REVIEW ARTICLE

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
DOI: 10.5603/pjnns.99747

ISSN: 0028-3843, e-ISSN: 1897-4260

Indomethacin-responsive trigeminal autonomic cephalgias: a review of key characteristics and pathophysiology

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ABSTRACT

Trigeminal autonomic cephalgias (TACs) are a well-defined subset of uncommon primary headaches that share comparable onset, pathophysiology and symptom patterns. TACs are characterised by the presentation of one-sided and high-intensity trigeminal pain together with unilateral cranial autonomic signs, which can include lacrimation, rhinorrhea, and miosis. The International Classification of Headache Disorders 3rd Edition recognises four different headache entities in this group, with cluster headache as the most recognised among them. Hemicrania continua (HC) and paroxysmal hemicrania (PH) are both distinctive cephalgias of which the diagnostic criteria include an absolute response to indomethacin. Consequently, for this reason they are often referred to as 'indomethacin-responsive' TACs.

The main focus of this review was to discuss the state of knowledge regarding the pathophysiology and key characteristics of PH and HC. Given the limited understanding of these conditions, and their exceptionally uncommon prevalence, a correct diagnosis can pose a clinical challenge and the search for an effective treatment may be prolonged, which frequently has a serious impact upon patients' quality of life. The information provided in this review is meant to help physicians to differentiate indomethacin-sensitive cephalgias from other distinct headache disorders with a relatively similar clinical presentation, such as cluster headache, trigeminal neuralgia, and various migraine conditions.

Keywords: trigeminal-autonomic cephalgias, Sjaastad syndrome, indomethacin, hemicrania continua, paroxysmal hemicrania

Introduction

Trigeminal autonomic cephalgias (TACs) are a clearly established group of rare primary headaches with similar patterns of attacks and symptoms. They feature a presentation of trigeminal pain with an association of unilateral cranial autonomic signs, which can include lacrimation, rhinorrhea, and miosis [1]. The International Classification of Headache Disorders 3rd Edition (ICHD-III) [1] distinguishes four headaches in this group: cluster headache (CH), hemicrania continua (HC), paroxysmal hemicrania (PH), and short-lasting unilateral neuralgiform headache attacks (SUNCT and SUNA).

In recent years, there has been considerable debate about the classification of HC. The previous ICHD-II did not recognise HC as a TAC-related headache disorder but assigned it as an "other primary headache" due to the lack of such prominent autonomic symptoms as encountered in paroxysmal hemicrania or cluster headache. The current classification (dating from 2018) considers HC to be a TAC [2], because of similar

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Received: 12.03.2024 Accepted: 13.05.2024 Early publication date: 27.06.2024

Table 1. Diagnostic criteria for paroxysmal hemicrania and hemicrania continua as provided in International Classification of Headache Disorders 3rd Edition [1]

Paroxysmal hemicrania (PH) diagnostic criteria	Hemicrania continua (HC) diagnostic criteria
A. At least 20 attacks fulfilling criteria B–E	A. Unilateral headache fulfilling criteria B–D
B. Severe unilateral orbital, supraorbital and/or temporal pain lasting 2–30 minutes	B. Present for > 3 months, with exacerbations of moderate or greater intensity
C. Either or both of following:	C. Either or both of following:
1. At least one of following symptoms or signs, ipsilateral to headache:	1. At least one of following symptoms or signs, ipsilateral to headache:
• conjunctival injection and/or lacrimation	• conjunctival injection and/or lacrimation
• nasal congestion and/or rhinorrhoea	• nasal congestion and/or rhinorrhoea
• eyelid oedema	• eyelid oedema
• forehead and facial sweating	• forehead and facial sweating
• miosis and/or ptosis	• forehead and facial flushing
2. A sense of restlessness or agitation	• sensation of fullness in ear
	• miosis and/or ptosis
	2. A sense of restlessness or agitation, or aggravation of pain by movement
D. More than five attacks per day for more than half of time	D. Responds absolutely to therapeutic doses of indomethacin*
E. Attacks are prevented absolutely by therapeutic doses of indomethacin*	E. Not better accounted for by another ICHD-3 diagnosis
F. Not better accounted for by another ICHD-3 diagnosis	

*In an adult, oral indomethacin should be used initially in a dose of at least 150 mg daily and increased, if necessary, up to 225 mg daily. Dose by injection is 100–200 mg. Smaller maintenance doses are often employed

clinical features shared among other TACs, with the evidence of ipsilateral posterior hypothalamus activity that would suggest trigeminal autonomic activation. [3]

CH is described as the most common syndrome within TACs, with a mean prevalence of 0.1% (1/1,000) in the general population [3] and a clear male preponderance [4]. PH is even less widespread, with a prevalence of 1/50,000, and for a long time was considered to be female-dominant [5, 6]. However, a recent study does not support this notion [7], suggesting an even gender distribution. Al-Khazali et al. [8] found that HC is present in 1.8% of adult patients who were evaluated for headache in a tertiary care unit. However, the true prevalence of HC and SUNCT/SUNA in the general population remains unknown, with only a few hundred cases reported in the literature [9]. They pose a clinical challenge due to their rarity and inadequate understanding, which results in underdiagnosis and undertreatment. Due to hemicranias' exceptionally uncommon prevalence, misdiagnosis can lead to delays in the search for effective treatment [10], often seriously impairing patients' quality of life [11].

