

Chapter 2

Diagnosis of Trigeminal Autonomic Cephalalgias

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Introduction

The trigeminal autonomic cephalalgias (TACs) refer to a specific group of primary headaches characterized by unilaterality, associated cranial autonomic features, and specific duration of pain. The major TACs as listed by the International Classification of Headache Disorders, third edition, beta version (ICHD-3) are listed in Table 2.1 and, to differentiate them, the Other Primary Headache disorders (covered in Chap. 3) are listed in Table 2.2.

The term “probable” is used in the ICHD-3 to mean a headache is missing one ICHD-3 criterion to make the diagnosis. Probable TACs are under ICHD number 3.5. The probable headaches are excluded from our tables for simplicity, utility, and clarity.

Remember that if the patient is missing a single criterion, the headache diagnosis becomes “probable.” As discussed in Chap. 1, when a patient is missing a criterion, the possibility of a secondary cause increases, and serious consideration should be given to doing a careful workup for secondary causes. Essentially, a probable diagnosis should raise your suspicions for sinister etiology.

Diagnostic Features of the TACs: How to Make the Diagnosis

As with any other painful condition, making a correct diagnosis is 90 % of the battle and helps direct proper therapy. This is particularly important with the TACs, as some of these headaches can be differentiated by a response to certain medications, such as indomethacin.

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Table 2.1 The major trigeminal autonomic cephalalgias (TACs), ICHD-3

ICHD-3 number, name (abbreviation)
3.1 Cluster headache (CH)
3.1.1 Episodic cluster headache (ECH)
3.2.1 Chronic cluster headache (CCH)
3.2 Paroxysmal hemicrania (PH)
3.2.1 Episodic paroxysmal hemicrania (EPH)
3.2.2 Chronic paroxysmal hemicrania (CPH)
3.3 Short-lasting unilateral neuralgiform headache attacks (SUNHA)
3.3.1 Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)
3.3.1.1 Episodic SUNCT
3.3.1.2 Chronic SUNCT
3.3.2 Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA)
3.3.2.1 Episodic SUNA
3.3.2.2 Chronic SUNA
3.4 Hemicrania continua (HC)

Table 2.2 The major Other Primary Headaches, ICHD-3 (covered in Chap. 3)

ICHD-3 number, name (abbreviation)
4.1 Primary cough headache
4.2 Primary exercise headache
4.3 Primary headache associated with sexual activity
4.4 Primary thunderclap headache (PTH)
4.5 Cold-stimulus headache
4.5.1 Headache attributed to external application of a cold stimulus
4.5.2 Headache attributed to ingestion or inhalation of a cold stimulus
4.6 External-pressure headache
4.6.1 External-compression headache
4.6.2 External-traction headache
4.7 Primary stabbing headache
4.8 Nummular headache
4.9 Hypnic headache
4.10 New daily persistent headache (NDPH) ^a

^a Also covered in Chap. 4

Table 2.3 Clinical pearls on probable headaches

- If a patient is missing a single criterion for an ICHD-3 diagnosis, the headache diagnosis becomes “probable”
- When a patient is missing a criterion, the possibility of a secondary cause increases, and serious consideration should be given to doing a careful workup for secondary causes
- A probable diagnosis should raise your suspicions for sinister etiology

Table 2.4 Duration of the TACs

• Hemicrania continua (HC): Continuous pain with exacerbations daily or several times a week lasting hours to days each
• Cluster headache (CH) attacks: 15–180 min
• Paroxysmal hemicrania (PH) attacks: 2–30 min
• Short-lasting unilateral headache attacks (SUNHA); short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)/Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) attacks): 1–600 s

