

Hemicrania Continua

Sanjay Prakash, Bansi Adroja¹

Departments of Neurology and ¹Medicine, Smt. B. K. Shah Medical Institute and Research Centre, Sumandeep Vidyapeeth University, Vadodara, Gujarat, India

Abstract

Hemicrania continua (HC) is an indomethacin responsive primary chronic headache disorder which is currently classified as a subtype of trigeminal autonomic cephalalgias (TACs). It is not very uncommon. There are >1000 cases of HC in the literature, and it constitutes 1.7% of total headache in the clinic settings. Misdiagnosis for HC is very common at all clinical settings. A diagnosis of HC is missed even by neurologists and headache specialists. It is characterized by a continuous strictly unilateral headache with superimposed exacerbations. Just like other TACs, exacerbations are associated with cranial autonomic symptoms and restlessness. A large number of patients may have migrainous features (nausea, vomiting, photophobia, and phonophobia) during exacerbations phase. The “key” feature of HC is persistent featureless background headaches. However, patients and physicians may focus only on the exacerbation part. As durations, frequency and associated symptoms of exacerbations are highly variables; it may mimic a large number of primary and secondary headache disorders. Migraine and cluster headache are two most common misdiagnosed conditions. Another specific feature of HC is remarkable repose to indomethacin. A “complete” response to indomethacin is as “sine qua non” for HC. However, a few other medications may also be effective in a subset of HC patients. Various surgical procedures have been tried with mixed results in patients who were intolerant to indomethacin or other drugs.

Keywords: Hemicrania continua, indomethacin-responsive headache, indomethacin, trigeminal autonomic cephalalgias

INTRODUCTION

Hemicrania continua (HC) is an indomethacin responsive primary headache disorder which is characterized by a continuous and strictly unilateral headache, with cranial autonomic symptoms and agitation during the episodes of pain exacerbation.^[1] It was first described by Medina and Diamond in 1981.^[2] The term “HC” was coined by Sjaastad and Spierings in 1984.^[3] It was first incorporated into the International Headache Society classification system in 2004 (second edition)^[4] under the heading of “other primary headaches.” However, in the third edition of the International Classification of Headache Disorder (ICHD-3 β , 2013), it has been put under the heading of trigeminal autonomic cephalalgias (TACs) with cluster headache (CH), paroxysmal hemicranias (PH), Short-lasting, unilateral, neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA).^[1]

EPIDEMIOLOGY

A response to indomethacin is an essential feature in the diagnostic criteria of HC. This makes it difficult to estimate

the true prevalence of (definite) HC in any epidemiological study. The Vaga study noted 18 patients with probable HC in 1,838 parishioners (1.0%).^[5] Initially, it was considered as a rare disease. There were only 100 cases of HC in the literature in the first 17 years of its discovery (1984–2001).^[7] However, various large case series have been published in the recent past. Several authors have suggested that HC is not rare and it is probably underdiagnosed and underreported condition. In a recent review, Prakash and Patel noted >1000 cases of HC in the literature.^[7] HC constitutes 1.3%–2.3% (mean-1.7%) of total headache patients in the clinic settings.^[7] In a pooled analysis of the strictly unilateral headaches, HC was the fourth most common etiology for the side-locked headaches (after CH, side-locked migraine and cervicogenic headache).^[8] After CH, it is probably the second most common TACs.^[8]

HC typically starts in the fourth or fifth decade of life.^[7] More than 80% patients in Marmura *et al.*^[9] series (36 out of

Address for correspondence: Dr. Sanjay Prakash,
Department of Neurology, SMT. B. K. Shah Medical Institute and Research
Centre, Piparia, Vadodara - 391 760, Gujarat, India.
E-mail: drprakashs@yahoo.co.in

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43 patients) were more than 30-year-old. About 70% patients were more than 40-year-old at the onset of HC in Cortijo *et al.*^[10] series of 36 patients. The pooled mean age of onset was 40 years in Prakash and Patel review.^[7] However, patients as young as 5 years^[6] and as old as 76 years^[11] have been reported.

HC is classically considered a disease with a female preponderance. The female: male ratio was 5:1 in the first review on HC.^[12] This ratio has reduced over the years. Now, this female: male ratio is closer to 1.8:1.^[7] There is just one case report of familial HC,^[13] and so far, no genetic predisposition has been established.

