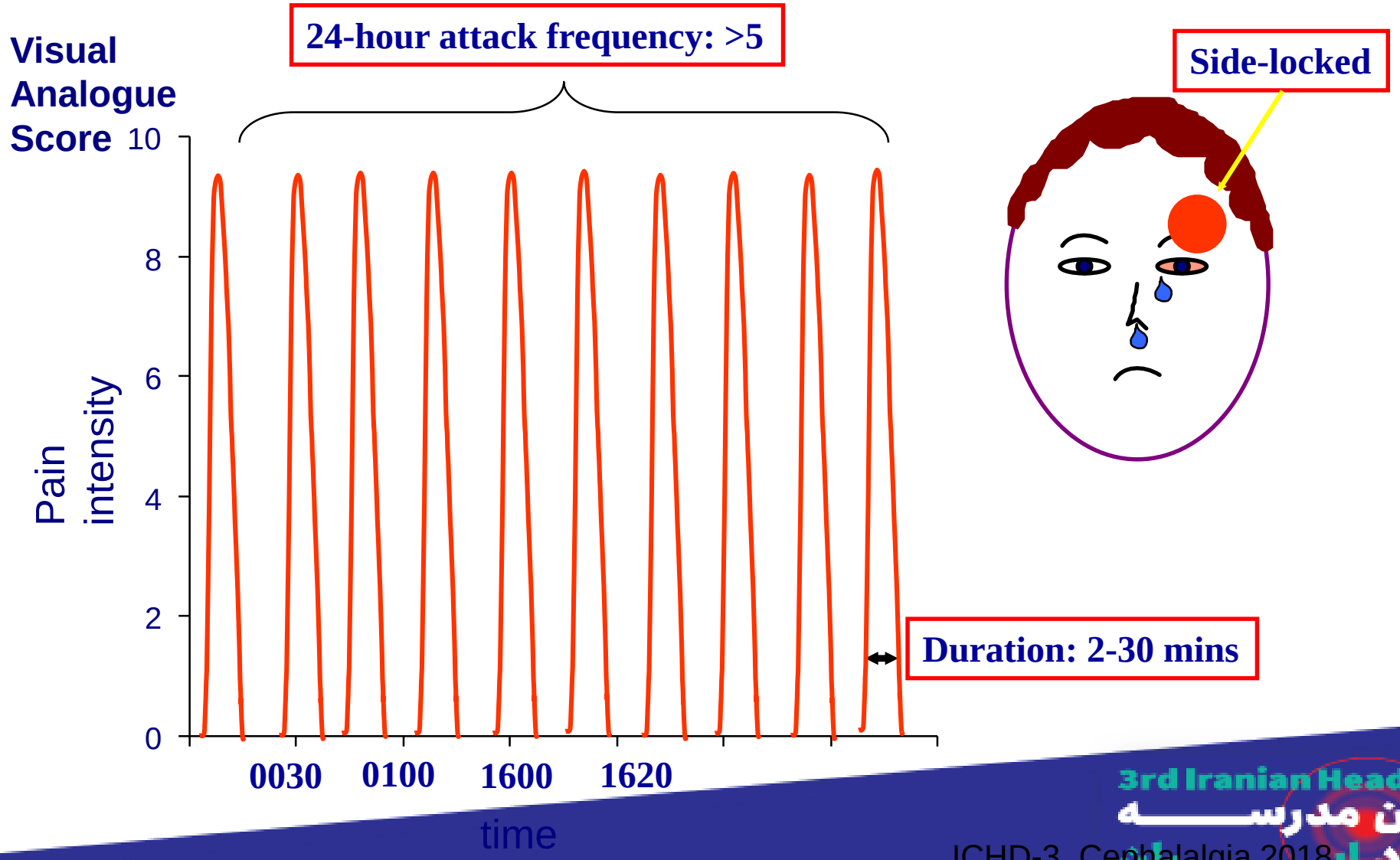
	TAC	Migraine
Autonomic Symptoms	• Prominent • Lateralized to side of pain • Consistent symptoms with every attack	• Bilateral • Mild • Do not always parallel the severity of the attacks
Photophobia/Phonophobia	Ipsilateral to the side of pain	Bilateral even when pain is lateralized

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.**

Levy et al. Brain 2005;128(Pt 8):1921-1930
Cittadini and Matharu. The Neurologist, 2009

Chronic Paroxysmal Hemicrania Headache Phenotype



ICHD-3. Cephalalgia 2018

Paroxysmal Hemicrania
ICHD-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 rhinorrhoea
        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

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.”*

ICHD-3. Cephalalgia 2018.

