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Review

Trigeminal autonomic cephalalgias: current insights into pathophysiology, diagnosis, and therapeutic strategies

Marina Alejandra Olivier[1,2], Margareth Alexandra Contreras Martínez[3], Carlos Andrés Díaz Garza[4], Javier Andrés Galnares Olalde[4], Adolfo Leyva Rendon[4], Paula Alexandra Martínez Corredor[5], Verónica Lourdes Molina[6], María Celeste Rada Fernández[7], María Soledad Smechow[8], Osvaldo Carlos Jesús Bruera[9]

[1]Headache unit, La Fe University and Polytechnic Hospital, Valencia, Spain
[2]La Fe Health Research Institute, Valencia, Spain
[3]Neurologist, Duitama Regional Hospital, Boyaca, Colombia
[4]Headache Clinic, Manuel Velasco Suárez National Institute of Neurology and Neurosurgery, México
[5]Favaloro Foundation University Hospital, Buenos Aires (CABA), Argentina
[6]José de San Martín Clinical Hospital, Buenos Aires (CABA), Argentina
[7]Señor del Milagro Hospital, Salta, Argentina
[8]CEINSA Comprehensive Neurological Center and Julio de Vedia Hospital, 9 de Julio, Buenos Aires Province, Argentina
[9]Head of the Headache and Pain Department at the Buenos Aires Institute of Neurosciences "INEBA", Buenos Aires, Argentina

✉ Marina Alejandra Olivier
marinaolivier@hotmail.com

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Marcelo Moraes Valença

Introduction
Trigeminal autonomic cephalalgias (TAC) are primary headache disorders characterized by unilateral craniofacial pain, usually periorbital or temporal, accompanied by ipsilateral autonomic symptoms such as tearing, nasal congestion, conjunctival injection, miosis, and ptosis. They include cluster headache, paroxysmal hemicrania, hemicrania continua, and short-lasting unilateral neuralgiform headache attacks (SUNCT and SUNA). Diagnosis depends on attack duration, frequency, and intensity, though clinical overlap may occur. Accurate identification is crucial, as treatment differs among subtypes. Understanding TAC pathophysiology, particularly trigeminal autonomic activation, is essential for improving diagnosis, distinguishing them from similar disorders like migraine, and optimizing therapeutic management.

Results
Trigeminal autonomic cephalalgias represent a group of rare but disabling primary headache disorders characterized by overlapping pathophysiological pathways involving the hypothalamus and trigemino-autonomic reflex. Advances in neuroimaging and neuromodulation have refined understanding of their mechanisms and expanded therapeutic options beyond traditional pharmacotherapy. Early recognition and tailored, mechanism-based interventions remain essential to improving outcomes.

Conclusions
We believe it is very important and necessary to offer a comprehensive and up-to-date review of trigeminal autonomic headaches, emphasizing their common and distinctive clinical features, the underlying neurobiological mechanisms, and current evidence-based approaches for timely diagnosis and treatment.

Keywords:
Trigeminal-autonomic cephalalgias
Cluster headache
Paroxysmal hemicrania
Hemicrania continua
SUNCT
SUNA

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Introduction

Trigeminal autonomic cephalalgias (TAC) are a group of primary disorders characterized by unilateral craniofacial pain, predominantly periorbital or temporal, accompanied by ipsilateral cranial autonomic symptoms. The most common symptoms include tearing, nasal congestion, rhinorrhea, conjunctival injection, miosis, ptosis, facial flushing, and sweating. These manifestations reflect the combined activation of the trigeminal and parasympathetic autonomic nervous systems (1).

This group includes cluster headaches, paroxysmal hemicrania, hemicrania continua, and attacks of short-term unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) and with other autonomic symptoms (SUNA). Differentiation is based primarily on the frequency, duration, and intensity of the episodes, although there is some clinical overlap that can make diagnosis difficult (1,2).

Accurate recognition of each subtype is essential, as therapeutic management differs; the differential diagnosis should consider entities such as migraine, trigeminal neuralgia, and hypnic headache, which may present similar clinical features (1–3).

Understanding the pathophysiological mechanisms of TAC, particularly trigeminal autonomic activation, is essential to improve their diagnosis and treatment, as well as to differentiate nonspecific autonomic pain responses from those characteristic of primary headaches (1–3).

Cluster Headache

Cluster headache is a primary trigeminal-autonomic cephalalgia, considered one of the most painful headache disorders. It predominantly affects young men, with an average age of onset between 20 and 40 years (4,5).

It is characterized by sudden unilateral pain located in the orbital, supraorbital or temporal region, reaching its maximum intensity within 5 to 15 minutes from its onset. The pain is described as excruciating or stabbing. Attacks can last between 15 and 180 minutes and may recur from once every two days to up to eight times per day (4,6). Episodes occur in clusters lasting 6 to 12 weeks, separated by pain-free intervals (4,6). In most cases, symptomatic periods appear once or twice a year, in the case of episodic presentation.

