

# Hemicrania continua: clinical review, diagnosis and management

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**Abstract:** Hemicrania continua (HC) is an indomethacin-responsive primary headache disorder which is currently classified under the heading of trigeminal autonomic cephalalgias (TACs). It is a highly misdiagnosed and underreported primary headache. The pooled mean delay of diagnosis of HC is  $8.0 \pm 7.2$  years. It is not rare. We noted more than 1000 cases in the literature. It represents 1.7% of total headache patients attending headache or neurology clinic. Just like other TACs, it is characterized by strictly unilateral pain in the trigeminal distribution, cranial autonomic features in the same area and agitation during exacerbations/attacks. It is different from other TACs in one aspect. While all other TACs are episodic, HC patients have continuous headaches with superimposed severe exacerbations. The central feature of HC is continuous background headache. However, the patients may be worried only for superimposed exacerbations. Focusing only on exacerbations and ignoring continuous background headache are the most important factors for the misdiagnosis of HC. A large number of patients may have migrainous features during exacerbation phase. Up to 70% patients may fulfill the diagnostic criteria for migraine during exacerbations. Besides migraine, its exacerbations can mimic a large number of other primary and secondary headaches. The other specific feature of HC is a remarkable response to indomethacin. However, a large number of patients develop side effects because of the long-term use of indomethacin. A few other medications may also be effective in a subset of patients with HC. Various surgical interventions have been suggested for patients who are intolerant to indomethacin. Several aspects of HC are still not defined. There is a great heterogeneity in types of patients or articles on the HC in the literature. Diagnostic criteria have been modified several times over the years. The current diagnostic criteria are too restrictive in some aspects. We suggest a more accommodating type of criteria for the appendix of International Classification of Headache Disorder (ICHD).

**Keywords:** side-locked headache, indomethacin, indomethacin-responsive headache, trigeminal autonomic cephalalgias

## Introduction

Hemicrania continua (HC) is an indomethacin-responsive primary headache disorder which is currently classified under the heading of trigeminal autonomic cephalalgias (TACs), along with cluster headache (CH), paroxysmal hemicrania (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).<sup>1</sup>

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## History of HC

Medina and Diamond<sup>2</sup> were probably the first authors to describe the clinical phenotype of HC. They reported 54 patients under the heading of cluster headache variants. A total of 28 patients had background vascular headache, and 15 patients (out of 28) had a complete or excellent response to indomethacin. Therefore, it is believed that a subset of patients of that series actually had HC. The term “Hemicrania continua” was later coined by Sjaastad and Spierings.<sup>3</sup>

Although more than 35 years have passed since the first description of HC, it is still an enigma in terms of clinical features, natural course, diagnostic criteria and therapeutic measures. The diagnostic criteria for HC have been repeatedly modified and revised over 2 decades. Even the nosological status of HC is debatable. The International Headache Society (IHS) Classification Committee (second edition, 2004) put it under the heading of “other primary headaches”.<sup>4</sup> However, International Classification of Headache Disorder, third edition (ICHD-3 $\beta$ , 2013), has considered it as a family member of TACs.<sup>1</sup>

## Literature review

Various aspects of HC have not yet been completely elucidated. Repeated modification of diagnostic criteria over the years is the evidence of it. There is a great heterogeneity in types of patients or articles on the HC in the literature. The first review of HC included only 18 patients.<sup>5</sup> The last review was published a long back in 2001, which included a total of 93 patients.<sup>6</sup> Several large case series have been published in the recent past. Therefore, we planned to review all cases reported in the literature.

We searched Medline/PubMed with “Hemicrania continua” as a keyword. All the case reports and case series of HC were reviewed. We carefully reviewed the reference lists of all the articles found on HC to look for additional cases. All articles that mentioned a case of HC were included for the review.

We noted 171 articles, in which at least one case of HC was described or mentioned. These articles include 1002 cases with a diagnosis of HC ([Supplementary materials](#)). More than 900 cases of HC are reported in the literature since the last review (2001).<sup>6</sup> However, a possibility of case duplication in the articles is also there. We included all the cases where the authors had claimed a possibility of HC. A large number of cases of HC have been presented in various conferences. We included only two of them.<sup>7,8</sup> Therefore, the total number of cases of HC in the literature may be even more than that. We did not verify it for the diagnostic accuracy according to the current ICHD-3 $\beta$  criteria.

In the past years, a large number of single case or small series on HC had been published. However, several large case series have been published in the recent past. There are at least 28 articles, each reporting  $\geq 10$  patients with HC. However, these cases have been described in different clinical settings. For epidemiological and clinical feature analyses, we included only those studies that described a consecutive series of HC patients (at least five patients).

There are several case series that have focused mainly on the different therapeutic aspects of HC. A few cases of HC were just the part of some epidemiological studies (and lack epidemiological and clinical details). A few studies have focused on the pathophysiological aspects of HC. As these cases do not truly represent the consecutive patients with HC, we excluded such cases for the epidemiological and clinical feature analyses. Secondary cases of HC were not included in this review and they were analyzed separately.

We noted 14 case series (a total of 472 patients) that described consecutive cases of HC. However, there was no uniformity in reporting HC cases in these publications, as they had followed only those diagnostic criteria that were prevalent at that time. Various epidemiological and clinical parameters were not available in some reports. Epidemiological and clinical data are summarized and pooled with descriptive statistics in different tables 1–9.

## Epidemiology

The literature lacks data about the prevalence of HC in the general population. A response to indomethacin is an essential feature in the diagnostic criteria of HC.<sup>1</sup> It makes it hard to find out the prevalence of (definite) HC in any general population. Sjaastad and Bakketveig<sup>9</sup> noted 18 patients (1.0%) with clinical features resembling HC in 1838 parishioners in the Vågå study.

Several clinic-based studies suggest that HC is not uncommon, but it is probably an underdiagnosed condition. Table 1 shows the prevalence of HC in the neurology or headache clinic. HC represents 1.7% (range 1.3%–2.3%) of total headache patients attending headache or neurology clinic.