Table 2.5 Initial clinical pearls on diagnosis of TACs

• Agitation is a common feature for both CH and HC, and is not listed as a criterion for PH or SUNHA in ICHD-3
• When no autonomic features are present and cluster is suspected, ask about agitation
• Unilateral photophobia is often present in TACs, especially HC
• Make sure the patient has had a very good MRI. Diagnosis of a TAC should provoke a workup for a hypothalamic or pituitary lesion; as many as 10% of patients with TACs will have an abnormality of this region or the posterior fossa
• Within SUNHA, SUNA is just SUNCT without a red eye or tearing
• SUNHA is in a different location (V1) compared to trigeminal neuralgia (TN; V2–3). SUNHA, unlike TN, is associated with autonomic features
• A woman with frequent CH-like attacks should make the clinician think of paroxysmal hemicrania (PH)

Duration of TACs

Wags have stated that the longer the name of the paroxysmal TAC, the shorter the duration. Hemicrania Continua (HC) is continuous. Eighty-five percent of Cluster Headache (CH) attacks last between 15 and 180 min. Paroxysmal Hemicrania (PH) attacks are between 2 and 30 min. And the duration of Short-lasting Unilateral Headache Attacks (SUNHA), including Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing (SUNCT) and Short-lasting Unilateral Neuralgiform headache attacks with cranial Autonomic symptoms (SUNA), is measured in seconds (1-600 s).

The current ICHD-3 criteria for the diagnosis of the TACs are listed in the subsequent tables. As noted above, the TACs are grouped into Section 3 of the ICHD-3, and while these headaches are similar in many ways, the response to medications can vary markedly. Each will be discussed separately, but not before some points are made. These clinical pearls on TACs are listed in Table 2.5.

In both HC and CH, if the autonomic features are not manifested, an equally important criterion listed is the sense of restlessness and inability to sit still during an attack. There is a minority of patients who, during an HC exacerbation or a cluster attack, will not manifest obvious ipsilateral sympathetic paresis (miosis, ptosis, Horner’s) or parasympathetic discharge (conjunctival tearing, rhinorrhea, etc.). In such cases, the patient must report (or a companion must report) that the patient

will rock, pace, or otherwise appear agitated. One of my cluster patient's wife told me that the patient was groaning and holding his involved eye; next to him on the pillow was a handgun! This degree of agitation is not required or listed for PH or SUNHA.

Never underestimate the severity of the pain of CH! CH is called the "suicide headache" for good reason.

As many as 50% of patients with TACs will refer their symptoms of photophobia to the ipsilateral, painful side, in contrast to migraineurs, who usually complain of bilateral light and sound sensitivity. HC, in particular, manifests unilateral photophonophobia in at least half of patients, and ipsilateral photophonophobia should make the clinician think seriously about a TAC diagnosis.

The diagnosis of a TAC should provoke a workup for a hypothalamic or pituitary lesion; as many as 10% of patients with TACs, in particular SUNHA, will have an abnormality of this region or the posterior fossa on a good imaging study, in particular SUNHA. If the clinician has not visualized a magnetic resonance imaging (MRI) with and without contrast as part of the workup, repeating one should be considered.

SUNA is simply a SUNHA without the red eye or tearing, so SUNA and SUNCT are very similar. Neither is indomethacin responsive; both tend to respond to anti-epilepsy drugs such as lamotrigine or gabapentin.

Trigeminal neuralgia (TN) does not manifest autonomic features and is only rarely in V1, so location and associated autonomic features distinguish SUNHA from TN, even when the duration of attacks is similar. In addition, SUNHA is usually heralded by stabs of pain, sometimes in a sawtooth pattern, not seen in TN.

A woman with frequent cluster-like attacks, especially if not terribly agitated, should make the clinician think of PH rather than CH, due to gender alone. After ruling out secondary causes, an indomethacin trial may be indicated.

Diagnosis of Cluster Headache

CH, the most common of the TACs, are generally more common in males, starting as early as the second decade. CH can persist well into life, as far as into the seventh decade. They are called clusters because they tend to cluster at the same time(s) of the year, with cycles or periods of daily attacks lasting for weeks to months in the episodic variety, and remissions lasting for months to years. This is considered to be a reflection of the relationship of these headaches with circadian and circannual periods and the effect of light–dark cycles on the suprachiasmatic nucleus of the hypothalamus, by way of the retinal–hypothalamic–pineal pathways.