CLINICAL FEATURES

HC is a subtype of TACs. Therefore, its clinical features overlap with other TACs. TACs are classically characterized by strictly unilateral pain in the trigeminal distribution and cranial autonomic symptoms (CAS) in the same areas.

Side and sites of pain

HC is a unilateral headache. Most of the patients have side-locked headache. However, a few patients may have side-alternating attacks. There are a total nine cases of side-shifting HC in the literature.^[14-20] A few cases of bilateral HC have also been reported in the literature.^[21-24] However, as side-shifting HC or bilateral HC is very rare, a diagnosis of HC should be considered only with strictly unilateral headache. Review of the literature suggested a slight preponderance for the right side involvement.^[7,12]

Just like other TACs, the pain in HC is predominantly located in the first division of the trigeminal nerve (orbital, supraorbital, or temporal).^[1] However, a substantial number of patients may have pain in the other areas, including extratrigeminal areas. Pain may spread to involve other division of trigeminal nerves and rarely to extra trigeminal nerves. It may radiate to involve cheek, jaw, ear, nose, periauricular region, neck, occiput, shoulder, arm, and oral cavity (including teeth and throat).^[7,20] In a few patients, the pain may be predominantly located in V2/V3 distribution of the trigeminal nerve (teeth, oral cavity, jaw, ear, temporomandibular joint [TMJ], and ear).^[25-28]

Pain characteristics and pattern

There are two components of HC: (i) continuous background unilateral headache and (ii) superimposed severe exacerbations. Continuous background headache is the central feature of HC. The background pain is typically dull and mild-to-moderate in intensity. The intensity of background pain varies from 3.3 to 5.2 in visual analog scale (VAS) (range 0–10).^[6,10,29] The background pain does not hamper physical activity.^[6]

Majority of the patients report superimposed exacerbations over the background pain. The superimposed exacerbations are extremely variables in the terms of character, intensity, duration, and frequency. The character of pain during exacerbation is typically throbbing or stabbing (jabs and jolts). The intensity of exacerbations is usually severe to very severe. The pooled mean VAS of exacerbations pain was 9.0 in Prakash

and Patel analyses.^[7] Almost all patients have some form of physical disability with the exacerbation.^[6] Just like CH and PH, about 50% patients in Cittadini series reported that their pain was the most painful condition they had ever experienced, comparing it to labor pain, a broken bone, toothache, and burned hands.^[20] Patients with HC may have suicidal thoughts during severe exacerbations.^[12]

CH is widely recognized as a most painful condition. However, clinical characteristics of HC during exacerbations suggest that it may be as severe as of CH attacks in a subset of HC patients.

The frequency and duration are well defined in the diagnostic criteria of CH, PH, and SUNCT/SUNA.^[1] However, the pattern of exacerbations of HC is highly variable in the terms of frequency and duration. The duration of exacerbations may vary from a few seconds to 2 weeks.^[7] Whereas the mean length of exacerbations was 32 min in Cortijo *et al.*^[10] observations, it was 31 h in Benítez-Rivero *et al.* study.^[29] The duration of exacerbations may vary from attack per attack in the same patient. The frequency of the exacerbations is also highly variable. It may vary from >20 attacks in a day to one attack in 4 months duration.^[7,20,30,31] About 49%–60% patients report at least one attack daily.^[20,31] About 17% patients had >5 attacks in a day in Prakash and Golwala observations.^[31]

More than 50% may have nocturnal exacerbations.^[20] Two patients in Cittadini *et al.* series have fixed timing for the exacerbations.^[20] Otherwise, a circadian periodicity for exacerbations (like CH) is largely unknown. There are a few cases in the literature in which worsening of exacerbations was noted in particular months (a circannual periodicity).^[20,32]

Cranial autonomic symptoms

Ipsilateral cranial autonomic features are one of the cardinal features of all five TACs. ICHD-3 β describes 10 different types of cranial autonomic features in relation to TACs. These CAS are related to eye/eye lid (conjunctival injection, lacrimation, ptosis, meiosis, and eyelid edema), nose (nasal congestion and rhinorrhea), ear (sensation of fullness in the ear), and face/forehead (sweating and flushing).^[1]