There are two clinic-based studies on the strictly unilateral headaches. Pooled analyses of these two studies indicate that HC is the second most common TACs in the clinical setting. Overall, HC is the fourth most common cause of side-locked headaches (after CH, side-locked migraine and cervicogenic headache).<sup>10</sup>

The diagnosis of HC may be missed even by neurologists and headache experts. Rossi et al<sup>11</sup> discussed the diagnostic issue of HC in their 25 newly diagnosed cases of HC. A total

**Table 1** Percentage of HC patients among total headache patients in clinical settings

| Study                              | Number of HC | Total headache patients | Proportion of HC of total headache patients (%) |
|------------------------------------|--------------|-------------------------|---|
| Prakash et al <sup>67</sup>        | 22           | 1687                    | 1.3   |
| Benítez-Rivero et al <sup>26</sup> | 12           | 520                     | 2.3   |
| Ramón et al <sup>68</sup>          | 8            | 528                     | 1.5   |
| Cortijo et al <sup>12</sup>        | 36           | 1800                    | 2.0   |
| Guerrero et al <sup>34</sup>       | 22           | 1150                    | 1.9   |
| Rossi et al <sup>11</sup>          | 25           | 1612                    | 1.6   |
| Total                              | 125          | 7297                    | 1.7   |

**Abbreviation:** HC, hemicrania continua.

of 20 cases (80%) were initially seen by neurologists without suspecting a diagnosis of HC, and seven cases (28%) were previously evaluated at headache centers without making a correct diagnosis. Therefore, with such a high rate of misdiagnosis, we can presume that the prevalence of HC should be much higher than the current data. With more inclusive type criteria in ICHD-3 $\beta$ , the prevalence will definitely rise.

## Age

The mean age at the onset of HC varies between 31 and 53 years in different case series. The pooled mean age at the onset was 40 years (n = 472). In Cortijo et al's<sup>12</sup> series (n = 36), 25 patients (69%) were  $\geq$ 40 years. However, no age group is immune and it can begin at any part of the life. The age range at the onset was 5–76 years (Table 2).

## Sex

HC is classically considered a disease with a female preponderance. In an earlier review, the female to male ratio was 5:1.<sup>5</sup> This female preponderance reduced to 2.8:1 in Peres

et al's<sup>6</sup> review. In the current pooled analysis of the 472 patients, the female to male ratio is 1.8:1 (Table 2).

## Familial HC

There is only one case report of familial HC (two members of the family).<sup>13</sup> However, no genetic susceptibility has been confirmed.

## Clinical features

HC is characterized by a strictly unilateral, continuous headache of moderate intensity, with superimposed exacerbations of severe intensity. The exacerbations are associated with cranial autonomic features, restlessness and migrainous features. By definition, there should be a complete response to indomethacin.

## Laterality

HC is a strictly unilateral head pain. There was a slight preference for the right side (53% vs 45%; n = 169). The preponderance for right side was also noted in an earlier review.<sup>5</sup> Only

**Table 2** Epidemiological parameters in HC as reported in a case series describing consecutive patients (>5 patients) and pooled analyses

| Study                               | Number of patients | Sex (male/female) |       | Age at the onset (years) |       | Delay in diagnosis (months) |        | Pattern of HC |           |
|-------------------------------------|--------------------|-------------------|-------|--------------------------|-------|-----------------------------|--------|---------------|-----------|
|                                     |                    | Number            | Ratio | Mean                     | Range | Mean                        | Range  | Continuous    | Remitting |
| Benítez-Rivero et al <sup>26</sup>  | 12                 | 4/8               | 1:2   | 47.1                     | 26–75 | 96                          | –      | –             | –         |
| Guerrero et al <sup>34</sup>        | 22                 | 8/14              | 1:1.7 | 41.8                     | 7–74  | –                           | –      | 86            | 14        |
| Cortijo et al <sup>12</sup>         | 36                 | 8/28              | 1:3.5 | 46.3                     | 14–74 | 75                          | 3–390  | 89            | 11        |
| Prakash and Golwala <sup>29</sup>   | 62                 | 29/33             | 1:1.1 | 41.8                     | 28–61 | 50                          | 3–264  | 78            | 22        |
| de Moura et al <sup>28</sup>        | 10                 | 4/6               | 1:1.5 | 31                       | 6–59  | 204                         | 21–456 | –             | –         |
| Cittadini and Goadsby <sup>14</sup> | 39                 | 15/24             | 1:1.6 | 38.7                     | 10–67 | –                           | –      | 82            | 18        |
| Rossi et al <sup>11</sup>           | 25                 | 11/14             | 1:1.3 | 45.3                     | 22–66 | 60                          | 6–204  | –             | –         |
| Marmura et al <sup>65</sup>         | 165                | 66/99             | 1:1.5 | –                        | –     | –                           | –      | –             | –         |
| Bigal et al <sup>37</sup>           | 10                 | 3/7               | 1:2.3 | 45.4                     | 34–61 | –                           | –      | –             | –         |
| Peres et al <sup>6</sup>            | 34                 | 10/24             | 1:2.4 | 28                       | 5–67  | 252                         | –      | 88            | 12        |
| Wheeler <sup>7</sup>                | 30                 | 1/29              | 1:29  | 42.3                     | 13–76 | 100                         | –      | –             | –         |
| Espada et al <sup>8</sup>           | 9                  | 5/4               | 1:0.8 | 53.3                     | 29–69 | 16                          | 1–48   | 89            | 11        |
| Newman et al <sup>25</sup>          | 10                 | 6/4               | 1:0.6 | 35                       | 12–45 | 47                          | 1–94   | 90            | 10        |
| Bordini et al <sup>5</sup>          | 8                  | 1/7               | 1:7   | 38.4                     | 22–58 | 52                          | 1–180  | 88            | 12        |
| Average                             |                    | 171/301           | 1:1.8 | 39.7                     | 5–76  | 95                          | 3–456  | 85            | 15        |

**Note:** '–' indicates data not available.

**Abbreviation:** HC, hemicrania continua.

one case series noted side-shifting HC. It composes 8% of total patients in that series.<sup>14</sup> However, on pooled analysis, the prevalence of side-shifting HC was ~2%. There are at least nine cases with side-shifting pain in the literature.<sup>15-20</sup> A few case reports of bilateral HC have also been reported in the literature. Pasquier et al<sup>21</sup> reported the first case of the bilateral HC in a 38-year female. The patient had a 7-year history of fluctuating holocephalic headaches without cranial autonomic features. The headache did not respond to any drug. However, there was a complete response to indomethacin. After that, three more cases of bilateral HC have been reported.<sup>22-24</sup>

## Site of pain

The pain of all TACs classically present in the ophthalmic division of the trigeminal nerve (V1).