In the diagnosis criteria, both HC and PH include an absolute responsiveness to therapeutic doses of indomethacin [1]. Indomethacin is a COX-1 selective inhibitor, and apart from its classic side effects shared by other NSAIDs, it has been proven to show a higher risk of gastrolesive effects when compared to other more commonly used NSAIDs [12]. Therefore, many patients who present complete resolution of headaches following a trial of indomethacin are forced to cease treatment due to the occurrence of complications.

Paroxysmal hemicrania

In 1974, Sjaastad and Dale [13] were the first to describe a new headache entity they called chronic paroxysmal hemicrania, while the first case of episodic paroxysmal hemicrania was reported by Kudrow, Esperanca, and Vijayan in 1987 [14]. Episodic paroxysmal hemicrania (EPH) is distinguished from chronic paroxysmal hemicrania (CPH) by its temporal profile: EPH has attack phases that span weeks to months and are separated by remission intervals that last months to years. This contrasts with CPH, which does not feature such remission periods [15]. Sjaastad went on to propose that EPH is a remittent type of CPH rather than a distinct clinical entity [16], but similarly to episodic and chronic cluster headaches, they are most likely at the opposite extremes of a spectrum [17].

Paroxysmal hemicrania (PH) is described as severe attacks of strictly unilateral pain localised in the orbital, supraorbital, temporal or any combination of these sites, lasting between two and 30 minutes and occurring several, or many, times a day [1]. The attacks are associated with ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, forehead and facial sweating, miosis, ptosis, and/or eyelid oedema [1]. They respond absolutely to indomethacin. PH follows the diagnostic criteria set out in Table 1.

According to Boes and Dodick [6], an attack lasts for an average of 26 minutes, and can occur up to 40 times a day (Fig. 1). The pain is severe and highly intense, and patients subjectively describe it as a sharp, shooting, stabbing, and burning sensation with a sudden onset. The majority of patients experience pain mostly in areas innervated by the ophthalmic division of

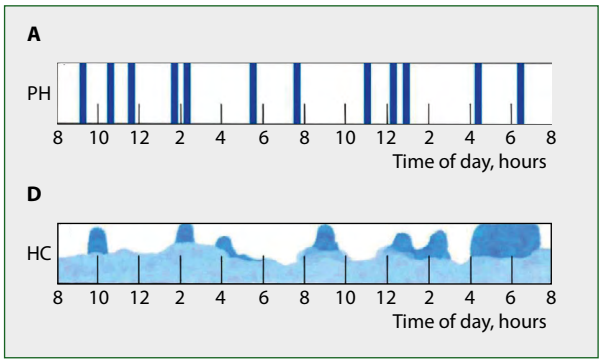

Figure 1. Daily distribution of PH attacks (**A**) compared to daily distribution of HC attacks (**B**), continuous background pain (light blue) and pain exacerbations (dark blue)

the trigeminal nerve (temporal, frontal, and orbital/retro-orbital), but some patients may also experience pain sensations derived from areas innervated by the second and third divisions of the trigeminal nerve (jaw, maxillary, and gums) [7, 13]. PH can further be divided into two subtypes based on the length of attacks and pain-free periods, as set out in Table 2. Resolution of pain should be achieved within the first 24 hours after indomethacin use. The dosage should be adjusted to the lowest possible amounts that preserve the analgesic effect [18].

A recent meta-analysis [19] found that the most prevalent cranial autonomic symptoms were lacrimation (77.3%), conjunctival injection (75%), nasal congestion (47.7%), ptosis (27.3%), and rhinorrhea (19.5%). Symptoms such as restlessness and agitation, which have just been added to the ICHD diagnosis criteria [1], were present in c.42% of patients [19].

Unlike CH, the timing of PH headaches is not influenced by the circannual or circadian cycles. When 12 months has passed without remission, those who persist are diagnosed with chronic PH. The chronic form represents c.65% of PH, meaning c. 35% is episodic [20].

Phonophobia and photophobia are present in three-quarters of those suffering from migraines and are one of the key characteristics used in the International Headache Society's definition of migraine [1]. Many studies indicate the occurrence of both of these symptoms in TAC patients, characteristically unilateral and ipsilateral to the pain site. Irimia et al. [21] reported that two-thirds of PH patients showed accompanying migrainous manifestations. In contrast to migraine, agitation and restlessness are prevalent during the attack. Interestingly, comorbid migraine may be present in up to half of PH patients [7].

Hemicrania continua

Hemicrania continua was first described (though not named) by Medina and Diamond [22] in 1981. They reported a series of patients suffering from cluster headache variants, and many of them achieved an excellent response with indomethacin. Three years later, Sjaastad and Spierings [23] described a headache characterised with a striking response to indomethacin (similarly to PH), that, due to its unique course and attack pattern, differed from other distinct types of chronic unilateral headaches and therefore was named 'hemicrania continua'.