Approximately 85% of all CHs are *episodic*; the cluster period or cycle, as it is called, spontaneously remits, and there will be freedom from CH attacks for a month or longer each year in episodic cluster headache (ECH).

The remaining cluster sufferers have *chronic* clusters in which they will have headaches daily or near daily and will not be free from a CH attack for any period of a month or more in a given year. Chronic cluster headache (CCH) may start de novo, but generally evolves from the episodic variety.

Table 2.6 Diagnostic criteria for cluster headache, ICHD-3

A.	≥5 attacks fulfilling B–D
B.	Severe or very severe unilateral orbital, supraorbital, or temporal headache attacks, untreated lasting for 15–180 min
C.	Either or both of the following <ol style="list-style-type: none"> 1. At least one of the following symptoms or signs, ipsilateral to the headache <ol style="list-style-type: none"> A) Parasympathetic activation <ol style="list-style-type: none"> a. Conjunctival injection or lacrimation b. Nasal congestion and/or rhinorrhea c. Eyelid edema d. Forehead and facial sweating e. Forehead and facial flushing B) Sympathetic paresis <ol style="list-style-type: none"> f. Horner's or partial Horner's (miosis, ptosis) C) Miscellaneous <ol style="list-style-type: none"> g. Sensation of fullness in the ear 2. A sense of restlessness and agitation
D.	The attacks have a frequency QOD to 8/day during an active period
E.	Secondary causes excluded
Episodic cluster headache (ECH)	
•	At least two cluster periods lasting 7 days to 1 year, separated by pain-free periods lasting ≥1 month
Chronic cluster headache (CCH)	
•	Attacks occur for >1 year without remission or with remission for <1 month
Probable cluster headache: attacks missing one criterion	

Table 2.7 Clinical pearls on diagnosing cluster

•	Attacks are short, sharp, and severe (triple S; SSS) and occur with an average frequency of 1–3/day
•	Attacks manifest parasympathetic activation and sympathetic paresis with agitation
•	Attacks occur with alarm clock periodicity
•	Circadian and circannual periodicity are seen frequently in CH, but usually not the other TACs
•	Cluster patients in cycle rarely, if ever, drink alcohol, due to the severity of the trigger
•	Smoking and obstructive sleep apnea are common in cluster patients
•	In about one-third of the cluster patients, there can be low-level ipsilateral interictal pain, making it sometimes difficult to differentiate from HC, but the intensity of the continuous pain is generally worse in HC

Most cluster attacks are severe and retro-orbital. They are not throbbing; rather, they are described as burning, boring, stabbing, or tearing. Attacks are short, sharp, and severe (triple S; SSS).

Cluster attacks are manifested by parasympathetic activation (scleral injection, lacrimation, diaphoresis, nasal stuffiness, and/or rhinorrhea). Less common is a Horner's or partial sympathetic paresis with ptosis and/or miosis. As noted above, agitation is the rule, and cluster attacks are generally shorter than 3 h in duration. Major diagnostic criteria for CH are listed in Table 2.6.

There is a circadian alarm clock periodicity to the attacks, attacks occurring at the same time of day or night, and a circannual periodicity with the cluster periods

occurring at the same time of year, often with the changing of the clocks for daylight savings time. The periodicity feature of CH, extremely useful in diagnosis and not usually seen in the other TACs, is not included in the ICHD-3 criteria.

Attacks can be precipitated by alcohol, fumes such as gasoline fumes, excessive exercise, and napping. Cluster patients in cycle rarely, if ever, drink alcohol. Cluster patients are commonly smokers, however.

In about 30% of cluster and PH patients, a low-level pain can persist ipsilaterally interictally. The patients describe this as a “ghost pain” between attacks. The continuous pain of HC is generally more severe, averaging 6–7/10 in intensity.

Diagnosis of the Paroxysmal Hemicranias

The Paroxysmal Hemicranias (PH) are defined by an absolute response to indomethacin. The headaches are similar in quality to cluster pain, but the pain is shorter lasting and more frequent during any given day.