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

Goadsby PJ. Continuum 2012.
Cephalalgia 2018

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

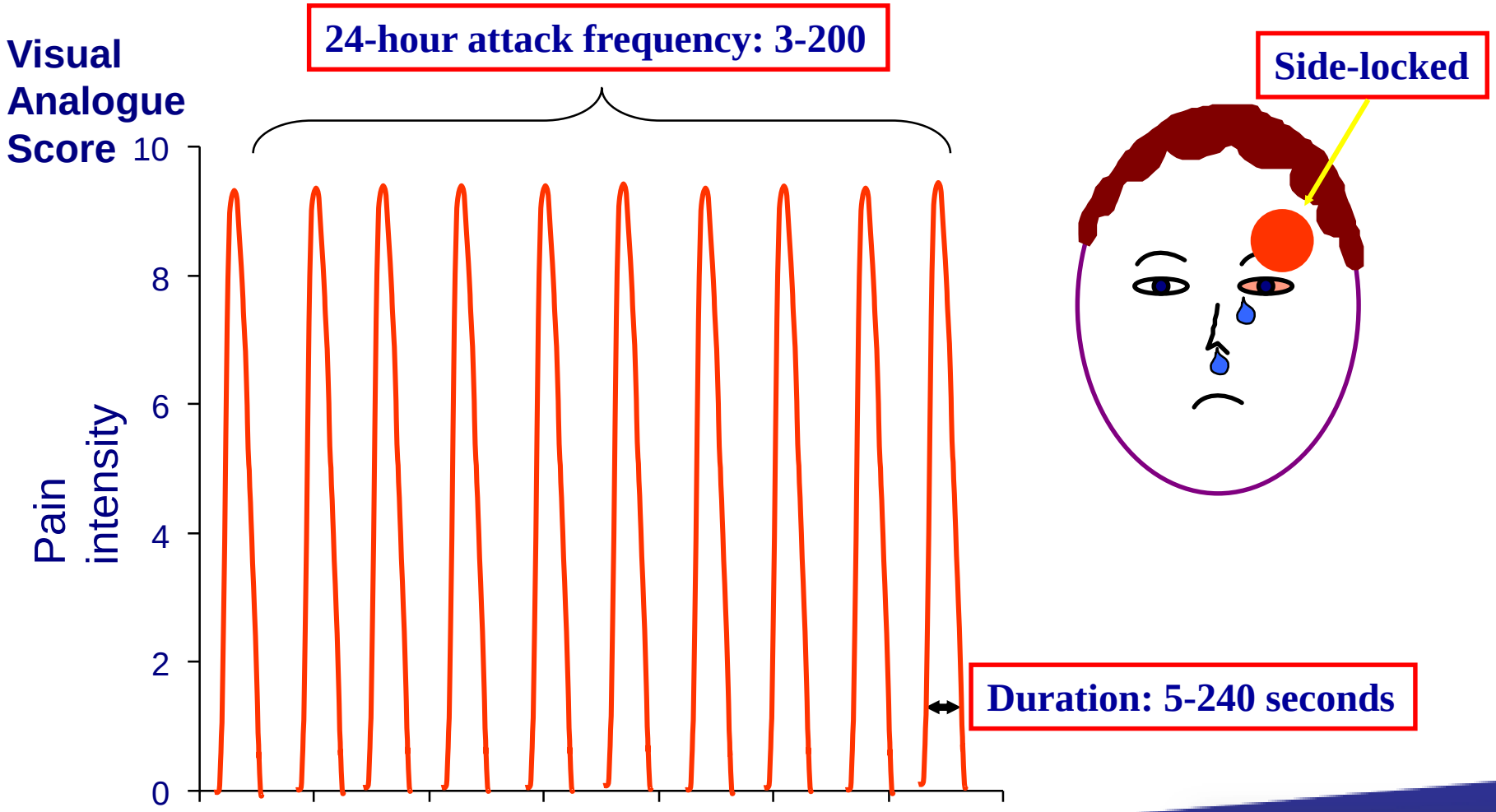
EFNS Guidelines. May A et al, Eur J Neurol 2006;13 (10):1066–1077
Goadsby PJ. *Continuum* 2012

- Treatment of paroxysmal hemicrania begins with an indomethacin trial. Patients should have a complete or near complete response to an oral indomethacin dose of 225 mg/d or less.
- A typical trial of indomethacin is 25 mg three times daily for 3 to 7 days, then if ineffective increasing to 50 mg three times daily for 3 to 7 days, then if ineffective increasing to 75 mg three times daily for 2 weeks.
- A gastroprotectant is generally recommended while taking indomethacin, and sometimes at high doses patients experience a headache different from paroxysmal hemicrania that is throbbing and migrainous in description.
- Indomethacin is often effective within 24 hours. If the medication is effective, it should slowly be titrated down to find the minimal effective maintenance dose, which may be less than 100 mg/d.
- If indomethacin is not effective at 225 mg/d for 2 weeks, an alternate diagnosis should be considered.