Hemicrania continua is described as a persistent, strictly unilateral headache with associated symptoms such as ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, forehead and facial sweating, miosis, ptosis, and/or eyelid oedema, and/or restlessness or agitation [1]. The headache is sensitive to indomethacin [1]. HC follows the diagnostic criteria set out in Table 1. HC can be further divided into two subtypes based on the characteristics of episodes of pain-free periods (Table 2).

Similarly to PH, some individuals can be maintained on reduced dosages following an initial response. In patients with HC, skipping a dose of indomethacin has been observed to induce an immediate recurrence of symptoms. Antonaci and Sjaastad [24] suggested in 2020 that it may even have more diagnostic value than its response to an indomethacin trial.

A recent meta-analysis [8] found that the most prevalent cranial autonomic symptoms were lacrimation (73%), conjunctival injection (70%), rhinorrhea (46%), and nasal congestion (45%). Less prevalent were forehead and facial flushing (15%), ptosis (12%), forehead and facial sweating (9%), and eyelid oedema (3%). Symptoms such as restlessness and agitation were present in c.60% of patients [8]. A comparison of the most prevalent cranial autonomic symptoms between PH and HC is set out in Table 3 [8, 19].

Autonomic symptoms are not as prominent as in PH or in CH. Prakash and Patel [25] reported in a recent study that the mean prevalence of at least one autonomic cranial symptom is 74% (pooled analyses of 433 patients), compared to PH and CH, where it was noted in more than 90% of the patients. Therefore, it is interesting to consider that around a quarter of HC cases can present without such autonomic symptoms, yet patients can still simultaneously meet the ICHD-3 criteria for HC because a sense of restlessness, agitation or aggravation of the pain is itself sufficient to fulfill the diagnostic requirements [1].

HC is often misdiagnosed as a migraine due to the common presence of migrainous features. Al-Khazali et al. [8] estimated that the prevalence rates of nausea, photophobia, and phonophobia in patients with HC were 43.8%, 34.6%, and 21.6%, respectively. The major causes of unsuccessful attempts to diagnose HC can be attributed to temporal patterns and migraine-like characteristics. A doctor can easily classify the condition as one of the migraine variants by mistake when a migrainous symptom is present. Restlessness and agitation, characteristic of HC, are certainly clinical features that help to distinguish those headaches. A comparison of the key features of paroxysmal hemicrania, hemicrania continua, and migraine is set out in Table 4 [1, 7, 26].

Table 2. Types of paroxysmal hemicrania and hemicrania continua as provided in International Classification of Headache Disorders 3rd Edition [1]

Paroxysmal hemicrania (PH) types	Hemicrania continua (HC) types
1. Episodic paroxysmal hemicrania (EPH), of which diagnostic criteria include:	1. Hemicrania continua, remitting subtype, of which diagnostic criteria include:
Attacks fulfilling criteria for paroxysmal hemicrania and occurring in bouts	Headache fulfilling criteria for hemicrania continua, and criterion B below
At least two bouts lasting from seven days to 12 months (when untreated) and separated by pain-free remission periods of at least one mont	Headache not daily or continuous, but interrupted by remission periods of one day without treatment
2. Chronic paroxysmal hemicrania (CPH), of which diagnostic criteria include:	2. Hemicrania continua, unremitting subtype, of which diagnostic criteria include:
Attacks fulfilling criteria for paroxysmal hemicrania, and criterion B below	Headache fulfilling criteria for hemicrania continua, and criterion B below
Occurring without a remission period, or with remissions lasting < 1 month, for at least 12 months	Headache is daily and continuous for at least 12 months, without a remission period of one day

Table 3. Comparison of frequencies of most common cranial autonomic symptoms in individual patients suffering from PH [19] and HC [8]

Autonomic features	Paroxysmal hemicrania	Hemicrania continua
Lacrimation	77.3%	73%
Conjunctival injection	75%	70%
Rhinorrhea	19.5%	46%
Nasal congestion	47.7%	45%
Ptosis	27.3%	12%

Table 4. Comparison of key features of paroxysmal hemicrania, hemicrania continua, and migraine [1, 7, 26]

	Paroxysmal hemicrania	Hemicrania continua	Migraine
Sex ratio, male to female	1:1	1:1.8	1:3
Pain location	Unilateral orbital, supraorbital and/or temporal	Unilateral	Unilateral, any part of head
Severity of pain	Severe	Any	Moderate to severe
Duration of attacks	2 to 30 minutes	Persistent	4–72 hours
Frequency of attacks	> 20/day	Continuous pain lasting > 3 months, with 5–12 exacerbations of moderate or greater intensity per day	Varies individually
Additional symptoms	Lacrimation, conjunctival injection, nasal congestion	Lacrimation, conjunctival injection, rhinorrhea	Nausea, phonophobia, photophobia
Autonomic features	Yes	Yes	No
Triggers	Stress, exercise, alcohol	Stress, alcohol, sleep disturbances	Stress, sleep disturbances, menstruation
First line treatment	Indomethacin	Indomethacin	Triptans, NSAIDs
Indomethacin effect	Yes	Yes	No

One study determined that the unremitting subtype of HC is eight times more common than the remitting type [27], and another study [25] reported that the remitting subtype makes up 15% of all HC cases. In addition, Peres [28] estimated that HC is chronic from the beginning in 53% of cases; in 35%, the condition starts as episodic but develops into a chronic form; and in 12% of patients, the disorder starts as episodic and continues to be so.