ICHD-3 $\beta$  defines the sites of pain for CH, PH and SUNCT/SUNA. The pain can be in orbital, supraorbital, temporal or in any combination of these sites. However, ICHD-3 $\beta$  is silent over the sites of pain in HC patients. It mentions just “unilateral pain.” Table 3 shows the sites of pain in patients with HC in different case series. It suggests that just like other TACs, HC patients have pain predominantly in V1 distributions. Therefore, we suggested to include the sites of pain (orbital, supraorbital or temporal) in the diagnostic

criteria of HC, as defined in the diagnostic criteria for CH, PH and SUNCT/SUNA.

A continuous background pain is usually localized in V1 distribution. However, the pain may spread during exacerbation phase to involve other areas such as occiput, neck, shoulder, maxilla, periauricular region and oral cavity (including teeth and throat).<sup>14</sup>

## Pain characteristics and pattern

The pain has two components: 1) continuous unilateral headache and 2) superimposed variable exacerbations. The recognition of both components is important for identifying a case of HC. Figure 1 shows the diagrammatic representation of pain pattern in HC.

Continuous baseline headache is the most consistent feature of HC. It is the central feature of HC.

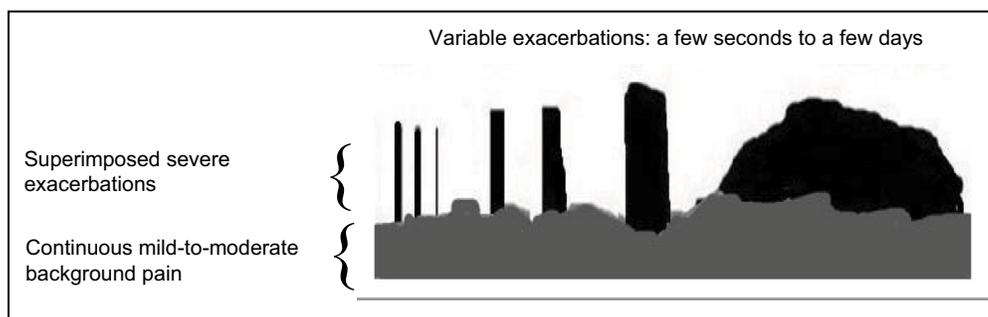
The majority of patients have superimposed exacerbations over the basal pain. Superimposed exacerbations are highly variable in terms of character, intensity, duration, frequency and associated features during exacerbations. Table 4 summarizes the various aspects of the exacerbation phase. This variability may be the reason for the high rate of misdiagnosis of HC. Therefore, an understanding of exacerbation phase is very important to reduce the misdiagnosis of HC.

**Table 3** Sites of pain in patients with HC in different clinical studies

| Sites of pain           | Benítez-Rivero et al <sup>26</sup> (%) | Cortijo et al <sup>12</sup> (%) | Prakash and Golwala <sup>29</sup> (%) | Cittadini and Goadsby <sup>14</sup> (%) | Newman et al <sup>25</sup> (%) |
|-------------------------|--|---------------------------------|---------------------------------------|---|--------------------------------|
| Orbital/retro-orbital   | 50                                     | 62                              | 83                                    | 67/59*                                  | 70                             |
| Frontal                 | 33                                     | 8                               | 57                                    | 64                                      | 20                             |
| Temporal                | –                                      | 8                               | 70                                    | 82                                      | 50                             |
| Parieto-occipital       | 25                                     | 8                               | 37                                    | 54                                      | 40                             |
| Periauricular/ear       | –                                      | –                               | 13                                    | 30                                      | –                              |
| Infra-orbital/maxillary | –                                      | –                               | 47                                    | 30                                      | 10                             |
| Teeth                   | –                                      | –                               | 20                                    | 20                                      | –                              |
| Neck                    | –                                      | –                               | 7                                     | 33                                      | 10                             |
| Shoulder                | –                                      | –                               | –                                     | 18                                      | 10                             |
| Hemicranial             | 25                                     | 31                              | –                                     | –                                       | 40                             |

**Notes:** \*Orbital and retro-orbital are described separately. ‘–’ indicates data not available.

**Abbreviation:** HC, hemicrania continua.



**Figure 1** Diagrammatic representation of hemicrania continua.

**Table 4** Clinical characteristics of superimposed exacerbations in HC as reported in case series describing consecutive patients (>5 patients) and pooled analyses

| Study                               | Intensity (VAS), M; R  | Character of pain                  | Duration (M and/or R)               | Frequency (M and/or R)            | Autonomic features, at least one (%) | Migrainous features |                                  | Agitation (%) |
|-------------------------------------|------------------------|------------------------------------|-------------------------------------|-----------------------------------|--------------------------------------|---------------------|----------------------------------|---------------|
|                                     |                        |                                    |                                     |                                   |                                      | At least one (%)    | Fulfilling migraine criteria (%) |               |
| Benítez-Rivero et al <sup>26</sup>  | 9.2                    | –                                  | M 31.4 hours<br>R 1–72 hours        | Daily – one attack in 2 months    | 81                                   | –                   | –                                | –             |
| Cortijo et al <sup>12</sup>         | 8.3; 5–10              | Stabbing 52%<br>Pulsatile 6%       | M 32.3 minutes<br>R 1–60 minutes    | Multiple daily attacks            | 69                                   | 17                  | –                                | –             |
| Prakash and Golwala <sup>29</sup>   |                        | Pulsatile 62%<br>Non-pulsatile 72% | R <5 minute to >24 hours            | <1/day to >5 attack/day           | 79                                   | 61                  | –                                | 56            |
| de Moura et al <sup>28</sup>        | 9–10                   | Pulsatile 50%                      | –                                   | –                                 | 100                                  | –                   | –                                | –             |
| Cittadini and Goadsby <sup>14</sup> | 9.3; 6.5–10            | Pulsatile 69%<br>Lancinating 43%   | R 30 minutes to 7 days              | Daily – one attack in 4 months    | 95                                   | 79                  | >53                              | 69            |
| Rossi et al <sup>11</sup>           | Moderate to severe     | Pulsatile 24%                      | R <15 minutes to 72 hours           | <1/day to >8/day                  | 100                                  | 56                  | 32                               | 32            |
| Marmura et al <sup>65</sup>         | –                      | –                                  | –                                   | –                                 | 59                                   | 58                  | 58                               | –             |
| Bigal et al <sup>37</sup>           | –                      | Pulsatile 30%                      | –                                   | –                                 | 70                                   | 40                  | –                                | –             |
| Peres et al <sup>6</sup>            | 9.3 ± 1.0              | Pulsatile 53%<br>Stabbing 41%      | –                                   | –                                 | 74                                   | 71                  | 71                               | –             |
| Wheeler <sup>7</sup>                | Severe                 | Pulsatile 53%<br>Stabbing 20%      | M 24 hours<br>R 1 second to 2 weeks | 10/day to 1–3 attacks/month       | 97                                   | 90                  | –                                | –             |
| Newman et al <sup>25</sup>          | Severe to excruciating | Pulsatile 30%<br>Stabbing 40%      | R 30 seconds to 12 hours            | 10–20/daily to 2–3/week           | 60                                   | 40                  | –                                | 10            |
| Bordini et al <sup>5</sup>          | Severe                 | Pulsatile 39%<br>Stabbing 100%     | R 5 hours to 8 days                 | –                                 | Present                              | Present             | –                                | –             |
| Average Range                       | 9.0; 5–10              |                                    | A few seconds to 2 weeks            | 20 attacks/day to one in 4 months | 74<br>59–100                         | 60<br>17–90         | 56<br>32–71                      | 52<br>10–69   |