- The mechanism of indomethacin in paroxysmal hemicrania is not clear. The cyclooxygenase function is unlikely to be the primary mechanism: other cyclooxygenase inhibitors are typically less effective.
- Although all cyclooxygenase inhibitors have effects on the trigeminovascular system, indomethacin may also have direct neuronal effects on the hypothalamus or autonomic system.
- Finally indomethacin has unique effects on the nitric oxide system

- When indomethacin is effective but is contraindicated or not tolerated, there are several other options. Other cyclooxygenase inhibitors, in particular cyclooxygenase2 selective inhibitors such as celecoxib, may have benefit.
- Melatonin is structurally similar to indomethacin and has been used as an adjunct to decrease the amount of indomethacin needed in hemicrania continua; however, there are limited data in paroxysmal hemicrania. Other treatments include those used for cluster headache, such as verapamil, topiramate, greater occipital nerve blocks, sphenopalatine ganglion blocks, and, more recently, noninvasive vagus nerve stimulation.

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 rhinorrhoea
   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

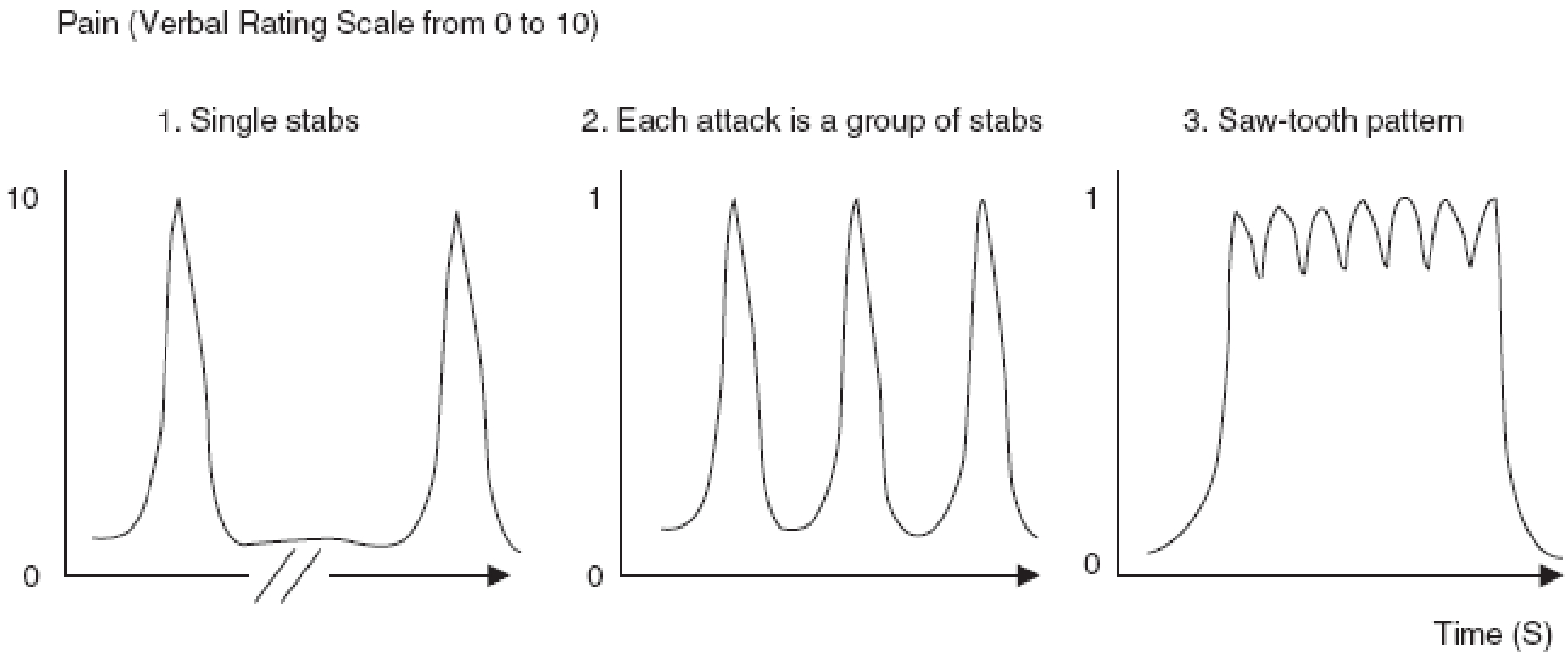
SUNCT vs SUNA: ICHD-3 criteria

- 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)