Pain characteristics in HC are very distinctive and include two components (Fig. 1):

- Mild intensity, continuous unilateral background pain
- Overlapping exacerbations (emerging over the constant basal pain and being highly variable in terms of frequency, intensity, associated symptoms, and duration, which can span from seconds to days).

Continuous background pain is an extremely consistent feature of HC; therefore, it can be looked at as a core component [25]. It can further be described as a dull and pressurising sensation, similar to a tension-type headache (TTH), and usually should not interfere with a sporting activity [29]. The

unpredictable nature of the second component may be the reason for the common misdiagnosis of HC. Pain exacerbations are perceived as throbbing and stabbing sensations, with the intensity of pain being severe or very severe.

The diagnosis of HC can be a struggle, even for experienced neurologists. Rossi et al. [30] in 2009 exposed an issue of misdiagnosis in HC patients. In 25 newly diagnosed HC individuals, 20 (80%) were evaluated by neurologists who did not suspect HC, and seven (28%) were enrolled in headache treatment centres without a successful diagnosis. The aforementioned data leaves a strong suspicion that the prevalence of HC may be higher than previously considered.

Age at onset

The mean age at onset for both PH and HC is around the age of 30 [25, 31]. However, headaches can be diagnosed at any time, having been seen in the first decade of life [7, 29, 32] up to the seventh or eighth decades [33, 34].

Family history

A genetic correlation between PH and HC is unclear due to the small number of patient samples, and has not been confirmed. Only a few cases of familial PH [35] and familial HC [36] have been reported.

Pathophysiology

Although our understanding of TACs remains incomplete, they are thought to share a similar pathogenesis [37]. It is not surprising that a headache problem involves certain regions of the pain neuromatrix, but certain hypothalamic activations revealed in TACs have given credence to the idea that a strong central component has a role in their aetiology [38, 39]. Different TACs have diverse hypothalamic activation patterns that are not entirely consistent. However, it appears certain that either all, or a portion, of the posterior hypothalamic region is activated [40].

Cranial autonomic symptoms (CAS) are the outcome of the trigeminal-autonomic reflex (present in many primary headache disorders [41] resulting in an increase in parasympathetic outflow [42] (Fig. 2**).** Several trigeminal nociceptive events, such as eating very spicy food or suffering local trauma from a blow to the head or from tooth extraction, can activate this pathway. In experimental settings, injecting capsaicin into the hypodermis supplied by the first division of the trigeminal nerve has a comparable impact [43]. The afferent loop emerges from the intracranial durovascular complex and is innervated mostly by the first part of the trigeminal nerve (V1) ophthalmic division, specifically the tentorial nerve [44], the activation of which is probably responsible for pain sensation. Sensory neurons (largely CGRP nerves) originating in the trigeminal ganglion innervate both extracranial and intracranial structures alongside meningeal vessels. Their cell bodies contained within the trigeminal ganglion lead their nociceptive signalling into the trigeminocervical complex (TCC), which consists of the trigeminal nucleus caudalis (TNC) and the C1/C2 dorsal horns [45].

The brainstem, medullary, diencephalic, hypothalamic, and thalamic regions are all connected to the TNC as functional neuroimaging in HC demonstrates PET activity in the dorsal rostral pons, ipsilateral ventrolateral midbrain, and posterior hypothalamus during the pain condition [3]. Additionally, the TCC has another reflex connection to the cell bodies of the premotor parasympathetic neurons of the VIIth cranial nerve (facial nerve), localised in the superior salivatory nucleus (SSN) in the pons [46]. The pathway of these neurons runs through the geniculate ganglion and then through the greater superficial petrosal nerve [47] running in the pterygoid canal, which connects to the sphenopalatine ganglion (SPG) [48] and otic ganglion. Acetylocholine, which activates nicotinic receptors, is the mediator of ganglionic transmission. Postganglionic fibres innervate each cranial vessel and supply parasympathetic autonomic sensory input to the lacrimal glands and nasal mucosa. Stimulation of nicotinic receptors in such ganglia creates postganglionic effects transferred by nerves that use a vasoactive intestinal polypeptide (VIP) as a neurotransmitter [49].

These mechanisms may explain parasympathetic CAS such as conjunctival injection, lacrimation, periorbital oedema, aural fullness, rhinorrhoea, facial flushing, or pallor. Other autonomic symptoms like miosis and ptosis, which are present in a partial form of Horner's syndrome, can be explained by a lack of sympathetic tone during pain attacks. The internal carotid artery's exterior surface is covered in sympathetic fibres. The swelling of the carotid wall caused by a pain attack is thought to compress these sympathetic fibres, causing a temporary loss of sympathetic tone that leads to Horner's syndrome's varied manifestations [50, 51].

Substance P (trigeminal marker peptides), nitric oxide (NO), vasoactive intestinal peptide (parasympathetic marker peptide), and calcitonin gene-related peptide (CGRP) may also play a role in these pain pathways [52]. Activation of the reflex has shown an increase in CGRP and VIP measured in the jugular blood on the same side as the headache attack, supporting the idea of trigeminovascular and cranial parasympathetic activation [53, 54].