Associated autonomic symptoms

During attacks, pain is accompanied by ipsilateral autonomic symptoms, including:

- Lacrimation (≈90%)
- Conjunctival injection
- Nasal congestion and/or rhinorrhea
- Ptosis and eyelid edema
- Forehead sweating
- Miosis
- Motor restlessness or agitation (4).

Some patients may experience mild interictal pain or migraineurs symptoms such as photophobia, phonophobia, and nausea, which can lead to diagnostic confusion (5,6).

Clinical forms

Two main variants are recognized, and both must have a minimum one-year period of presentation:

• Episodic cluster headache (80–90%), with remission periods longer than three months.

• Chronic cluster headache, without remission or with pain-free intervals shorter than three months (4,6).

Circadian and seasonal rhythmicity

Cluster headache exhibits a marked circadian and circannual rhythmicity, meaning that attacks often occur at the same time of day, frequently during nocturnal sleep. Cluster periods are more common in spring and autumn (4–6).

Diagnostic criteria for Cluster Headache (ICHD-3, 2018) (5).

A. At least five attacks fulfilling criteria B–D.

B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 minutes when untreated.

C. Either or both of the following during headache:

C1. At least one of the following ipsilateral symptoms or signs:

- Conjunctival injection and/or lacrimation
- Nasal congestion and/or rhinorrhea
- Eyelid edema
- Forehead and facial sweating
- Miosis and/or ptosis

C2. A sense of restlessness or agitation.

D. Attacks occur with a frequency from one every other day to eight per day.

E. Not better accounted for by another ICHD-3 diagnosis.

Episodic Cluster Headache

Attacks fulfilling criteria for cluster headache occurring in cluster periods lasting from 7 days to 1 year, separated by pain-free remission periods of ≥ 3 months.

Chronic Cluster Headache

Attacks fulfilling criteria for cluster headache occurring for ≥ 1 year without remission, or with remission periods lasting < 3 months.

Common triggers

The most recognized triggers include alcohol consumption (50–80%), sleep disorders, emotional or physical stress, exposure to heat, altitude, and weather changes (4). Pharmacological triggers include nitroglycerin, isosorbide dinitrate and mononitrate, histamine (IV or SC), sildenafil, tadalafil, and sodium nitroprusside.

Diagnostic evaluation

The diagnosis of cluster headache is clinical. However, brain magnetic resonance imaging (MRI) with fine cuts through the sellar and parasellar regions is recommended at onset or when atypical features are present, along with a basic pituitary hormonal panel, in order to rule out secondary causes, particularly pituitary adenomas and other sellar lesions (4,5).

Differential Diagnosis

Differential diagnoses include other trigeminal-autonomic cephalalgias, as well as other primary headaches or secondary disorders that may mimic cluster headache.

Primary Trigeminal-Autonomic cephalalgias

- Paroxysmal hemicrania (5,6).
- Hemicrania continua (6,7).
- SUNCT/SUNA syndromes (6,7).

Other primary headaches

- Side-locked unilateral migraine (5,6).
- Trigeminal neuralgia, mainly the classical form; secondary presentations may be considered, but the percentage is minimal (6,7).

Secondary headaches mimicking cluster headache

Among the secondary causes that may mimic cluster headache are temporal arteritis, acute glaucoma and various structural lesions or inflammatory processes involving the sellar or cavernous region (6):

- Pituitary adenomas (especially prolactinomas)
- Meningiomas
- Arteriovenous malformations
- Tolosa–Hunt syndrome

Pathophysiology of Cluster Headache

Although CH site of origin remains unclear, its pathophysiology is thought to involve a combination of central and peripheral nervous system changes (8,9).

The three key components contributing to the characteristic presentation of CH are the hypothalamus, the trigeminovascular system, and the autonomic nervous system (4,8–10). These systems work together through the trigemino-autonomic reflex, creating the unique symptoms of CH.

The trigeminovascular pathway consists of bipolar neurons located in the trigeminal ganglion, which innervate cerebral blood vessels and the dura mater. These neurons also project to the central nervous system, specifically to the trigeminal cervical complex, which includes the trigeminal nucleus caudalis in the medulla and dorsal horns at levels 1 and 2 in the cervical spinal cord. When the trigeminovascular pathway is activated, projections from the trigeminal cervical complex to the thalamus trigger activation of cortical regions involved in pain processing, such as the frontal cortex, insula, and anterior cingulate cortex (4,8,10).

Environmental triggers like weather changes, alcohol consumption, and strong odors can activate nociceptive fibers, predominantly in the ophthalmic branch of the trigeminal nerve, leading to the release of neuropeptides like CGRP and substance P. These neuropeptides promote vasodilation and neurogenic inflammation (8).