The mean prevalence of CAS during exacerbations is about 74%.^[7] This prevalence is slightly lower than the prevalence of CAS observed in CH and PH patients. Tearing and conjunctival injection are two most common cranial autonomic feature.^[6,20,31] Less frequent autonomic features such as ptosis, miosis, eyelid edema, and facial sweating may also occur with exacerbations. A sense of aural fullness has been recently incorporated as one of the autonomic features in ICHD-3 β criteria. It was reported in 19% cases in Cittadini *et al.* case series.^[20]

A feeling of foreign body sensation in the eye (or sand in eye sensation or itching eye) is a peculiar feature during exacerbation of HC. It may be noted in more than one-third patients with HC.^[10,20,31] It is considered as a part of CAS. It is not reported in other TACs or any other primary headache disorder.

Intensity and components of CAS are usually meager in HC as compared to other TACs.^[9,31] The patients may not be aware of its presence. Therefore, an objective assessment of the patients for the presence CAS during exacerbations should be done in doubtful cases of HC.^[31]

Restlessness or agitation

Just like CH and other TACs, HC patients may have restlessness during exacerbations. It is noted in about 50% of HC patients.^[7,20,31] They may show pacing or jogging like activity. The patients may rock from side to side, hit their heads, or even hit the head against the wall. They may press on the eye or temples with the hand or a cloth or with an ice pack. Patients find difficulty in sitting or lying down comfortably during exacerbations.

Restlessness or agitation has recently been included in HC criteria.^[1] It provides an alternative to cranial autonomic features in the diagnostic criteria.

Migrainous features

Migrainous features (nausea, vomiting, photophobia, and phonophobia) are quite common in patients with HC during exacerbations. The mean prevalence of at least one migrainous feature was 60% in Prakash and Patel observation.^[7] About 56% fulfilled the migraine criteria during exacerbation phase.^[7] However, auras are not that common. There are just a few case reports of visual auras in HC.^[33,34] One case with olfactory aura has also been reported in the literature.^[35]

PATHOPHYSIOLOGY

As there are considerable overlaps among the TACs, it has been hypothesized that all TACs have a common pathophysiology.^[36] However, the pathophysiological studies on HC are relatively sparse. A PET study in HC patients has demonstrated the activation of the contralateral posterior hypothalamus, ipsilateral dorsal rostral pons, ipsilateral ventrolateral midbrain, and bilateral pontomedullary junction.^[37]

A number of hypothalamic connections have been suggested for the clinical features of TACs, including HC. The orexinergic system is probably the main circuit to influence the hypothalamus in patients with HC and other TACs.^[38] Somatostatinergic, serotonergic, and opioidergic circuits may also modulate hypothalamus.

It has been suggested that dysfunction in the hypothalamus may result in destabilization of various inputs on the trigeminovascular system, leading to various clinical features of HC and other TACs. The cranial autonomic features of TACs are probably because of the central disinhibition of the trigeminal autonomic reflex by the hypothalamus, possibly through direct hypothalamic-trigeminal connections.^[39]

DIAGNOSIS

The diagnosis of HC is made according to ICHD-3 β criteria [Table 1] for HC and exclusion of a secondary cause.^[1]

Table 1: Diagnostic criteria of different subtypes of hemicrania continua (International Classification of Headache Disorder-3 β)

3.4. HC

- A. Unilateral headache fulfilling criteria B-D
- B. Present for >3 months, with exacerbations of moderate or greater intensity
- C. Either or both of the following
 - 1. At least one of the following symptoms or signs, ipsilateral to the headache
 - a) Conjunctival injection and/or lacrimation
 - b) Nasal congestion and/or rhinorrhea
 - c) Eyelid edema
 - d) Forehead and facial sweating
 - e) Forehead and facial flushing
 - f) Sensation of fullness in the ear
 - g) Miosis and/or ptosis
 - 2. A sense of restlessness or agitation, or aggravation of the pain by movement
- D. Responds absolutely to therapeutic doses of indomethacin
- E. Not better accounted for by another ICHD-3 diagnosis

3.4.1. HC, remitting subtype

- A. Headache fulfilling criteria for 3.4 HC and criterion B below
- B. Headache is not daily or continuous but interrupted by remission periods of \geq day without treatment

3.4.1. HC, unremitting subtype

- A. Headache fulfilling criteria for 3.4 HC and criterion B below
- B. Headache is daily and continuous, for at least 1 year without remission periods of \geq day