Direct connections exist between the hypothalamus and the trigeminal nerve [55, 56], and the hypothalamus is known to modulate the nociceptive and autonomic pathways [57]. Intramuscular indomethacin has been shown to prevent the activation of the hypothalamus and other previously mentioned brain regions specific for HC, clearly connecting their source to the pain related to HC [3]. Moreover, in PH patients, the administration of indomethacin has been shown able to block the previously identified activation in numerous pain processing areas including contralateral posterior hypothalamus, contralateral ventral midbrain, ipsilateral lentiform nucleus, anterior and posterior cingulate cortex, bilateral insulae, bilateral frontal and contralateral temporal cortex,

contralateral postcentral gyrus, precuneus, and cerebellum as shown by H215O-PET imaging, proving their role in the origin of PH symptoms [3].

Secondary hemicrania

Despite the fact that in the majority of cases PH and HC seem to have arisen *de novo*, there is a possibility that both can be caused by, or co-exist with, benign or life-threatening underlying pathologies.

Secondary PH is frequently linked to vascular disease (ischaemic lesion in the basal ganglia and pons, ophthalmic arterio-venous malformation, vascular loop compressing the trigeminal nerve) [7] or tumours (meningiomas [7] or pituitary lesions like macroprolactinoma [58], prolactin-secreting adenoma [59] and microadenoma [60]). The most significant causes of PH and other TACs certainly comprise pituitary gland abnormalities. Patients with unusual symptoms or those who are resistant to indomethacin should have their pituitary hormone levels checked [7]. Moreover, secondary HC has been reported to be associated with 25 different pathologies [25, 61–75]. Trauma to the head and neck region is also a significant factor in developing secondary headaches, making post-traumatic PH and HC common entities [76–78]. There may be some explanations for the association of pituitary lesions with TACs. Tumours on their own may have a mechanical effect; secondly, an increase in interstellar pressure may play a part in the origin of the headaches [79]; and lastly, the headache attacks may be triggered by hormonal changes [80]. Even so, there are no available prospective studies on the true prevalence of causative lesions for TACs.

Nevertheless, it is not always clear how headaches relate to the alleged pathologies. However, the association may be considered more obvious [1] when elimination of the pathology leads to complete resolution of the headache. However, even then, a possibility that the improvement is a result of placebo mechanisms or natural history cannot be ruled out. In recent years, the topic of neuroimaging in patients with a TAC has gained more significance. Since the late 2000s, the number of papers on secondary TACs has dramatically increased [81]. Therefore, to exclude other potential symptom-triggering pathologies such as vertebral and/or carotid artery dissection [82], thrombosis, aneurysm, and infectious diseases, in addition to performing a standard brain MRI scan in a patient with a TAC, clinicians should consider additional dedicated imaging (e.g. MRI or MRA) of the pituitary gland, intranasal and/or intraorbital structures, and even of intracranial and cervical blood vessels [81]. In particular, abnormal neurological examination in cases of vascular and other lesions should direct attention toward neuroimaging techniques, since early identification of cranial or cervical lesions may prevent the disease from worsening and also the development of potentially fatal neurological conditions.

Considering the heterogeneity of all factors mentioned previously (from benign causes and lesions to life-threatening disorders like lung carcinoma or aneurysm), a thorough physical examination, a complete medical history and a head MRI (ideally in addition to an angio-MRI with a clear pituitary view) should always be performed on newly diagnosed PH and HC patients. They are the key to successfully ruling out secondary hemicrania or the co-existence of any comorbidities.

Triggers

In PH, attacks can be unpredictable and spontaneous. Nonetheless, Antonaci and Sjaastad [34] demonstrated that mechanical triggers such as rotation of the head may be a cause in c.10% of patients, and alcohol consumption may be a trigger in c.7%. Putting pressure over the greater occipital nerve or C2 nerve root can also result in triggering an attack, as reported by Cittadini et al. [7]. Common triggers involve stress or relaxation after stress, which were the cause in 26% of patients, exercise (in 23% of patients), and alcohol (in 19% of patients) [7]. Five patients (16%) stated coughing, bending over, a warm environment, cold weather, and strong odours to have been triggers. Sneezing was the cause in 13% of patients, and tiredness and straining in 10% [7]. Other less common triggers were cutaneous stimuli, weather or temperature changes, hot or cold winds, irregular or lack of sleep, menstruation, lifting a heavy weight, skipping a meal, flickering lights, and certain foods such as cream, chocolate, cheese, coffee, and citrus fruits. Compared to other TACs, in CH alcohol and nitroglycerine both play a much bigger role in inducing headache attacks [83], while in SUNCT/SUNA, attacks are more easily triggered by cutaneous stimuli such as touching your face or scalp, eating, coughing, or brushing your teeth [84].

In HC, the background pain is constant, but there are some factors that can influence the occurrence of pain exacerbations. Most of the attacks are spontaneous, but in Cittadini and Goadsby's research of 39 patients with HC [65], c.51% had a pain exacerbation related to stress or relaxation after a stressful event. Alcohol and irregular sleep were factors in c.38% of patients, bright lights in 36%, exercise in 31%, and a warm environment in 28%. Neck movement and skipping a meal were each a cause in 23% of patients. Less common triggers were a strong smell, coughing, sneezing, weather changes, tiredness, tobacco smoke in the environment, menstruation, nitroglycerine, bending over, dehydration, straining, and cold wind/weather plus a few others.