The trigeminal-autonomic reflex is another critical aspect of CH. Stimulation of the trigeminal nerve triggers the activation of parasympathetic pathways through the superior salivatory nucleus in the pons (4,8,10).

These pathways project via the facial nerve to synapse in ganglia, such as the sphenopalatine ganglion, which is responsible for autonomic symptoms like tearing, nasal congestion, and conjunctival injection. Neurotransmitters like nitric oxide and vasoactive intestinal polypeptide are released, contributing to vasodilation and glandular secretion, which underlie these symptoms.

The hypothalamus is a third essential player in CH pathophysiology (8,10). It is involved in the circadian and circannual pattern of CH episodes and mediates neuroendocrine changes. The hypothalamus receives sensory input from the trigeminal nerve through the trigeminal-hypothalamic tract and engages neuropeptides like orexin and somatostatin, which modulate pain perception.

Disruptions in hypothalamic regions, such as the suprachiasmatic nucleus, may explain the circadian rhythm disturbances commonly seen in CH patients. Increased blood flow and volume in specific hypothalamic areas ipsilateral to the headache are also reported in CH.

Disruption has been observed in brainstem structures involved in regulating nociceptive input from the trigeminal nerve, like periaqueductal gray matter, locus coeruleus, and dorsal raphe nucleus. These brainstem regions also exhibit altered connectivity with the hypothalamus, pointing to disruptions in pain control mechanisms (8,11).

A mesocorticolimbic imbalance has been identified (8,11). The ventral tegmental area, which is involved in reward and motivation, may play a significant role in CH. Patients with chronic CH show abnormalities in functional connectivity between the posterior hypothalamus and the ventral tegmental area, suggesting dysregulation between homeostatic and motivational systems. This imbalance contributes to chronic pain and altered emotional processing.

The salience network, consisting of regions like the anterior cingulate cortex and insula, is also affected (8). This network is involved in attention, affective processing, and autonomic regulation, and its persistent involvement may contribute to pain susceptibility and autonomic dysfunction in CH. Additionally, thalamic involvement in central sensitization correlates with symptoms such as hyperalgesia and allodynia.

Functional connectivity between the left thalamus and regions of the default mode network is reduced in CH, distinguishing it from migraine (8). Behavioral disturbances, such as agitation, are likely related to autonomic responses rather than the pain itself, and altered cerebellar connectivity may further contribute to these symptoms (8,10).

Management of Cluster Headache

Treatment for CH includes a combination of acute, transitional, and preventive medications (9,12,13). Acute treatments are primarily designed to relieve symptoms and shorten the duration of attacks (12,13). Transitional treatment that can be used as a short-lasting preventive if bouts are short or, more often, to obtain a "bridging" effect in the period a preventive is titrated to its therapeutic threshold (15). Preventive treatments are intended to decrease the attack frequency (13).

In addition to medications, lifestyle changes are recommended in patients with CH, in particular the avoidance of known triggers such as alcohol (12).

Acute Medications. The mainstays are high-flow oxygen, which should be administered at 100% via a nonrebreather mask at a rate of 12 L/min to 15 L/min for at least 20 minutes; and triptans, quicker routes of administration are preferred, Sumatriptan: 6 mg subcutaneous; 20 mg nasal spray and zolmitriptan: 5 mg nasal spray (12,13).

Simple analgesics and opioids are not effective.

Transitional Medications. Are greater occipital nerve blocks (with local anesthetic plus steroids) in the area of the ipsilateral greater occipital nerve or a course of oral steroids, prednisone (dose recommended: 10-80 mg/ d, tapering by 20 mg every 2–3 days) (12,14).

Preventive Medications. Patients with episodic and chronic cluster should start preventive treatment. Because of possible side effects, doses of available drugs have to be increased slowly to prevent adverse events (12).

The drug of choice for cluster headache prevention is verapamil.

Verapamil: the mechanism of action in Cluster Headache remains unclear, among the suggested are vasospasm inhibition, GABA-A inhibition, circadian rhythm modulation, and hyperpolarization-activated cyclic nucleotide-gated channel mediated decreasing of parasympathetic activity (8,13).

Treatment is started at a dosage of 40–120 mg administered three times daily, slowly increasing to 720–960 mg per day as needed (11).

Cardiac contraindications include untreated II and III atrioventricular block, bradycardia and heart failure, severe hypotension, and Wolff-Parkinson-White-Syndrome (8,12–14).

Adverse events are hypotension, fatigue, constipation, edema, bradycardia, and atrio ventricular block (14).

The possible interactions including medications as atorvastatin (increased risk of myopathy and rhabdomyolysis), domperidone (risk of prolonged QT interval), clopidogrel (decreased antiplatelet effect), fluconazole (increased verapamil exposure), lithium (neurotoxicity and bradycardia) and beta blockers (increased risk of bradycardia and atrioventricular block)

(8,12).