- The pain in SUNCT and SUNA is often burning, stabbing, or electric but is typically not as painful as cluster headache.
- It generally occurs in the ophthalmic distribution of the trigeminal nerve. It can occur as a single stab, a series of stabs, or a sawtooth pattern (a period of elevated pain punctuated by stabs on top).
- Attack duration is typically seconds, attack frequency 30 per day (although 100 attacks or more have been seen), and episodic patients usually have 1 to 2 symptomatic periods per year lasting weeks to months.

SUNCT: Attack Phenotypes



Cohen *Cephalalgia* 2006

Abnormal Examination and Imaging Findings in SUNCT

	SUNCT
Abnormal examination	
Ipsilateral reduced sensation to pinprick	5 (12%)
Ipsilateral hyperaesthesia	1 (2%)
Ipsilateral changes post procedures	1 (2%)
Other neurological abnormalities	6 (14%)
Intracranial imaging	
Total number imaged	37
Normal intracranial appearances	20 (54%)
Incidental findings	6 (16%)
Abnormal intracranial appearances:	
Vascular loops	3 (8%)
Pathological white matter changes	2 (5%)
Pituitary lesions	3 (8%)
Space occupying lesions	2 (5%)
Unusual configuration in brainstem and lacune in thalamus	1 (3%)
Total abnormal intracranial appearances	11 (29%)

Cohen *Cephalalgia* 2006

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*

- SUNCT/SUNA vs PSH: look for autonomic symptoms!

Prophylactic Treatments in SUNCT

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

Cohen *Cephalalgia* 2006

- The differential for SUNCT and SUNA also includes primary stabbing headache, which has a similar duration but can vary in location and lacks cranial autonomic features. Other disorders that can be confused for SUNCT and SUNA include cluster headache and paroxysmal hemicrania (because of the interictal milder pain in SUNCT and SUNA), herpes zoster, and dental issues. Symptomatic cases of SUNCT and SUNA include primarily pituitary tumors and posterior fossa tumors, although vascular malformations, herpes zoster, and compression of the trigeminal nerve by the superior cerebellar artery have also been described.

- The mainstay of treatment is lamotrigine, usually at a dose of 100 to 200 mg/d. A very gradual uptitration is recommended because of the risk of Stevens-Johnson syndrome.
- The most effective treatment of SUNCT and SUNA, however, seems to be intravenous lidocaine at a dose of 1 to 3.5 mg/kg/h for up to 1 week.

- There are a variety of other medications that have shown effectiveness in SUNCT and SUNA. Several reports have suggested topiramate, gabapentin, duloxetine, or oxcarbazepine as second-line treatments.
- Other treatment options include carbamazepine, pregabalin, greater occipital nerve blocks, and oral steroids.
- For refractory patients research has begun to explore occipital nerve stimulation and microvascular decompression of the trigeminal nerve

Hemicrania Continua: ICHD-3 Diagnostic Criteria

A. Unilateral headache fulfililng 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)
  - Lacrmiation: 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 is often difficult to distinguish from migraine or cluster headache.
- Like migraine, flares often have throbbing unilateral pain with photophobia, phonophobia, nausea, and vomiting; auras have rarely been described. Hemicrania continua is best differentiated from migraine by the following:
- 1. Side-switching: hemicrania continua rarely switches sides; migraine often switches sides or is bilateral
- 2. Remission: hemicrania continua rarely remits completely; migraine typically has pain-free periods
- 3. Indomethacin response: hemicrania continua always responds to a therapeutic dose of indomethacin.

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

- For patients who cannot tolerate or have contraindications to indomethacin, several other treatments have been proposed. Celecoxib, topiramate, gabapentin, and melatonin have been suggested as second- or third-line medications.
- Melatonin may be used as an adjunct to reduce the amount of indomethacin needed.
- For refractory patients, occipital nerve stimulation as well as radiofrequency of the sphenopalatine ganglion may be beneficia

Trigeminal Autonomic Cephalgias

Feature	PH	SUNCT	Cluster
Sex F:M	2:1	1:2	1:3
Attack duration	~15 mins	~ 1 min	60 mins
Attack frequency	11	~ 30	1
Treatment of choice	Indomethacin	Lamotrigine	Verapamil

Thank you