Indomethacin — hemicrania's miracle drug

Indomethacin is a nonsteroidal anti-inflammatory drug (NSAID) with considerable antipyretic, analgesic, and anti-inflammatory activity. The therapeutic and adverse event profiles of indomethacin are brought about by a reduction in prostaglandin production, which is similar to the mechanisms of action of other NSAIDs. NSAIDs block the enzyme cyclooxygenase (COX), which stops arachidonic acid from converting to prostaglandins.

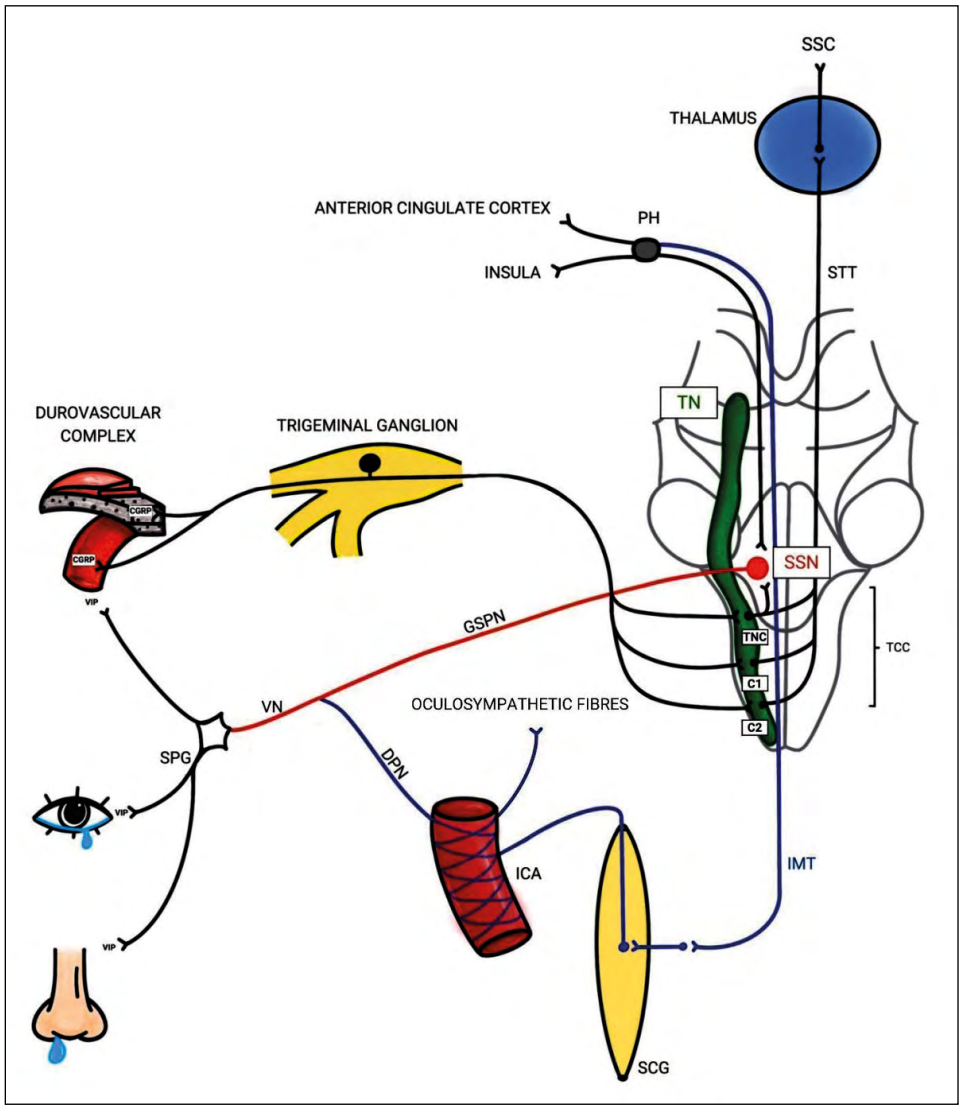

Figure 2. Neuroanatomy of trigeminal autonomic reflex. TN — trigeminal nucleus; TNC — trigeminal nucleus caudalis; TCC — trigeminocervical complex; SSN — superior salivatory nucleus; PH — posterior hypothalamus; STT — spinothalamic tract; IMT — interomediolateral tract; SCG — superior cervical ganglion; ICA — internal carotid artery; GSPN — greater superficial petrosal nerve; DPN — deep petrosal nerve; VN — Vidian nerve; SPG — sphenopalatine ganglion; SSC — somatosensory cortex