Treatment should last for the expected duration of a bout plus a few weeks after cluster attacks have finished. For discontinuation of verapamil, slow tapering is strictly recommended to avoid cardiac complications (14).

Second-line medications include lithium and topiramate (12–14).

Lithium: dose 600-1,500 mg/daily, slowy titrating.Require monitoring of lithium plasma concentrations and kidney and thyroid function. With serum levels between 0.6 and 0.8 mEq/L, it is considered optimal (8,13,14).

Adverse events are tremor, acne, hypothyroidism, and muscle weakness.

Topiramate: dose 50-200 mg/daily (14) the benefit of topiramate is that cardiac monitoring is not required.

Adverse events are depression, especially in people with pre-existing depressive symptoms, cognitive impairment and paresthesia (13,14).

Topiramate cannot be used in people with neprolithiasis and glaucoma (14).

Other medications

Melatonin: 10 mg/daily. Preventive treatment is based on the circadian nature of cluster headaches and the observed low melatonin levels during and between bouts in patients with episodic cluster headaches (9). Used as an adjunct preventive (12,14).

Gabapentin: dose 1,000-1,800 mg. There is evidence only from open-label small observational series that some patients with refractory chronic cluster headache may respond to gabapentin (14).

Monoclonal Antibodies Against Calcitonin Gene-Related Peptide:

Galcanezumab: 120 mg subcutaneously once monthly. Approved in the USA for the prophylaxis of episodic cluster headache (14).

Clomifeno: dose 50-100 mg. Treatment may be effective in refractory chronic cluster headache (15).

Interventional Management of Cluster Headache (CH):

Interventional management of CH represents a valuable therapeutic alternative for patients who are refractory to pharmacological treatments. These procedures encompass abortive, transitional and prophylactic approaches targeting key structures of the trigemino-autonomic system (Table 1) (9).

Table 1. Sites of interventional treatments, target areas, and clinical practice algorithms for Cluster Headache (CH)

	"ATECH"	"PTECH"	TRANSITIONAL	"AT"	"PT" IN "MICCH"
IT-CH		Currently not indicated	GON'I	SPG'S	GON'I RFAT/PRFAT of SPG ONS DBS
Hypothalamus					DBS
Sphenopalatine ganglion					SPGS RFAT LTPRFAT GKRS
Occipital Nerve					ONS
Greater Occipital Nerve					GON'I
Vagal Nerve	"AT"				n'VNS

Interventional Management of CH: "IT-CH"
"AT": Abortive Therapy
"ATECH": Abortive Therapy Episodic Cluster Headache
"PT": Preventative Therapy
PTECH": Preventative Therapy Episodic Cluster Headache;
"MICCH": Medically intractable Chronic Cluster Headache;
"GON'I": Greater Occipital Nerve Injections;
"SPG": Sphenopalatine Ganglion;
"SPG'S": Sphenopalatine ganglion stimulation;
"n' VNS": Noninvasive Vagus Nerve stimulation;
"ONS": Occipital Nerve Stimulation
"RAF": Radiofrequency Ablation Therapy,
"RFAT: Radiofrecuency Ablation Therapy,
"PRFAT": Pulsed Radiofrecuency Ablation Therapy,
"DBS": Deep Brain Stimulation,
"LTPRFAT": Low-temperature Plasma Radiofrequency Ablation
"GKRS", Gamma Knife Radiosurgery;
"SSN": superior salivatory nucleus;

Among peripheral interventions, "GON" blockade is one of the most widely used. It involves subcutaneous infiltration of local anesthetics combined with corticosteroids on the side of the pain. Its efficacy has been demonstrated in both "ECH" and "CCH", showing a favorable safety profile with mostly mild and transient adverse effects (9,16).

Radiofrequency ablation therapy of the "SPG" is another relevant therapeutic option. By applying controlled heat, this technique interrupts ganglionic activity at the onset of CH bout, which mediates the autonomic symptoms of CH attacks due to "SPG" involvement in the trigeminal parasympathetic reflex (9). Variants such as "PRFAT" (17) or "LTPRFAT" (18) offer potentially safer alternatives, mainly for "MICCH", but further larger comparative studies are required to confirm their benefits.

Neuromodulation therapies have gained increasing importance over the past decade, particularly in "MICCH". Among non-invasive techniques, "n'VNS" has proven effective both as abortive and preventive therapy, with minimal adverse events (19).

Invasive neuromodulation, including "SPG'S" (20), and "ONS", has shown significant reductions in attack frequency and intensity through modulation of nociceptive and autonomic pathways.

Occipital Nerve Stimulation, in particular, could reduce the attack frequency and provide sustained long-term relief. Hardware complications like lead migration and battery depletion remain concerns (9,21).

Deep brain stimulation targeting the hypothalamus is reserved for the most severe and "MICCH". Neuroimaging evidence of hypothalamic hyperactivity in CH supports this approach, which has shown response rates between 50 to 70% in both attack frequency and intensity in observational studies, despite inherent surgical risks (9).