As with CH and HC, there are both *episodic* and *chronic* PH subforms. Episodic Paroxysmal Hemicrania (EPH) occurs in periods lasting 1 week to a year, and its occurrence is separated by pain-free periods lasting 1 month or longer (remissions). When cycles of attacks of PH last more than 1 year without remissions lasting 1 month or longer, the headache qualifies as Chronic Paroxysmal Hemicrania (CPH). This distinction is identical to that in CH.

EPH is more rare than CPH, the opposite of CH, where the episodic subform is more common. In EPH, the disorder occurs equally in males and females, while in CPH there is a female predominance. CH always has a male predominance, regardless of subform.

Attacks of PH can be less severe than CH, but in the same location. The attacks are quite short, up to 30 min only, allowing for 15 min of overlap with CH attacks. The usual duration of a PH attack is 14 min, so it is usually easy to tell from SUNHA or TN. SUNHA attacks are from 1 s to 10 min, but average duration is 50 s. However, there is an overlap of a 2–10-minute duration between SUNHA and PH, so indomethacin can be the important distinguishing feature, as SUNHA does not respond to indomethacin. TN attacks are much shorter, there are no autonomic features, and are usually in V2–3, while PH is in V1.

More than half of the time, PH attacks occur more than five times per day by ICHD-3 criteria, so attacks usually occur more frequently in PH than CH. The frequency of CH attacks can be up to eight times per day, so the frequency of the two disorders can overlap, but this is rare. In general, CH attacks occur one to three times daily, and PH attacks occur with a mean frequency of eight times per day. SUNHA attacks can occur hundreds of times per day.

Patients are less frequently agitated in PH than with CH. Agitation is not a diagnostic criterion for PH, but is for CH.

There is no circadian or circannual periodicity. PH attacks occur at random.

Table 2.8 Diagnostic criteria for paroxysmal hemicrania, ICHD-3

A. ≥ 20 attacks fulfilling B–E
B. Attacks of severe unilateral orbital, supraorbital, or temporal pain lasting 2–30 min
C. Headache is accompanied by \geq one of the following: <ol style="list-style-type: none">1. Ipsilateral conjunctival injection or lacrimation2. Ipsilateral nasal congestion or rhinorrhea3. Ipsilateral eyelid edema4. Ipsilateral forehead and facial sweating5. Ipsilateral forehead and facial flushing6. Sensation of fullness in the ipsilateral ear7. Ipsilateral miosis and/or ptosis
D. Attacks have a frequency of $> 5/\text{day}$ for $> 50\%$ of the time, although periods with lower frequency can occur
E. Absolute responsiveness to therapeutic doses of indomethacin
F. Secondary causes excluded
Episodic Paroxysmal Hemicrania (EPH)
• At least two PH periods lasting 7 days to 1 year, separated by pain-free periods lasting ≥ 1 month
Chronic Paroxysmal Hemicrania (CPH)
• Attacks occur for > 1 year without remission or with remission for < 1 month

Table 2.9 Clinical pearls on diagnosing paroxysmal hemicrania

• Since cluster is a disease of men, think PH when you see a woman who reportedly has CH
• EPH occurs equally in men and women. CPH is more common in women
• If the cluster is refractory, especially if there is no response to subcutaneous sumatriptan or O ₂ , think PH
• If there is no alarm clock periodicity or agitation, think PH
• If attack frequency is high ($> 5/\text{day}$) or attack duration is short (30 min), think PH over CH
• If you think PH, try an indomethacin trial before proceeding with CH treatment
• There is an overlap in duration of attacks between CH, PH, and SUNHA, so once again, indomethacin may be the way to the diagnosis of PH

Finally, and most importantly, the diagnosis of PH is made by absolute responsiveness to indomethacin. If you have ruled out secondary causes and think the patient could have PH, try an indomethacin course first before treating as if it is cluster.