**Notes:** “–” indicates data not available.

**Abbreviations:** HC, hemicrania continua; M, mean; R, range; VAS, visual analog scale.

## Character and intensity of pain

The background pain is usually perceived as dull and pressure (like tension-type headache [TTH]; Peres et al 73%; Wheeler et al 67%). However, a few patients may have throbbing or stabbing background pain. It is usually mild to moderate in intensity. The mean visual analog scale (VAS 0–10) of the continuous background pain varies from 3.3 to 5.2. However, a few patients may have a persistent severe headache (>7 in VAS). In a series of 39 patients reported by Cittadini and Goadsby,<sup>14</sup> two patients had continuous pain with a severity score of 10. The background pain usually does not hamper physical activity. In a case series of 34 patients reported by Peres et al,<sup>6</sup> 82% patients had either no or very mild physical disability because of the baseline pain.

The character of pain during exacerbation phase are largely either throbbing or stabbing (jabs and jolts). Therefore, whereas the characteristics of basal pain are predominantly like TTH, the exacerbations are predominantly like migraine.

The intensity of exacerbations is usually severe to very severe (VAS score >7). The pooled mean VAS of exacerbations

was 9.0 (n = 121). However, it ranges from 5 to 10. Approximately 38% patients rated the severe pain at 10. In Cittadini and Goadsby's series,<sup>14</sup> 49% patients said that their pains were the most painful conditions they had ever experienced, comparing it to childbirth, a broken bone, toothache and burned hands. In this regard, it matches with the patients with CH and PH. Like CH and PH, the patients with HC may have suicidal thoughts during severe exacerbations. There are a few cases of HC where patients attempted suicide because of the intolerable pain.<sup>5</sup>

CH is considered as a most painful condition. The pain intensity of PH is almost similar to CH. The data on HC suggest that the intensity of the exacerbation attacks of HC may be as severe as of CH and PH in a large number of patients. However, on the other hand, up to 18% patients may have VAS score <7 (i.e., only moderate exacerbations).<sup>11,12,14</sup> Moreover, a few patients may not experience exacerbation phase and will have only continuous background pain without much fluctuation.<sup>14,25</sup>

## Duration and frequency of exacerbations

CH, PH and SUNCT/SUNA follow a predictable pattern in relation to frequency and duration of attacks.<sup>1</sup> However, the pattern of exacerbations of HC does not follow any rule (Table 4). It is highly variable. This may vary from attack per attack. The mean duration of exacerbations in one series was 32 minutes.<sup>12</sup> However, in another series, it was 31 hours.<sup>26</sup> The range of duration of exacerbations varies from a few seconds to 2 weeks.<sup>7</sup> The frequency of the attacks is also variable. It varies from more than 20 attacks in a day to one attack in 4-month duration (Table 4). Pooling of the data of frequency and durations was meaningless here. The key point is to know that the duration and frequency of exacerbations do not have any boundary.

Nocturnal exacerbations are quite common in HC (up to 53%).<sup>14</sup> However, a circadian periodicity for exacerbations remains absent. However, a few patients noted worsening of exacerbations in particular months.<sup>14,27</sup> Cittadini and Goadsby reported three patients, where the worsening of the pains was noted in particular months.

## Ipsilateral cranial autonomic symptoms (CAS)

These are very important accompanying features of all five types of TACs, including HC. ICHD-3 $\beta$  recognizes 10 different types of cranial autonomic features. These CAS are related to eye/eyelid (conjunctival injection, lacrimation, ptosis, meiosis and eyelid edema), nose (rhinorrhea and nasal congestion), ear (sensation of fullness) and face (flushing and sweating).<sup>1</sup>

The mean prevalence of at least one cranial autonomic feature was 74% in pooled analyses (n = 433). In an earlier review, the prevalence of at least one cranial autonomic feature was 63%.<sup>25</sup> This prevalence is slightly lower than the prevalence of CAS in CH and PH patients, where it is noted in more than 90% cases. However, a few case series of HC have also reported CAS in more than 90% cases.<sup>7,11,14,28</sup> Variability in the prevalence of CAS may be because of the selection bias in the particular series, as the importance of CAS for the diagnostic purpose has repeatedly been changed over the time.

Moreover, CAS may be subtle in a subset of patients and patients may not be aware of its presence. In a series of 62 patients reported by Prakash et al,<sup>29</sup> nine patients initially denied the presence of any CAS. However, CAS were noted later, on an objective assessment of the patients for CAS. Therefore, an objective assessment of autonomic feature is important before labeling it as “absent”.

Tearing was the most common cranial autonomic feature (36%–77%) in all reported case series.<sup>7,11,14,25,28,29</sup> Conjunctival injection, ptosis, nasal congestion and rhinorrhea are

other common CAS in patients with HC. A sense of aural fullness has been recently included as one of the autonomic features of all TACs in ICHD-3 $\beta$ . It has been reported only in Cittadini and Goadsby's<sup>14</sup> case series, and they found it in 19% cases with HC.

Another important and a peculiar feature of HC is a feeling of foreign body sensation in the eye (or sand in eye sensation or itching eye). It is considered as part of CAS. It is noted in several large case series of HC (Prakash et al 43%; Cittadini and Goadsby 32%; Cortijo et al 32%; Bordini et al 17%). The feeling of foreign body sensation in the eye has not been reported in any other TACs or any primary headache disorder. It is not included in ICHD-3 $\beta$  criteria. We would suggest to include it in the diagnostic criteria of HC as a part of CAS.