New treatment modalities include SPG pulsed RF, GKRS, is also being investigated. Despite this, the findings available to date have shown considerable variation, with therapeutic effects that also tend to diminish overtime (9).

High frequency spinal tonic cord stimulation "STCS" without paresthesia by electrical pulses targeting the TCC as a preventive treatment in patients with "MICCH" has also been investigated. However, the outcomes to date have varied (9).

Finally, combined stimulation of the SPG and GON emerges as a promising therapeutic strategy capable of providing durable control of "MICCH" (22).

These interventions are increasingly used in the management of CH, but further multicenter and long-term studies are required to ensure their use.

Paroxysmal Hemicrania

Paroxysmal hemicrania (PH) is a rare primary headache disorder within the spectrum of trigeminal autonomic cephalalgias (TACs), characterized by recurrent, short-lasting, strictly unilateral attacks of severe pain associated with ipsilateral cranial autonomic symptoms and an absolute response to indomethacin. Its precise prevalence remains uncertain due to diagnostic challenges and the requirement for an indomethacin trial. Estimates suggest a prevalence of approximately 0.5 to 1 per 50,000 individuals, with PH accounting for 0.75% of patients in a specialized headache clinic cohort (23).

The median age of onset is in the fourth decade, although cases have been reported from early childhood to late adulthood (range: 5–81 years) (24). While earlier studies suggested a female predominance (F:M ≈ 2.3:1), more recent cohorts show a more balanced sex distribution (25).

Clinical features

PH is strictly unilateral but not side-locked; approximately 15% of patients may experience alternating sides, and rare bilateral cases have been described. Pain typically involves the orbital, supraorbital, and temporal regions (first division of the trigeminal nerve), but may also extend to the parietal, occipital, cheek, jaw, neck, and even shoulder regions (23).

Attacks are severe, with a stabbing, throbbing, or claw-like quality, lasting 2–30 minutes, and occurring more than five times per day—up to 40 or even 50 attacks in some cases. A chronic form is more common than the episodic variant. Chronic PH is defined by the absence of remission periods longer than three months over at least one year, while episodic PH includes remissions >3 months (26).

Ipsilateral cranial autonomic features are present in over 80% of patients and may include lacrimation, conjunctival injection, rhinorrhea, nasal congestion, eyelid edema, ptosis, miosis, facial sweating, and aural fullness. Restlessness and motor agitation occur in up to 80% of cases. Migrainous features such as photophobia, phonophobia, nausea, and even aura are reported in a minority of cases, complicating the clinical picture (23).

Treatment

Indomethacin remains the gold standard for diagnosis and treatment. A complete response to therapeutic doses (typically 75–150 mg/day) is diagnostic and part

of the ICHD-3 criteria. The 'Indotest'—an intramuscular administration of 50–100 mg of indomethacin—was the originally proposed protocol to evaluate treatment responsiveness (23). However, in clinical practice, an alternative approach using oral indomethacin at doses of 25–75 mg administered three times daily is widely employed, with response often observed within days, although longer trials may be required in some patients (24). In a meta-analysis of over 160 patients, 89% achieved complete relief; however, adverse effects such as gastrointestinal intolerance, renal dysfunction, and cardiovascular risks may limit long-term use (25). The exact mechanism of indomethacin's efficacy in PH remains incompletely understood. Unlike its use in rheumatologic conditions, indomethacin in PH appears to act as a preventive agent rather than an acute analgesic. It is a potent COX-1 inhibitor, but its unique therapeutic effect may involve modulation of central pain processing, including inhibition of nitric oxide-induced vasodilation and normalization of elevated CGRP levels observed during attacks (26).

Functional imaging studies have demonstrated activation of the posterior hypothalamus during PH attacks, suggesting hypothalamic dysregulation as a central pathophysiological mechanism. The exact interplay between hypothalamus, trigeminal-autonomic reflex pathways, and indomethacin responsiveness remains a focus of ongoing research (27). Alternative treatments for indomethacin-intolerant patients include selective COX-2 inhibitors (e.g., celecoxib, etoricoxib), topiramate, melatonin, and piroxicam. In a prospective cohort, melatonin (median dose: 8–10 mg) led to partial relief in ~50% of patients, though not complete remission (28). Peripheral nerve blocks and neuromodulation techniques have not demonstrated consistent efficacy.

Secondary PH

While PH is typically a primary disorder, rare secondary cases have been linked to structural lesions such as pituitary adenomas, meningiomas, arteriovenous malformations, and trauma. In these cases, the phenotype is usually indistinguishable from primary PH and may still respond to indomethacin, underscoring the need for neuroimaging in all new-onset cases (26).