ICHD = International Classification of Headache Disorder,
HC = Hemicrania continua

Exclusion of secondary hemicrania continua (by clinical features and investigations)

Prakash and Patel noted 66 cases of secondary HC in a recent review.^[7] There are a total 25 different pathologies related to secondary HC in the literature.^[7] A few secondary HC may be temporally related to certain events (head injury, intracranial surgeries, other surgeries, and postpartum state).^[40] A large number of secondary HC (up to 55%) are related to such events.^[7] Posttraumatic headache is the most common secondary HC.^[7,40] It constitutes 39% of total cases of secondary HC. Postcraniotomy HC is the second most common secondary HC.^[7] Event-related secondary HC is mostly benign.^[40] Therefore, a history inquiring about such events preceding the onset of HC is very important.

Intracranial space occupying lesion, head and neck vessel pathology, and pathologies related to extracranial surrounding tissues (sinus, nose, eye, neck, oral cavity, etc.) may mimic HC.^[40] Prolactinoma is the most common intracranial structural pathology associated with HC.^[7] Internal carotid artery (ICA) dissection is the most common vascular pathology.^[7] Extracranial pathologies such as sinus pathologies, dental lesions, TMJ pathologies, neck pathologies, and eye lesions may cause continuous pain in the trigeminal or surrounding distribution.^[7] A pathology in the thorax may cause referred pain in head and face and may mimic HC. There are several

cases of facial pain because of carcinoma lung. A few of them mimic HC.^[41,42,43]

Hence, a large number of intracranial and extracranial pathologies may simulate HC. Therefore, thorough physical and neurological examinations are essential in each patient with a putative diagnosis of HC. However, several secondary HC mimic primary HC, and there may be normal physical or neurological examinations. Therefore, MRI study has been recommended in all the patients presenting as HC-like headaches.^[40] MRI study should include the screening of pituitary, orbit, and trigeminal pathway. Headache and neck vessel pathologies (especially ICA dissection and aneurysm) require urgent therapies. Features suggesting vessels pathology include a short duration of illness, frequent and short-lived exacerbations, recent neck or head trauma, neck tenderness, and the presence of miosis. Magnetic resonance angiogram or digital subtraction angiography should be recommended for such patients. Carcinoma lung is the most dangerous condition associated with HC-like headaches. The red flag for carcinoma lung includes older age, smoking habit, short duration of complaint, constitutional and respiratory symptoms and signs, and raised erythrocyte sedimentation rate.^[40] Such patients should be subjected for computed tomography thorax, as carcinoma lung may be missed with routine chest X-ray.^[40,44]

A diagnosis of primary hemicrania continua

Once you rule out secondary HC, a diagnosis of primary HC can be made according to ICHD-3 β criteria for HC [Table 1]. The criteria seem to be easy. However, a misdiagnosis is very common for HC. A misdiagnosis of HC is perhaps maximum among all primary headache disorders. The pooled mean delay of diagnosis for HC is 8 ± 7.2 years.^[7] A case of HC is missed by even neurologists and headache experts. None of the neurologists and headache experts made the correct diagnosis of HC in Rossi *et al.* series of 25 patients.^[45] 20 neurologists, and seven headache experts had seen these case before.

There are classically three features in the diagnostic criteria (i) strictly unilateral continuous pain for 3 months, (ii) presence of either ipsilateral cranial autonomic or agitation during exacerbations, (iii) a complete response to indomethacin. A “complete” response to indomethacin is as “sine qua non” for HC. Typically, oral indomethacin is given to find out the response. However, injectable indomethacin 50–100 mg IM (“INDOTEST”) has also been advocated as a diagnostic test for HC.^[46] A complete response is usually noted within 2 h of injection. A few authors suggested a trial of indomethacin in all patients with chronic unilateral headache to find out the cases of HC.^[6,45]

Another important feature of HC is “immediate reappearance of headache (within 6–24 h) on skipping indomethacin.”^[31] Antonaci and sjaastad, and a few other authors advocated that its diagnostic value (i.e., reappearance of headache after skipping of indomethacin) is stronger than INDOTEST itself.^[47,48] A subset of HC patients may show a complete or excellent response to drugs other than indomethacin. A few

patients may receive such effective drugs even without getting a correct diagnosis of HC.^[48] The skipping or withdrawal of even such drugs may lead to immediate reappearance of headaches.^[31] Therefore, if patients with side-locked headaches had a history of complete or excellent response to some drugs as long as they had continued those drugs, a possibility of HC exists, as no other headache reappears so fast on withdrawal of the effective drugs.