Diagnosis of SUNHA (SUNCT and SUNA)

In the third edition of the ICHD, the category SUNHA includes the two recognizable forms of SUNCT and SUNA. SUNCT and SUNA are very brief headaches with prominent cranial autonomic features that can deceive the clinician because they can be triggered by cutaneous stimuli, similar to TN. These headaches are characterized by paroxysms of short-lasting (1–600 s) stabbing tic-like pain. Average duration of each attack is around 50 s. The duration of these severe attacks was expanded from 5–240 s in ICHD-2 to 1–600 s in ICHD-3.

Table 2.10 Diagnostic criteria for SUNHA (SUNCT/SUNA), ICHD-3

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- A. ≥ 20 attacks fulfilling B–D
- B. Attacks of unilateral orbital, supraorbital, or temporal moderate to severe stabbing or pulsating pain, lasting 1–600 s and occurring as single stabs, series of stabs, or in a sawtooth pattern
- C. Pain is accompanied ipsilaterally by \geq one of the following
1. Ipsilateral conjunctival injection or lacrimation^a
 2. Ipsilateral nasal congestion or rhinorrhea
 3. Ipsilateral eyelid edema
 4. Ipsilateral forehead and facial sweating
 5. Ipsilateral forehead and facial flushing
 6. Sensation of fullness in the ipsilateral ear
 7. Partial Horner's: ipsilateral miosis and/or ptosis
- D. Attack frequency of \geq one/day for $\geq 50\%$ of the time when the disorder is active
- E. Secondary causes excluded
- SUNCT: Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing
 - SUNA: Short-lasting Unilateral Neuralgiform headache attacks with cranial Autonomic symptoms
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^a The absence of conjunctival injection and tearing but the presence of other cranial autonomic features suggests SUNA

Table 2.11 Clinical pearls on SUNHA

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- Pain is maximal in V1 distribution, unlike trigeminal neuralgia (TN)
 - There are autonomic features invariably, unlike TN
 - As in TN, cutaneous triggers are common in SUNHA, but unlike TN, movement of the neck can also be a trigger in SUNHA
 - Moderate to severe intensity
 - Pain is stabbing, burning, electric-like
 - Brief paroxysms of pain lasting 1–600 s each (mean 50 s)
 - Attacks peak within 2–3 s
 - Attack frequency varies from 1/day to 30/hour
 - No latency or refractory period
 - Stabs are the rule, either alone, as a herald for an attack, or in a sawtooth pattern
 - SUNHA is not indomethacin responsive and usually responds to lamotrigine or gabapentin
 - Remember: SUNHA is rare, which is why the workup is crucial! The most common secondary cause is a pituitary lesion
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The attacks can present with isolated stabs of pain in the orbit or the temporal region or anywhere in the head, and can occur hundreds of times a day. SUNCT/SUNA can alternately present with groups of stabs (sawtooth pattern) separated by complete or incomplete resolution of the pain. A single stab can herald an attack. There may be periods of remission, or there may be no days of remission.

Unlike TN, which as noted above, SUNHA attacks might resemble because of cutaneous triggers and duration, SUNHA attacks generally do not exhibit a refractory period. Also, TN occurs $< 5\%$ of the time in V1; SUNCT/SUNA pain is usually in V1. Time to peak for SUNHA is about 2–3 s. SUNHA attacks are longer in duration (typically 30–120 s) than TN (typically 1–3 s). SUNCT, as the names infers, is

associated with both conjunctival injection (redness) and tearing, and there may be other ipsilateral autonomic signs. SUNA may have conjunctival injection or tearing but not both together, and other autonomic features occur.

Secondary headaches may masquerade as SUNHA, including brainstem strokes, arteriovenous malformations, pituitary tumors, arterial dissections of the vertebral artery, or demyelination. It is therefore mandatory to investigate all suspected cases of SUNCT/SUNA or to personally review high-quality imaging if it has been performed.

There have been several small case series of SUNCT being cured by resection of pituitary tumors. The pathophysiology and explanation for these cures is mysterious.

Remember, SUNHA is rare. Be vigilant in a search for secondary causes.