Hemicrania continua

Hemicrania continua (HC) is also an indomethacin-responsive headache with trigeminal-autonomic symptoms. The pooled prevalence in outpatient tertiary care centers is 1.8%. There are no population-based studies about epidemiology (29). The mean age onset lies between the 4th and 5th decades. It is slightly more prevalent in women than in men, with men to female ratio between 1:1 and 1:2.4. (30).

Clinical characteristics

The pain is described as strictly unilateral and continuous with periods of exacerbation, but with no moments without pain. The localization is orbitofrontal. The most common accompanying symptoms are lacrimation and rhinorrhea (31).

A common clinical situation in which HC should be suspected is a patient presenting with a chronic daily headache resembling chronic migraine, but with the key distinction that the pain remains strictly unilateral and is accompanied by mild ipsilateral autonomic symptoms. In such cases, when the continuous baseline pain and side-locked pattern raise diagnostic uncertainty, a therapeutic trial of indomethacin may help differentiate HC from chronic migraine.

Treatment and approach to resistant patients

Indomethacin is the gold standard treatment for hemicrania continua, and a complete response constitutes part of the ICHD-3 diagnostic criteria. An indomethacin trial is commonly performed using an approach similar to that employed in paroxysmal hemicrania. The mean effective dose usually does not exceed 200 mg per day (30). Although no standardized oral protocol exists, the authors' experience is consistent with previously suggested regimens (24), which recommend initiating treatment with 25 mg three times daily for one week, followed by 50 mg three times daily for one week, and subsequently 75 mg three times daily for up to two weeks. Further dose escalation is unnecessary if a complete response is achieved. Concomitant use of a proton pump inhibitor is common clinical practice. Symptom resolution typically occurs within 1 to 28 days (30).

Indomethacin represents the cornerstone long-term treatment for hemicrania continua, functioning not only as an acute therapy but primarily as a preventive agent. Long-term adherence, however, may be limited by gastrointestinal adverse effects. Over extended follow-up, up to 40% of patients are able to reduce their indomethacin dose by approximately 60% while maintaining a sustained pain-free course (31). For patients who are intolerant to indomethacin, alternative options include melatonin, a pineal hormone with structural similarity to indomethacin, which has been associated with symptomatic improvement in up to 61% of cases (28). Other potential options include selective COX-2 inhibitors, anticonvulsants, and calcium channel blockers (32).

Short-lasting unilateral neuralgiform headaches (SUNHAs)

Short-lasting unilateral neuralgiform headaches

(SUNHAs) belong to the group of trigeminal autonomic cephalalgias (TACs) and share clinical characteristics with each other, such as unilateral headache with ipsilateral parasympathetic cranial autonomic signs. They have been included since 2018 in the third edition of the International Classification of Headache Disorders (ICHD-3) (5).

There are two types: 1. Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT), 2. Short-lasting unilateral neuralgiform headache with autonomic symptoms (SUNA), explained in detail below (33).

Epidemiology

The prevalence is uncertain, but SUNCT and SUNA are estimated to be 6.6 per 100,000, with an annual incidence of 1.2 per 100,000. The age of onset is between 35 and 65 years, with an average of 48 years (12).

Previously, it was known that SUNHA predominantly affected males; however, more recent reports have indicated that there is no predominance of SUNCT and that SUNA predominantly affects females (34).

Clinical characteristics

SUNHA manifests as moderate to severe pain of short duration, which may be stabbing, burning, or electric shock-like in the orbital, periorbital, or unilateral area with ipsilateral cranial autonomic symptoms. Occasionally, pain may occur in other areas such as the top, side, or back of the head or in the V2 and V3 branches of the trigeminal nerve (34).

The duration of the attacks can be from 1 to 600 seconds each, and may overlap with the duration of paroxysmal hemicrania, which usually lasts between 2 and 30 minutes. They can occur in a "sawtooth" pattern, when paroxysms of pain occur without intervals of relief. The frequency varies, from 1 to 600 times a day, with an average of less than 100 episodes per day (34).

There are two forms: episodic and chronic, which share diagnostic criteria but have certain differences, as shown below. SUNCT (Short-lasting Unilateral Neuralgiform Headache Attacks with Conjunctival Injection and Tearing) and SUNA (Short-lasting Unilateral Neuralgiform Headache Attacks with Cranial Autonomic Symptoms), each with episodic and chronic forms, as defined by the International Classification of Headache Disorders, third edition (ICHD-3). Across all subtypes, diagnostic criteria require at least 20 attacks of moderate to severe unilateral pain in trigeminal distributions, lasting 1–600 seconds, occurring at least once daily, and accompanied by at least one ipsilateral cranial autonomic symptom, with no better alternative diagnosis. SUNCT is characterized by the obligatory presence of ipsilateral conjunctival injection and lacrimation, whereas SUNA allows for the presence of no more than one of these two features. Episodic forms occur in bouts lasting 7 days to 1 year, separated by pain-free remissions of at least 3 months, while chronic forms persist without remission or with remissions shorter than 3 months for a minimum duration of one year (5).