Classification and variants of hemicrania continua

ICHD-3 β identifies two forms of HC (i) HC, unremitting subtype and (ii) HC, remitting subtype. In remitting HC, the pain is not continuous but is interrupted by remission periods of at least 1 day. Remitting form HC constitutes 15% of total HC.^[1,7] Unremitting HC is characterized by the continuous pain for at least 1 year, without any symptom-free period. Unremitting HC can arise *de novo* (i.e., chronic from the onset) may or evolve from HC, remitting subtype. About 50%–60% HC have the unremitting subtype from onset. Other 25%–35% HC evolved into unremitting subtype from the remitting form.^[7]

DIFFERENTIAL DIAGNOSIS

Recognizing the continuous pain in any side-locked headache is the essential step for making a diagnosis of HC. However, the patients may be more worried for the superimposed exacerbations. The patients may not utter anything about background headaches, and even physician may miss to ask about the background headaches. The frequency and duration of the headache attacks are the important clinical clues for diagnosing various primary headaches, neuralgias, and even secondary headaches. Therefore, if you ignore the continuous background pain and put emphasis only on the exacerbations, the (mis) diagnosis will depend on the frequency, duration, and other characteristics associated with exacerbations.^[7] As the duration of the exacerbations in HC vary from a few seconds to a few days, the diagnosis may include side-locked migraine, other TACs (CH, PH, and SUNCT/SUNA), neuralgias (especially supraorbital and trigeminal neuralgia), etc. Rarely, superimposed exacerbations are not severe or physicians concentrate only on the continuous pain (ignoring exacerbations), the differential diagnosis could be new daily persistent headache (NDPH), atypical facial pain, CTTH, and various local pathologies.^[7]

Hemicrania continua versus side-locked migraine

Migraine is the most common misdiagnosed condition for HC.^[6,45] Up to 71% patients of HC may fulfil the diagnostic criteria of migraine during exacerbations. The treatment modalities and the natural course of migraine and HC are entirely different. Therefore, it is a challenge to differentiate HC with migraine. Table 2 highlights the differentiating features between two. Features that distinguish HC from side-locked migraine include older age of onset, continuous daily pain, ipsilateral cranial autonomic features, and agitation during attacks. The restlessness or agitation during painful

Table 2: Differentiating features between a side-locked migraine and hemicrania continua

Parameters	HC	Side-locked migraine
Age at onset	Fourth-fifth decade ^[7]	Second-third decade
Pain-free period	No	Usually present
Duration of attacks/exacerbations	Highly variables. Several attacks will be of <4 h	Attacks of <4 h-uncommon
Site of pain	Predominantly anteriorly	Variables
Cranial autonomic features	More common, ipsilateral, itchy eye	Less common, bilateral, no itchy eye
Restlessness or agitation	Present. Patient cannot lie comfortably	Absent. Patient preferable to lie down
Response to previously used drugs (other than indomethacin)	Usually no or partly response If complete response: Immediate reappearance of headache on skipping the effective drugs ^[63]	Several drugs may be effective. Reappearance of headache on skipping the effective drugs is not immediate
Response to indomethacin	Immediate and dramatic	Variables

HC = Hemicrania continua

attacks may be the best clinical clue to differentiate HC from migraine, as migraineurs are quiet and avoid any movement.

Response to previously used drugs (other than indomethacin) may also give some hints. Typically, HC does not respond to drugs other than indomethacin. Therefore, if a side-locked migraine has not shown any response to any antimigraine and other drugs, think about an alternative diagnosis (HC). However, a subset of patients with HC (without getting a correct diagnosis) may show response to various other drugs. However, there will be immediate relapse of symptoms on skipping the drugs. Therefore, if patients with side-locked migraine claim that they get response as long as they continue drugs and symptoms reappear on skipping the drugs, think about a possibility of HC.