Two distinct COX isoforms have been identified: COX-1, which is widely present in the majority of body tissues and is involved in the synthesis of prostaglandins and thromboxane A2, and COX-2, which is produced mostly in response to damage or inflammation [85, 86]. Absolute responsiveness to indomethacin is a diagnostic criterion for hemicrania continua as well as paroxysmal hemicrania [1]. While the exact mechanism of indomethacin's effectiveness in these unilateral headache disorders remains unknown, research suggests that indomethacin penetrates the blood-brain barrier and prevents the activation of the ventrolateral midbrain, dorsal rostral pons, and posterior hypothalamus, i.e. brain regions which are probably essential in understanding the pathophysiology of this syndrome [3, 87]. Moreover, indomethacin stands out among nonsteroidal anti-inflammatory drugs due to its ability to control cerebral blood volume and cerebrospinal fluid pressure [88]. Additionally, Vincent [89] reported that indomethacin, together with other NSAIDs, manages to inhibit the relaxant effect of vasoactive intestinal polypeptide (VIP), substance P, or calcitonin gene-related protein (CGRP) in an isolated porcine ophthalmic artery. Goadsby and Edvinsson [54] noted elevated blood levels of VIP and CGRP during exacerbation periods of hemicrania. Therefore, they may be considered to play a role in the syndrome's origin. Nitric oxide (NO) synthase is found in the sphenopalatine, otic, and facial nerve (VII cranial) parasympathetic outflow ganglia, and the vasodilator reactions of this system involve NO generation [90]. It has been demonstrated that the development of

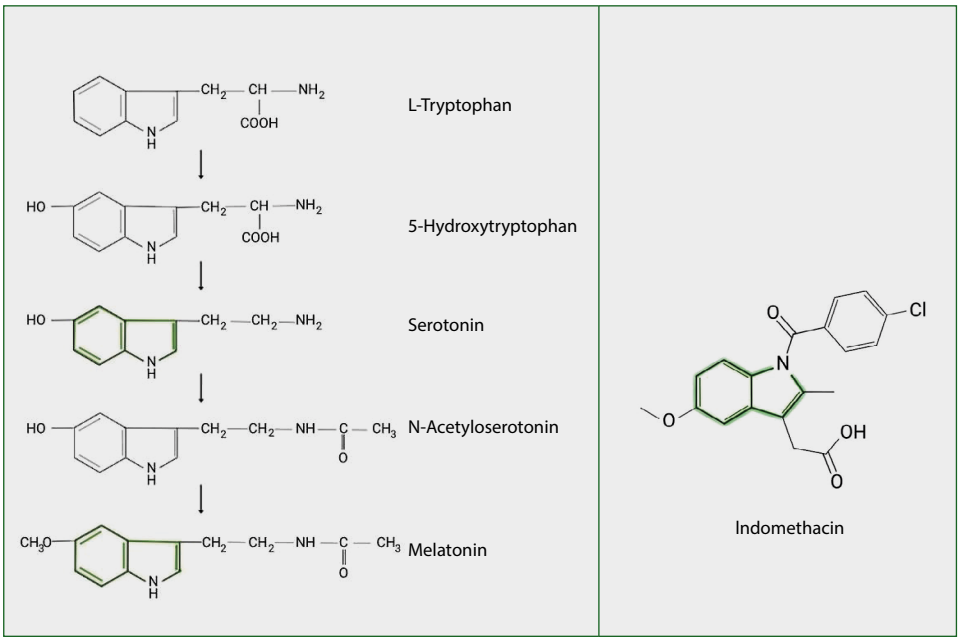

Figure 3. Synthesis pathway of melatonin (**A**) and chemical structure of indomethacin (**B**)

PH involves a nitric oxide-cyclic guanosine monophosphate (NO-cGMP) signalling pathway that activates the calcitonin gene-related peptide (CGRP) in the trigeminal ganglion, both *in vivo* in humans and in animal models [50, 91]. Nitric oxide (NO) generation by inducible nitric oxide synthase and endothelial cells is inhibited by unique mechanisms of indomethacin [92, 93] (Fig. 3), subsequently inhibiting vasodilation and especially within trigeminal activity [91] and SSN [88, 94]. All these facts point to a distinct pathophysiology of the two indomethacin-sensitive headaches, PH and HC.

A considerable drawback of indomethacin therapy is represented by its adverse reactions, which include gastrointestinal (e.g. nausea, dyspepsia, heartburn, ulceration, and bleeding), cardiovascular (e.g. chest pain, arrhythmia, palpitations), hematological (anaemia, agranulocytosis, neutropenia), and numerous side effects from other systems [85]. The risk of gastrolesive effects for indomethacin is significantly higher when compared to other NSAIDs [12]. Especially worth noting are psychiatric side effects such as dizziness, anxiety, fear, agitation, affective lability, depersonalisation, paranoia, and hallucinations [95] as these are often forgotten and not linked to indomethacin. The postulated mechanism of central nervous system response in this case is the structural similarity between indomethacin and serotonin [96] (Fig 3). Interestingly, indomethacin may also induce a different type of headache called indomethacin-induced headache, which not only impedes hemicrania's pharmacological treatment but may also make the diagnosis of hemicrania more challenging [97–99].

The consequence of all of the above is that when receiving indomethacin at standard therapeutic levels, 30–60% of patients report side effects, and 10–20% stop taking it altogether [100, 101]. As of 2024, there are still no established guidelines to follow when treatment with indomethacin fails to provide satisfactory results for patients suffering from HC or PH.