Differential diagnosis

SUNCT and SUNA can be differentiated from other trigeminal autonomic cephalalgias (TACs) such as paroxysmal hemicrania and cluster headache by the frequency of their attacks and lack of response to indomethacin and oxygen. On the other hand, the key difference with trigeminal neuralgia and primary stabbing headache is that these lack autonomic symptoms and the latter presents with different pain locations between attacks (Table 2) (12,34).

Table 2. Clinical characteristics of short-lasting unilateral neuralgiform headaches (SUNHAs), cluster headaches, and trigeminal neuralgia.

Feature	Male: female ratio	Pain distribution	Spreading	Duration	Quality	Intensity	Frequency (attacks/ day)	Refractor and period	Triggers	Autonomic symptoms	Restlessness/ agitation	Main treatment
SUNHA	1.0:3–2.3	Unilateral orbital, supraorbital, temporal	May stay stationary	1–600 seconds (<10 minutes)	Sharp, stabbing, throbbing	Moderate or severe	3–200 (mean 59), series of stabs or saw-tooth pattern	Usually not present	Cutaneous stimuli, neck movement	Prominent conjunctival injection and/ or lacrimation; combined cranial autonomic symptoms	Present	Intravenous lidocaine, lamotrigine
Cluster headache	3:1	Unilateral orbital, supraorbital, temporal	May stay stationary	15–180 minutes	Throbbing, stabbing, burning	Severe or very severe	0.5–8	Not present	Alcohol, nitroglycerin	At least one of: (a) conjunctival injection/ lacrimation, (b) nasal congestion/ rhinorrhea, (c) eyelid edema, (d) forehead/ facial sweating, (e) miosis/ ptosis	Usually present	Oxygen, triptan
Trigeminal neuralgia	1:2.3	Mostly 2nd or 3rd division or both, restricted to trigeminal distributions	May radiate to another division	A fraction of a second to two minutes	Electric shock-like, shooting, stabbing, sharp	Extreme	Higher than SUNHA	Typically present	Cutaneous stimuli, neck movement	Rarely and mild	None	Carbamazepine

Reports describe symptomatic cases of SUNHA (Short-lasting unilateral neuralgiform headache), especially associated with pituitary and posterior fossa tumors. The recommended diagnostic method is nuclear magnetic resonance imaging (MRI) with attention to areas such as the trigeminal nerve root, brainstem, cavernous sinus including the pituitary gland, and studies such as head and neck angiography, Figure 1 (34).

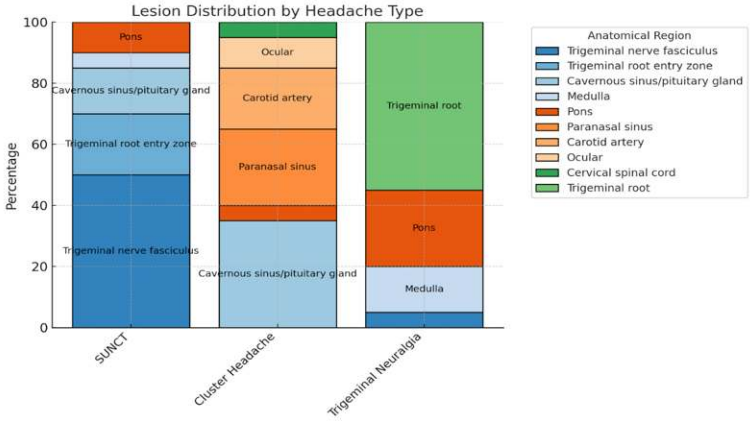

Figure 1. Location of secondary causes associated with SUNCT, cluster headache, and trigeminal neuralgia. SUNCT (Short-lasting Unilateral Neuralgiform Headache Attacks with Conjunctival Injection and Tearing). Data on lesion distribution and imaging findings are derived from the previously published study cited as reference (12).

Pathophysiology

SUNCT and SUNA are very rare primary trigeminal autonomic cephalalgias (TACs) (35); because of this, the existing literature on their pathophysiological mechanism is scarce (36). A complex interaction between central and peripheral mechanisms has been proposed, involving the posterior hypothalamus and a possible demyelination of the preganglionic trigeminal sensory root due to neurovascular contact (34).

Central role of the posterior hypothalamus

The most widely accepted theory of the pathophysiology of TACs is that they are caused by a hypothalamic abnormality, which leads to hypothalamic activation with subsequent activation of the trigemino-autonomic reflex through a trigemino-hypothalamic pathway.

The posterior hypothalamus regulates pain pathways and autonomic pathways, specifically the trigeminovascular nociceptive pathway; dysfunction of this pathway can catalyze the excessive production of nociceptive orexin B (34), thus activating the trigemino-hypothalamic tract, initiating the pain pathway.