## Restlessness or agitation

A sense of restlessness or agitation is an important feature of TACs. It has been the part of the diagnostic criteria of CH since long. Very recently, restlessness has also been included in HC criteria.<sup>1</sup> It is included as an alternative to cranial autonomic features. The mean prevalence of agitation or restlessness was 52% in pooled analyses (n = 136; range 10%–69%).

## Migrainous features

Nausea, vomiting, photophobia and phonophobia are called as migrainous features. It is quite common in patients with HC. The prevalence of at least one migrainous feature varies from 17% to 90% (with mean pooled prevalence of 60%). A few studies compared the migraine criteria to the exacerbation phase of HC. Approximately 32%–71% (mean 56%) patients meet the criteria for migraine in the exacerbation period. Visual auras have been reported during exacerbations in a few patients with HC.<sup>30,31</sup> Olfactory aura has also been reported in one case of HC.<sup>32</sup>

## Triggers of exacerbations

Stress was the most common trigger in Cittadini and Goadsby's<sup>14</sup> series. Approximately 51% patients noted exacerbations after stress or relaxation after stress. Exacerbations with alcohol and irregular sleep were noted in 38%.<sup>14</sup> Menstruation was a trigger in some patients.<sup>14</sup> Prakash et al<sup>33</sup> reported a case of relapsing–remitting HC that used to occur only during menstruation.

## Classification and variants of HC

HC, by definition, is a chronic headache disorder. A minimum of 3-month duration is required before labeling a case as HC.

ICHD-3 $\beta$  recognizes two forms of HC, based on whether the patient gets any symptom-free day or not: 1) HC, unremitting subtype and 2) HC, remitting subtype (Table 5).<sup>1</sup>

Unremitting HC is characterized by continuous pain for at least 1 year, without any symptom-free period. Interruption of pain for even 1 day is not required. In remitting HC, the patient remains symptom free for at least 1 day. Unremitting HC (i.e., continuous pain for 1 year) can arise de novo or may evolve from remitting subtype. Table 2 lists the diagnostic distribution of both forms of HC in the literature. The prevalence of remitting HC varies between 10% and 22% of total HC cases (mean pooled prevalence 15%; n = 220).

Unremitting HC arising de novo (i.e., chronic from the onset) is more common than evolving from remitting subtype. Approximately 50%–60% HC is chronic from the onset and 25%–35% HC evolves into continuous phase from the remitting form.<sup>12,14,25,26,29,34</sup>

## Secondary HC

Table 6 lists all the cases of HC that were claimed to be secondary HC. However, the diagnostic accuracy of HC and the causal association of headaches to the claimed pathologies are

**Table 5** Diagnostic criteria of different subtypes of HC (ICHD-3 $\beta$ )

|       |   |
|-------|---|
| 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 $\beta$ 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 $\geq 1$ day without treatment |
| 3.4.2 | 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 $\geq 1$ day             |

**Note:** Data from The International Classification of Headache Disorders, 3rd (beta version).<sup>1</sup>

**Abbreviations:** HC, hemicrania continua; ICHD-3 $\beta$ , International Classification of Headache Disorder, third edition.

not obvious in each case. All secondary HCs were classified and arranged according to ICHD-3 $\beta$  criteria. We noted a total of 66 cases of secondary HC. It included a total of 25 different pathologies. Posttraumatic HC was the most common entity. It composed 39% of total cases of secondary HC. Finkel et al<sup>35</sup> studied the headache pattern in military service members with a history of mild traumatic brain injury. They noted 12 patients with HC (consisting 7.2% of total cases). This review is very important for two reasons. 1) It highlights that post-traumatic HC may be very common in the general population. 2) It will respond strikingly to indomethacin. Therefore, there is a need to make physicians aware of this entity. Second most common secondary HC is post-craniotomy HC. It is almost equal to posttraumatic HC. Postpartum and postoperative HCs are two other secondary HCs that are in temporal relation to certain events. Therefore, any side-locked headache should be inquired about the presence of certain events preceding to HC (such as head injury, any type of surgery and postpartum). Event-related secondary HC is largely benign.<sup>36</sup>

However, other secondary HC is not that benign and a few of them may be life threatening and may require early diagnosis and urgent therapy. Intracranial space-occupying lesion (especially pituitary tumor, CP angle tumor, etc), vessels-related pathology (especially internal carotid artery [ICA] dissection, cortical venous thrombosis, etc) and pathologies related to extracranial surrounding tissues (sinusitis, nasopharyngeal carcinoma, eye pathology, etc) are very important causes of secondary HC. Prolactinoma is the most common intracranial structural pathology (n = 4). ICA dissection (n = 3) is the most common vascular pathology. Carcinoma lung is probably the most dangerous pathology associated with secondary HC.

## Other associated headache disorders

HC has been observed in association with various other primary headaches and facial pain, including different neuralgias. Jabs and jolts like pain (stabbing headache) are important associated pains during exacerbation phase. They were noted in 20%–41% patients with HC in different case series.<sup>6,14,37</sup> However, this prevalence matches with the normal prevalence of stabbing headache in the general population. Table 7 presents all other associated headaches reported in the literature. It can be classified into three groups: 1) “both HC and other primary headache disorder existing simultaneously”: one headache may precede to other or both headaches may start simultaneously. However, patients may not be able to differentiate that they are having two diseases simultane-