Hemicrania continua versus other trigeminal autonomic cephalalgias

There are marked similarities among all TACs. They all have maximum pain in the trigeminal distribution (V1), ipsilateral cranial autonomic features, and agitation. The fundamental feature of HC and other TACs is strictly unilateral (maybe side-shifting, but always unilateral). TACs constitutes more than one-third cases (35%) of side-locked headaches in clinic settings.^[8] Therefore, a strictly unilateral headache always raises a possibility of TACs. A mnemonic-3As for side-locked headache-have been suggested to identify TACs.^[8] 3As includes (i) Anteriorly located (orbital, frontal, and temporal) pain, (ii) autonomic features in the same area (ipsilateral) during attacks/exacerbations, and (iii) Agitation or restlessness during attacks/exacerbations.^[8]

If all three components of 3As are present, it is one of the forms of TACs. Even with the presence of 2As in a side-locked headache, a possibility of one of the TACs is very high. One TAC can be differentiated with other TACs on the basis of the pattern of the headaches (frequency and duration). Whereas CH, PH, and SUNCT/SUNA are episodic disorders, HC patients have a continuous headache with exacerbations. The attack duration and frequency are quite predictable in SUNCT/SUNA, PH, and CH. The duration of attacks in SUNCT, PH, and CH is <10 min, 2–30 min, and

15–180 min, respectively.^[1] However, the attack duration in HC (exacerbations) is highly variables, and many attacks are very prolonged (more than the upper limit of CH i.e., >3 h).^[7]

A few patients with chronic CH and chronic PH may have interparoxysmal pain and may simulate HC.^[49] However, the interparoxysmal pain is usually not felt throughout the day and it is usually mild in the intensity.^[49] Moreover, a variable pattern of severe attacks (especially of >3 h) will suggest HC. Always ask about the presence of continuous background pain in patients with CH in whom significant proportions of attacks are >3 h.

Hemicrania continua versus NDPH

HC and NDPH are, by definition, continuous daily headache. Up to 18% patients with NDPH may have strictly unilateral headache.^[8] Mild autonomic features may also be noted in NDPH. Side-locked NDPH with migrainous features may mimic HC. If patients remember the exact onset of their headaches (1st day of continuous headache), a possibility of NDPH is likely.^[1] In doubtful cases, a trial of indomethacin can be given to find out HC.

Hemicrania continua associated with other primary headache disorders

A large number of other primary headaches have been reported in patients with HC. There can be three different types of association. (i) Both headache disorder existing simultaneously: CH is the most common associated headache with HC.^[50,51] Other reported headaches are migraine,^[52] TTH,^[53] trochlear headache,^[54] sexual headache,^[55] and trigeminal neuralgia,^[56] (ii) other primary headache orders evolving into HC: there are case reports where CH,^[57] PH,^[58] SUNCT,^[59] migraine,^[60] and Raeder syndrome^[61] have evolved into HC, (iii) HC evolving into other primary headaches: there are two such cases where HC have transformed into other headaches (PH and LASH syndrome).^[62]

The diagnosis of such association is very important for therapeutic purpose. Patients may require two different class of drugs at a same time (if both headaches exist simultaneously)

or there may be need to change the previously used drug (if one headache have transformed into other).

MANAGEMENT

Indomethacin

Indomethacin is usually started at the dose of 25 mg three times a day. However, only 10%–18% patients showed complete response on this dose (≤ 75 mg).^[20,31] Therefore, the drug is slowly titrated (25 mg tid every 3–5 days) up to 100 mg tid or until the patient gets complete relief.^[31] About 40%–50% HC patients show complete response at or below to 150 mg/day. >40% patients may require ≥ 225 mg indomethacin per day.^[20,31]

A response to indomethacin usually starts immediately. However, the patients may take time to show a complete response (depending on the duration of titration of effective doses). Patients with longer duration may have delayed response.^[63] In Prakash and Golwala observation, 20% patients took >4 weeks to show complete response to indomethacin.^[31]

A gradual reduction of the dose is recommended every 3–6 months to find out the lowest effective dose in particular

patients, as about 60% HC patients may need a lower dose with the passage of time.^[64] In this way, we can also find out the remitting form of HC. Dose reduction is usually done by 25 mg every 3 days, until either the pain resurfaces or the patient gets completely off indomethacin.