Unfortunately, SUNHA does not respond to indomethacin as do PH and HC. Treatment for SUNCT/SUNA will be discussed in Chap. 11, but is usually lamotrigine or gabapentin.

Pathophysiology of the TACs: What you Need to Know

There is now a substantial body of evidence that the spectrum of TACs and the Other Primary Headaches are related in their pathophysiological origin, as one would suspect, since they generally share many clinical features. Recent advances with positron emission tomography (PET) scanning and functional MRI have demonstrated areas of activation in the posterior hypothalamus for all of the TACs during the headache phase. In addition, the expected areas of the cortical and subcortical pain matrix show activity in response to the pain. Table 2.12 displays the areas of hypothalamic activation.

HC offers a mirror image of CH and migraine functional imaging. Cluster manifests activation in the ipsilateral hypothalamus, HC the contralateral hypothalamus. Some scientists feel that migraine manifests activation in the contralateral upper brainstem, HC the ipsilateral upper brainstem.

Anatomically, there are reciprocal connections between the posterior hypothalamus and the trigeminal nucleus caudalis (TNC), the site of origin of the second order nociceptive neuron. In the last decade, there have been more than 50 patients who have had implantation of deep brain stimulators (DBS) in the ipsilateral hypothalamus for drug refractory CH and other TACs. There are no controlled studies of DBS for TACs, except to note that turning off working stimulators without patient knowledge has resulted in return of headaches.

For CH, in 60% of patients there has been a greater than 50% decrease in the frequency of headaches, and in 30% there has been a complete response with DBS. However, there has been one death and several transient ischemic attacks (TIAs) and strokes in the course of implanting DBS for CH.

It is now apparent that stimulation of this hypothalamic site promotes the relief of the headache and does not stimulate the pain, suggesting that the posterior hypothalamus is a key area of modulation for cluster and TAC pain. This is discussed further, along with other stimulation approaches, in Chap. 12 on treatment of the TACs and other primary headaches.

Table 2.12 Areas of hypothalamic stimulation seen with the TACs

Headache	Hypothalamic activation area (with respect to side of pain)
Cluster headache	Ipsilateral posterior hypothalamus
Paroxysmal hemicrania	Contralateral hypothalamus
Hemicrania continua	Contralateral hypothalamus and ipsilateral upper brainstem
SUNCT	Ipsilateral or bilateral hypothalamus
SUNA	Absent in patients with extraocular autonomic phenomena

Table 2.13 Differential points among the paroxysmal TACs. (Adapted from Goadsby et al. 2010)

Features	Cluster headache	Paroxysmal hemicrania	SUNCT/SUNA
Gender (M/F)	3–6/1	1/1	1.5/1
Pain quality	Stab/sharp/throb/poker	Stab/sharp/throb/poker	Stab/sharp/throb/poker
Severity	Very severe	Severe–very severe	Severe
Distribution	V1 > C2 > V2 > V3	V1 > C2 > V2 > V3	V1 > C2 > V2 > V3
Attack frequency	Every other day–8/day	Mean 11; up to 30/day	Mean 100; >100/day
Attack length	15–180 min	2–30 min	1–600s
Migraine features			
Nausea	50 %	40 %	25 %
Photo-/phonophobia	65 %	65 %	25 %
Triggers			
Alcohol	Yes	Yes	No
Nitroglycerin	Yes	Yes	No
Cutaneous	No	No	Yes
Agitation/restlessness	90 %	80 %	65 %
Episodic/chronic	9/1	1/2	1/9
Circadian/circannual periodicity	Yes	No	No
Treatment efficacy			
Oxygen	70 %	None	None
Sumatriptan subcutaneously	90 %	20 %	10 % or less
Indomethacin	Almost none	100 %	None

M male, *F* female, *C* cervical, *V* trigeminal

The Paroxysmal TACs: Telling Them Apart

CH, PH, and SUNHA constitute the paroxysmal TACs, in that the minority of patients have continuous pain, and the continuous pain is generally not severe. HC, on the other hand, is a continuous TAC. Table 2.13 outlines major points that help differentiate the paroxysmal TACs from one another.

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