**Table 6** Secondary HC (classified and arranged according to ICHD-3 $\beta$  criteria)

| ICHD-3 $\beta$ code | Diagnosis  | Number of patients                                  |           |
|---------------------|--|---|-----------|
| 5                   | Headache attributed to trauma or injury to head and/or neck                            | Posttraumatic HC <sup>14,29,35,36,42,69-71</sup>    | 26        |
|                     |  | Post-craniotomy HC <sup>29,42,72</sup>              | 6         |
| 6                   | Headache attributed to cranial or cervical vascular disorder                           | Poststroke HC <sup>42</sup>                         | 1         |
|                     |  | Internal carotid artery aneurysm <sup>42</sup>      | 1         |
|                     |  | Venous malformation <sup>42</sup>                   | 1         |
|                     |  | Internal carotid artery dissection <sup>42,73</sup> | 3         |
|                     |  | Cerebral venous thrombosis <sup>74</sup>            | 1         |
|                     |  | Angiolipoma in temporal region <sup>42</sup>        | 1         |
| 7                   | Headache attributed to nonvascular intracranial disorder                               | Prolactinoma <sup>42,75</sup>                       | 4         |
|                     |  | Pituitary infarct <sup>14</sup>                     | 1         |
|                     |  | CP angle epidermoid <sup>42</sup>                   | 1         |
|                     |  | Pineal cyst <sup>42</sup>                           | 1         |
| 8                   | Headache attributed to a substance or its withdrawal                                   | Transdermal nitroglycerine <sup>76</sup>            | 1         |
|                     |  | Analgesic rebound <sup>42</sup>                     | 1         |
| 9                   | Headache attributed to infection   | HIV <sup>42</sup>                                   | 1         |
| 11                  | Headache or facial pain attributed to disorder of the cranium and structures around it | Sphenoidal tumor <sup>42</sup>                      | 1         |
|                     |  | Sphenoid sinusitis <sup>42</sup>                    | 1         |
|                     |  | Nasopharyngeal carcinoma <sup>29,77</sup>           | 2         |
|                     |  | Orbital tumor/pseudotumor <sup>78</sup>             | 1         |
|                     |  | Disk herniation <sup>42</sup>                       | 1         |
|                     |  | Vitreous hemorrhage <sup>14</sup>                   | 1         |
| 13                  | Painful cranial neuropathies and other facial pains                                    | Leprosy <sup>79,80</sup>                            | 2         |
| 14                  | Other headache disorders   | Postpartum <sup>42</sup>                            | 2         |
|                     |  | Postoperative (non-intracranial) <sup>36</sup>      | 2         |
|                     |  | Carcinoma lung <sup>81-83</sup>                     | 3         |
|                     |  | <b>Total secondary HC</b>                           | <b>66</b> |

**Note:** Data from The International Classification of Headache Disorders, 3rd (beta version).<sup>1</sup>

**Abbreviations:** HC, hemicrania continua; ICHD-3 $\beta$ , International Classification of Headache Disorder, third edition.

ously. The diagnosis of both diseases at the same time is very important as patients may require two different classes of drugs. CH is the most common associated headache in this group. Other reported headaches are migraine, TTH, trochlear headache, sexual headache and trigeminal neuralgia. 2) "HC evolving from other primary headaches": again CH is the most common entity. PH, SUNCT, migraine and Raeder syndrome are other diseases in this group. Cosentino et al<sup>38</sup> described a patient with CH who first evolved into SUNCT, and later on SUNCT changed into HC. The diagnosis of this group is important for therapeutic purpose as treatment will change if patients evolve into HC. 3) "HC evolving into other primary headaches": Muller et al<sup>39</sup> described an HC patient who developed PH on withdrawal of the effective drug. Rozen et al<sup>40</sup> reported a patient with post-PH. The patient first developed HC and later on HC turned into LASH (long-lasting autonomic symptoms with associated hemicrania).

## Diagnosis

### Diagnostic delay

The pooled mean delay of diagnosis of HC (n = 231) was 95  $\pm$  75 months (8  $\pm$  7.2 years). The range of the mean delay of diagnosis was 16–252 months (1.3–21 years). Various reasons can be speculated for this high rate of misdiagnosis.

Although HC is not rare, there is a perception that it is still rare. Various authors still mention Peres et al's<sup>6</sup> old review and suggest that there are just 100 cases in the literature. Physicians usually do not prefer to make a diagnosis of a rare headache disorder. Currently, we noted more than 1000 cases of HC in the literature. Unawareness about HC may be another important issue for the high rate of misdiagnosis of HC. However, a case of HC is missed even by neurologists and headache experts. It may be because of the wrong history or misinterpretation of the clinical features of HC

**Table 7** Occurrence of different headaches in patients with HC

| Case (reference)                                    | Associated headache             | Side concordance | Interrelation between two headaches   |
|---|---------------------------------|------------------|---|
| HC concurrent with other primary headache disorders |                                 |                  |   |
| Totzeck et al <sup>84</sup>                         | CH                              | Same side        | Both CH and HC were started simultaneously                                  |
| Lisotto et al <sup>85</sup>                         | CH                              | Contralateral    | A patient with HC simultaneously developed (after 4 years) contralateral CH |
| Saito et al <sup>86</sup>                           | CH                              | Same side        | HC evolved during cluster period of CH                                      |
| Robbins et al <sup>87</sup>                         | CH and migraine                 | Same side        | HC and CH evolved simultaneously in a migraineur                            |
| Evers et al <sup>88</sup>                           | FHM                             | Same side        | HC evolved over FHM (after several years of migraine onset)                 |
| Allena et al <sup>89</sup>                          | CTTH                            | Same side        | The authors believed that a patient had both HC and CTTH simultaneously     |
| Cuadrado et al <sup>90</sup>                        | Primary trochlear headache      | Same side        | An HC patient had probable trochlear headache simultaneously                |
| Prakash and Rathore <sup>91</sup>                   | TN (two cases)                  | Same side        | Case 1: HC developed after several years of TN                              |
|   |                                 | same side        | Case 2: Both HC and TN probably developed simultaneously                    |
| Prakash <sup>92</sup>                               | Sexual headache                 | Same side        | Headache with sexual activity developed over the undiagnosed case of HC     |
| HC evolving from other primary headaches            |                                 |                  |   |
| Porzukowiak <sup>23</sup>                           | Raeder paratrigeminal neuralgia | Same side        | Initial symptoms of HC closely mimicked Raeder paratrigeminal neuralgia     |
| Koutsis et al <sup>94</sup>                         | Benign Raeder syndrome          | Same side        | Benign Raeder syndrome turned into HC over 10 months                        |
| Castellanos-Pinedo et al <sup>95</sup>              | PH                              | Same side        | A patient with episodic PH developed HC after a long remission from PH      |
| Terlizzi et al <sup>96</sup>                        | Migraine                        | Same side        | HC evolved after 10 years of episodic migraine                              |
| Palmieri et al <sup>97</sup>                        | Migraine                        | Same side        | A side-locked migraine (with aura) turned into HC after 25 years            |
| Cosentino et al <sup>38</sup>                       | CH-SUNCT                        | Same side        | A CH patient first changed pattern as SUNCT, and later on HC                |
| Lambru et al <sup>98</sup>                          | CH                              | Same side        | A refractory CH suddenly evolved into HC                                    |
| Centonze et al <sup>99</sup>                        | CH                              | Same side        | HC evolved after 10-month remission of CH                                   |
| Rozen <sup>100</sup>                                | CH                              | Contralateral    | HC evolved in remission phase of CH   |
| Rozen <sup>40</sup>                                 | PH                              | Same side        | Posttraumatic PH that turned into HC. Later, it turned into LASH syndrome   |
| HC evolving into other primary headaches            |                                 |                  |   |
| Müller and Bekkelund <sup>39</sup>                  | PH                              | Same side        | A HC patient developed PH on withdrawal of the effective drug               |
| Rozen <sup>40</sup>                                 | LASH                            | Same side        | Posttraumatic PH that turned into HC. Later, it turned into LASH syndrome   |