Other medications for hemicrania continua

About 20%–75% may develop indomethacin-related side effects and may require alternative drugs.^[65] Various drugs have been found effective in case reports and open-label studies. It includes COX-2 inhibitors (celecoxib and rofecoxib.), topiramate, melatonin, gabapentin, ibuprofen, piroxicam, naproxen, aspirin, acemethacin verapamil, and steroids.^[65] However, the response of these all drugs are not predictable and may not show any response in a particular patient. You can find the best effective drug only by trial and error method.

Surgical interventions for hemicrania continua

Surgical interventions can be tried in patients who are intolerant to indomethacin. Table 3 summarizes the various surgical interventions tried in HC patients.

Table 3: Different surgical interventions in hemicrania continua patients

Type of intervention/first author	Number of patients	Effects/remarks
Peripheral nerve block		
Antonaci <i>et al.</i> ^[66]	7	Partial response to SON in 4 patients
Afridi <i>et al.</i> ^[67]	7	Complete response in one patient, partial in 5 patients
Cittadini and Goadsby ^[20]	23	One-third responded to greater occipital nerve injection
Guerrero <i>et al.</i> ^[68]	9	Five patients - complete response, rest had partial response. Effects for 2-10 months. More effective if local tenderness is considered before the block
Ganglion block (sphenopalatine)		
Androulakis <i>et al.</i> ^[69]	1	Repetitive block. Initially - twice/week. Maintenance treatment every 4-5 weeks. Significant improvement (not complete)
Radiofrequency ablation		
Weyker <i>et al.</i> ^[70]	3	Radiofrequency ablation of the SON. Complete relief of headache for 7-12 months [*]
Beams <i>et al.</i> ^[71]	4	Ablation of the C2 ventral ramus, C2 dorsal root ganglion, or sphenopalatine ganglion. Complete response for 1-2.5 years
Occipital nerve stimulation		
Schwedt <i>et al.</i> ^[72]	1	Significant improvement in pain (although not complete). Episodes of cranial autonomic manifestation occurred without headache
Schwedt <i>et al.</i> ^[73]	2	Marked improvement. Developed complications that include stimulator lead migration and infection
Burns <i>et al.</i> ^[74]	6	Used newer device (Bion). Four patients had 80%-95% improvement. One patient - 30% improvement
Miller <i>et al.</i> ^[75]	16	>50% reduction in monthly moderate to severe headache days in 50% patients
Vagus nerve stimulation		
Nesbitt <i>et al.</i> ^[76]	2	Good response (not complete). Abort exacerbations of HC within 15 min
Eren <i>et al.</i> ^[77]	1	Immediate reduction of intensity of exacerbations (not complete). Reduced background pain intensity. No effect on frequency of exacerbations
Botulinum toxin		
Garza and Cutrer ^[78]	1	Marked improvement (not complete). Episodes of cranial autonomic features occurred even in the absence of pain
Khalil and Ahmed ^[79]	1	Complete response for 10-12 weeks
Miller <i>et al.</i> ^[80]	9	Five subjects had a response of $\geq 50\%$ reduction in moderate to severe headache days. Effects for 12 weeks

HC = Hemicrania continua, SON = Supraorbital nerve

Controversial issues

The nosological status of HC is still debatable. Currently, it has been put into Group-3 under TACs. However, a few authors believe that it should not be the part of TACs.^[7]

The diagnostic criteria for HC have been revised several times over two decades. However, no large case study has been reported following present ICHD-3 β (2013) criteria. The most debatable part in the criteria is about “complete response to indomethacin.” ICHD-3 β exclude the existence of indomethacin resistant HC. However, there are several large case series of typical HC-phenotype headache, but without showing any response to indomethacin.^[31,81] The literature is silent on how to classify/diagnose patients with HC-phenotype who do not show response to indomethacin. The literature acknowledges that several drugs (other than indomethacin) may produce complete response in a subset of patients with HC.^[65] However, such patients may not receive the correct diagnosis of HC in the event that a response of other medication occurs before a trial of indomethacin.

The presence of CAS was a must before the current ICHD-3 β criteria.^[4] Now, it is not a must if exacerbations are associated with agitation. We believe that some option/alternative should also be given for the indomethacin response to HC in the criteria. There is a need of more accommodating type alternative criteria in the appendix section of ICHD-3 β , as clinical features, therapeutic measures, and many other aspects are still to be determined in HC.^[7,31]

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Conflicts of interest

There are no conflicts of interest.

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