This theory is supported by functional imaging studies that identified the hypothalamus as central in the pathophysiology of TACs, and similar imaging findings in SUNCT/SUNA provide justification for classifying them within TACs (35).

The secondary activation of cortical regions intensifies the pronounced pain characteristic of this disorder.

Peripheral mechanisms

SUNCT/SUNA share clinical similarities with trigeminal neuralgia (TN), and many of these patients present ipsilateral trigeminal neurovascular compression to the side of the pain (34).

There is an ongoing debate about the relationship between SUNCT/SUNA and TN, and the possibility that both entities represent a clinical spectrum; or whether it is an incidental finding or truly the underlying pathophysiology in these cases. Moreover, the efficacy of sodium channel blockers in SUNCT/SUNA indicates that, at least in some patients, a dysregulation of sodium channels could constitute a relevant pathophysiological mechanism that deserves further exploration (36).

Despite the ongoing debate, current data indicate that there are indeed differences between TN and SUNCT/SUNA (40), since in TN, to date, hypothalamic dysfunctions have not been reported (37).

Treatment (12,33–36)

To indicate treatment, we must distinguish between episodic and chronic SUNCT/SUNA; moreover, in episodic cases we have a transitional or bridge treatment (36), indicated while the benefit of preventive treatment begins; these treatments can also be indicated in decompensations and/or exacerbations; and the daily preventive treatment (Table 3). High doses are usually required before considering a medication ineffective; invasive treatments are reserved for chronic cases (Table 4). SUNCT and SUNA appear to show similar responses to drug treatments (36).

Table 3. SUNCT/SUNA episodic. Preventive Treatment

Treatment Phase	Medication / Procedure	Dosage / Protocol	Notes
Transient / exacerbations	**IV Lidocaine**	1–3.5 mg/kg/h	Patient under cardiac monitoring; relief in 24–48 hours; benefit lasting up to several months. Contraindicated in patients with cardiac conduction abnormalities.
Daily Preventive Treatment	**GON Blockade**	80 mg methylprednisolone + 2 ml of 2% lidocaine	Dosage or mixture may vary based on the center's experience.
	First-line	Lamotrigine (up to 700 mg/day)	
	Second-line	Oxcarbazepine (up to 2400 mg/day)	
		Duloxetine (up to 120 mg/day)	
		Carbamazepine (up to 1600 mg/day)	
		Topiramate (up to 800 mg/day)	
	Third-line	Gabapentin (up to 4800 mg/day)	
		Pregabalin (up to 600 mg/day)	
		Lacosamide (up to 400 mg/day)	
		Mexiletine (up to 1200 mg/day)	

Table 4. SUNCT/SUNA cronic. Treatment

Type of Treatment	
Non-surgical	Botulinum toxin: 75–100 IU, in mesh pattern over the pain area
Surgical	Anti-CGRP antibodies: erenumab and galcanezumab
	Bilateral occipital nerve stimulation
	Microvascular decompression of the trigeminal nerve
	(if neurovascular contact is confirmed)
	Radiosurgery with Gamma Knife
	Pulsed radiofrequency of the sphenopalatine ganglion
	Deep brain stimulation of the ventral tegmental area (DBS)

Future multicenter studies with prospective registries are needed, where standardized individual-level data are systematically collected and sample sizes are sufficient to generate adequate controlled clinical trials.

Conclusion

Trigeminal autonomic cephalalgias represent a group of rare but disabling primary headache disorders characterized by overlapping pathophysiological pathways involving the hypothalamus and trigemino-autonomic reflex. Advances in neuroimaging and neuromodulation have refined understanding of their mechanisms and expanded therapeutic options beyond traditional pharmacotherapy. Early recognition and tailored, mechanism-based interventions remain essential to improving outcomes.

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Osvaldo Carlos Jesús Bruera
https://orcid.org/0009-0006-6848-7718
Margareth Alexandra Contreras Martínez
https://orcid.org/0009-0004-1932-8070
Carlos Andrés Díaz Garza
https://orcid.org/0000-0001-7049-5406
Javier Andrés Galnares Olalde
https://orcid.org/0000-0003-3004-6221
Adolfo Leyva Rendon
https://orcid.org/0000-0001-8774-1407
Paula Alexandra Martínez Corredor
https://orcid.org/0009-0001-0654-5234
Verónica Lourdes Molina
https://orcid.org/0009-0007-6684-0263
Marina Alejandra Olivier
https://orcid.org/0009-0000-7836-3205
María Celeste Rada Fernández
https://orcid.org/0009-0008-9810-660X
María Soledad Smechow
https://orcid.org/0009-0008-4994-5247

Authors' contributions: OCJB, MAO: conceptualization, project administration, supervision, visualization, writing – review & editing; OCJB, MACM, CADG, JAGO, ALR, PAMC, VLM, MAO, MCRF, MSS: investigation, methodology, validation, writing – original draft.
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