**Abbreviations:** CH, cluster headache; CTTH, chronic tension-type headache; FHM, familial hemiplegic migraine; HC, hemicrania continua; LASH, long-lasting autonomic symptoms with associated hemicrania; PH, paroxysmal hemicrania; SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; TN, trigeminal neuralgia.

patients. The patients may be worried of their superimposed exacerbations and may not volunteer about background headache. Even physician may not ask about background headaches. Patients may also not be aware of subtle cranial autonomic features. Objective assessment during attacks may be required. Phenotypic variability of HC may lead a physician to make a wrong diagnosis. Frequency and duration of headaches are important clues for diagnosing various primary headaches, secondary headaches and neuralgias. The duration and frequency of superimposed exacerbations mimic almost all primary headaches and neuralgias.

### Effects of diagnostic delay

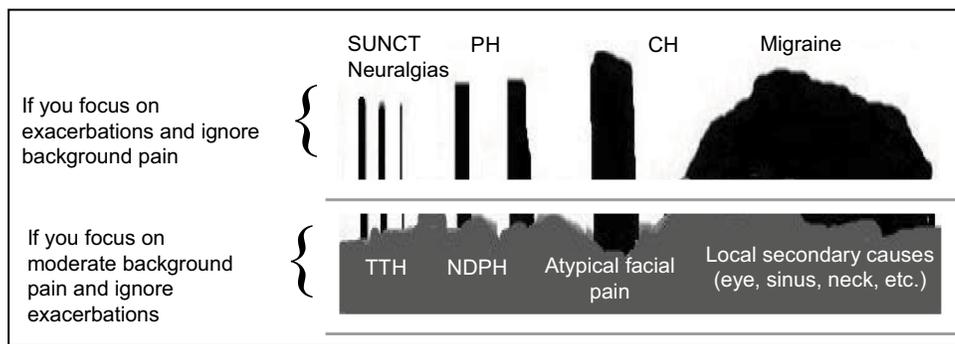
Patients who unnecessarily suffer from severe pain are very much treatable. Delay in diagnosis leads to unnecessary therapeutic intervention, including surgical procedures.

Approximately 36% patients with HC had undergone ineffective and unnecessary surgery in Rossi et al's<sup>11</sup> series. Dental extraction and sinus surgery are two common unnecessary surgical interventions in HC.

### Differential diagnosis

There are two components of HC: 1) strictly unilateral continuous background headache and 2) superimposed exacerbations (Figure 1). Differential diagnosis depends on which components you are focusing (Figure 2).

The diagnosis could be very easy if one can recognize both components in a patient. Here, one will have to differentiate HC with CH or PH with interparoxysmal pain. However, HC can be easily differentiated with CH/PH with interparoxysmal pain on the following grounds: 1) Interparoxysmal pain is not present throughout the day and it is usually very



**Figure 2** Differential diagnosis of HC pain.

**Abbreviations:** CH, cluster headache; HC, hemicrania continua; PH, paroxysmal hemicrania; SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; TTH, tension-type headache; NDPH, new daily persistent headache.

mild.<sup>41</sup> 2) The duration and frequency of attacks are quite predictable in both PH and CH patients. The duration of attacks in PH and CH patients is 2–30 and 15–180 minutes, respectively. However, the duration of attack in HC patients is highly variable and many attacks are very prolonged (more than the upper limit of CH). 3) Migrainous features are more common in HC patients than CH and PH patients.

If the physicians or the patients focus only on the exacerbation part and ignore continuous background pain, the diagnosis can be anything.<sup>6</sup> As the duration of exacerbations can vary from a few seconds to a few days, the diagnosis may include neuralgias (especially supraorbital and trigeminal neuralgia), SUNCT/SUNA, PH, CH, migraine, TTH, etc.

Most of the exacerbations in HC last for a few hours. Exacerbations are usually throbbing in character and accompanied by migrainous features. In addition, we know that up to 71 patients may fulfill the criteria of migraine.<sup>6</sup> Therefore, migraine is the most important differential diagnosis. Besides continuous background headaches, the presence of unilateral cranial autonomic features and restlessness or agitation during headache attacks favors HC over migraine. The age at the onset may also be helpful. The mean pooled age at the onset of HC was 40 years. The most common age at the onset of migraine is in the second and third decade of life. Therefore, before making a diagnosis of side-locked migraine, the presence of continuous background headache, presence of unilateral cranial autonomic features and agitation during an attack should be asked. In doubtful cases, a trial of indomethacin can be taken to see the response.

In Rossi et al's series, 32% patients with HC fulfilled the diagnostic criteria for CH during the exacerbations. Differentiation of HC with PH or CH depends on two factors: 1) recognition of continuous background headache and 2) variable exacerbations. A few attacks in CH and PH patients may fall beyond the criteria prescribed by ICHD-3 $\beta$  for CH

and PH. However, if a patient with CH or with PH has several attacks beyond the defined duration in the criteria, think about a possibility of HC.

On the contrary, if exacerbations are not severe or physicians focus only on continuous pain (ignoring exacerbation part), the differential diagnosis could be new daily persistent headache (NDPH), chronic tension-type headache (CTTH), atypical facial pain and various local pathologies. Side-locked NDPH with migrainous features may mimic HC. Approximately 11%–18% NDPH patients may be side locked.<sup>10</sup> Up to one-third of patients with NDPH may have migrainous feature.<sup>1</sup> Mild autonomic features have also been reported with NDPH. If patients remember the exact onset of their headaches (first day of continuous headache), a possibility of NDPH is likely. In doubtful cases, a trial of indomethacin can be given to find out HC.

Dental lesions, temporomandibular joint pathologies, sinus pathologies, neck pathologies and eye abnormalities may cause continuous pain in the trigeminal or surrounding distribution. All these structural pathologies are dealt with different experts of the medical field. Therefore, because of the wrong history or unawareness to HC, a diagnosis of secondary headaches may be made. The patients may be subjected to even interventional surgeries for the incidental or unrelated pathologies.