Conclusions

Paroxysmal hemicrania and hemicrania continua are rare but aggravating conditions. As such, neurologists should be particularly conscious of these indomethacin-responsive trigeminal autonomic cephalgias, since delay in diagnosis can leave patients with long-lasting impairment to their quality of life. Early evaluation of patients with hemicranias may be crucial to avoid unnecessary and ineffective medical treatments and interventions. Taking a complete medical history, emphasising associated cranial autonomic symptoms, pain pattern, frequency, and duration of the attacks is essential to establishing a correct diagnosis. Special attention should also be drawn to a thorough physical examination as well as diagnostic imaging of the head and neck region, with bloodwork when suspecting other pathologies that may be associated with secondary hemicrania. Patients meeting the ICHD-III criteria [1] for either PH or HC should start a trial with therapeutic doses of indomethacin. If the patient presents with contraindications to the indomethacin treatment (i.e. gastric ulcers, prior cardiovascular episodes, renal insufficiency, or drug allergy), alternative treatments should be sought. It is necessary to closely and actively monitor an individual during indomethacin treatment focusing on gastrointestinal

side effects. This is best supported by proton pump inhibitor prophylaxis, which significantly lowers the risk of developing peptic ulceration.

Knowledge regarding autonomic symptoms is necessary to understand their diverse nature and allow proper differentiation between TACs and other primary headache disorders. Although symptoms such as conjunctival injection, nasal congestion, rhinorrhea or ptosis are characteristic features of TACs, different common headache entities such as migraine and TTH may also present with other central nervous autonomic symptoms, often leading to disability on a daily basis [1]. Gazerani and Cairns [102] emphasised that the autonomic nervous system may be crucial in every aspect of migraine autonomic symptoms. A few studies have reported that both migraine and TTH show a higher prevalence of autonomic dysfunction symptoms, such as insomnia, dizziness and 'cold and clammy palms and soles' (CCPS) compared to control groups [103, 104]. Rabner et al. [103] reported that in children the TTH group noted a much higher frequency of CCPS than did the migraine group. They hypothesised that the incidence of CCPS is caused by increased sympathetic hyperfunction, which may activate the small nerve fibres connected to sweat glands and cause excessive sweating [105]. Even though TTH is the most common headache disorder, its pathophysiology still remains poorly understood, with studies indicating that both peripheral and central mechanisms may play essential roles [106]. Additionally, studies have shown that TTH sufferers [107], together with migraine sufferers [108], may have lower heart rate variability, indicating a lower flexibility of autonomic nervous system [107, 108].

Considering the small number of large cohort studies on PH and HC patients and highly heterogeneous clinical manifestations of these cephalgias, additional research is required regarding safe and reliable therapy options. Different pharmacological and interventional approaches to replacing indomethacin have been reported mostly in case reports and case series, which has led to a lack of clear guidelines and the proper evaluation of therapy options.

Some studies have reported a treatment benefit with various other NSAIDs, such as acemethacin [109, 110] and piroxicam [111, 112]. Numerous groups of medications like COX-2 selective inhibitors [113], anticonvulsants [114, 115], and antidepressants [112], as well as non-pharmacological treatment approaches including nerve stimulators [116, 117] and peripheral nerve blocks [118], have also proved to be useful. Interestingly, previous studies reported that melatonin, which shares a similar chemical structure to indomethacin (Fig. 3), may be effective for HC [76, 119], and recently Cheung et al. [120] demonstrated that it shows efficacy in the treatment of PH.

Although melatonin does not have the same responsiveness as indomethacin, it offers a considerable alternative therapy option for a significant group of patients, and with a relatively good safety profile [120]. Trigemino-vascular system activation with the release of CGRP leads to pain along with associated symptoms in certain primary headaches, including migraine and TACs. CGRP monoclonal antibodies have already been reported to be beneficial in cases of episodic cluster headache [121] and HC [122]. In migraine, drugs targeting CGRP or its receptor have become an effective treatment option in about half of patients [123], yet despite their efficacy a significant amount of migraine patients are still classified as 'non-responders' [124].

Because **human models provocation studies** have already provided crucial understanding into the pathomechanisms of migraines, this leads us to a conclusion that there is still more to discover in migraine and TACs, as the aforementioned headaches share many overlapping features. Thus, the development in preventative treatment of other potential pathogenetic targets, not only CGRP-based, is necessary (i.e. targeting VIP, amylin, adrenomodullin, PDE3 and others) [124].

Further multi-centre studies need to be performed in order to obtain a clearer view of these rare primary headaches.

Article information

Acknowledgements: *We would like to thank Tomasz Iskra, MD who helped with conceptualisation of the study. We would also like to express our gratitude to Professor Peter J. Goadsby, MD, PhD who helped us with elucidating the pathomechanism of paroxysmal hemicrania and hemicrania continua and emphasised the importance of increasing awareness about these rare cephalgias.*

Authors' contributions: *AO, KS: concept and design, acquisition of data, analysis and interpretation of data, drafting and revising article; KB: graphic design, drafting and revising article; MO: analysis and interpretation of data, drafting and revising article; TK, DT: drafting and revising article, supervising study*

Funding: *None.*

Conflicts of interest: *None.*

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