## Approach to diagnose HC

The diagnosis of HC is made according to ICHD-3 $\beta$  criteria for HC (Table 5). A suspicion of HC and other TACs starts once one can see strictly unilateral headache (may be side shifting, but always unilateral). All TACs share some common clinical features. A mnemonic “3 As for unilateral headache” have been suggested to identify TACs.<sup>10</sup> 3 As include the following: 1) “anteriorly located” (orbital, frontal and temporal) pain, 2) “autonomic features” in the same area (ipsilateral) during attacks/exacerbations and 3) “agitation” during attacks

or exacerbations. If all components of 3 As are present, most likely it is one of the types of TACs. Even the presence of two As in the side-locked headache (anteriorly located pain with autonomic features or anteriorly located pain with agitation or agitation with autonomic features) is highly indicative of one of the forms of TACs.

Strictly unilateral headache is always a red flag sign. Therefore, a detailed history, investigations and appropriate investigation are a must in such patients (for details, the readers are encouraged to see a review on this topic).<sup>42</sup> Once secondary causes are ruled out, we can diagnose primary TACs.

All TACs are episodic, except HC. Therefore, first of all, patients should be asked for the presence of continuous background headache. The patients themselves may not volunteer about it. As we know, the memory for pain is better for severe and the recent attacks. Therefore, a few patients, even on asking, may deny the presence of continuous headache. However, the patients with HC will have some form of headache even at the time of reporting to physicians. So, you can ask “Do you have headache right now”. If the answer is “yes”, it can be presumed that the patients may have continuous background headache. After saying “yes”, many patients accept such mild continuous type of headaches in the past or between two attacks. Even if there is any doubt, one can wait for a few days to see prospectively whether there is continuous pain. Therapeutic response to indomethacin will confirm the diagnosis.

## Diagnosis by management

Response to indomethacin is a must for HC. Oral indomethacin should be started to see the response. Intramuscular indomethacin 50–100 mg (INDOTEST) has been suggested as a diagnostic test for HC and PH.<sup>43</sup> Complete response usually occurs within 2 hours (mean 1.2 hours). Its role in atypical cases of HC may be very important. However, a few authors suggested that it can be a test of choice for chronic unilateral headache.<sup>44</sup> Unfortunately, injectable indomethacin is not routinely available in every part of the world. Therefore, a therapeutic oral trial must be performed.

## Management Indomethacin

A “complete” response to indomethacin is as “sine qua non” for HC. It is usually started at a dose of 25 mg three times a day (tid). The drug is gradually titrated (25 mg tid every 3–5 days) up to 100 mg tid or until the patient gets complete relief.<sup>29</sup> The dose required ranges from 25 to 500 mg/day.<sup>6,14</sup>

The mean indomethacin dose varies between 94 and 176 mg/day in various case series<sup>6,8,14</sup>

It is said that response to indomethacin is immediate and complete. Several earlier case reports mentioned immediate response.<sup>44</sup> However, this part has not been studied much. There is just one case series that mentioned the time interval between administrations of indomethacin and a complete response.<sup>29</sup> Only 10% patients showed a complete response within 24 hours. A total of 43% patients showed complete response in a week. A few patients showed a marked response within a few days of starting treatment, but the complete response was noted only after 4 weeks.<sup>29,45</sup> In a series of 39 patients reported by Cittadini and Goadsby, at least 15 patients received  $\geq 225$  mg indomethacin. This dose (after titration) must have been given over 6–10 days. Therefore, we can presume that a large number of patients took more than 1 week to show complete response. All chronic painful conditions, including chronic headache, produce significant morphological changes in the pain matrix.<sup>46</sup> Therefore, any chronic pain syndrome may lead to incomplete or delayed response to a specific drug. Therefore, HC with a very long history may take more time to show a complete response.<sup>46</sup>

A long-term follow-up study on 16 patients with HC suggests that ~60% patients with HC may require a lower dose of indomethacin with the passage of time.<sup>47</sup> Moreover, 15% patients may have relapsing–remission course. Therefore, a gradual reduction in the dose is recommended every 3–6 months.<sup>29</sup> Dose reduction should be performed by 25 mg every 3 days, until either the pain reappears or the patient gets completely off indomethacin. In this way, we can find out the remission phase of the patient or the lowest possible dose for a particular patient. There are a few case reports where HC symptoms remained controlled with 25 mg daily or 25 mg every alternate day. A sign of tolerance (tachyphylaxis) to indomethacin has not been reported in patients with HC.

Skipping of the drug leads to an immediate appearance of the symptoms. This is also a very characteristic feature of HC. Antonaci and Sjaastad<sup>44</sup> suggested that its diagnostic value (i.e., reappearance of headache after skipping of indomethacin) is stronger than INDOTEST itself.

## Alternative drugs for HC

Indomethacin is not a very safe drug for long-term use. Incidence and prevalence of indomethacin-related side effects in patients with HC vary between 20% and 75%.<sup>14,48</sup> Various drugs and other interventions have been tried in patients who developed various indomethacin-related side effects.

**Table 8** Drugs other than indomethacin producing complete response in patients with HC

| Drugs   | Number of patients | Effective dose (mg/day) |
|---|--------------------|-------------------------|
| Topiramate <sup>14,20,28,29,31,48,101,102</sup> | 16                 | 100–200                 |
| Cyclooxygenase-2 inhibitors                     | 15                 |                         |
| Rofecoxib <sup>11,37,39,103,104,105</sup>       | 8                  | 50–100                  |
| Celecoxib <sup>103,106</sup>                    | 7                  | 200–600                 |
| Corticosteroid (MPS) <sup>14,29,107</sup>       | 14                 | Oral–injectable         |
| Ibuprofen <sup>29,25,108</sup>                  | 9                  | 600–2400                |
| ASA <sup>5,8</sup>                              | 8                  | 1400–2800               |
| Gabapentine <sup>28,109,110</sup>               | 7                  | 900–3600                |
| Melatonin <sup>49,111–113</sup>                 | 6                  | 6–9                     |
| Piroxicam derivative <sup>23,28,114</sup>       | 6                  | 20–60                   |
| Amitriptyline <sup>28</sup>                     | 6                  | 25–75                   |
| Acemethacin <sup>115</sup>                      | 3                  | 90                      |
| Verapamil <sup>100,116</sup>                    | 2                  | 120                     |
| Methysergide <sup>14</sup>                      | 1                  | *                       |
| Nimesulide <sup>11</sup>                        | 1                  | *                       |

**Notes:** \*Dosing details not available.

**Abbreviations:** ASA, acetyl salicylic acid; HC, hemicrania continua; MPS, methylprednisolone.

Table 8 summarizes the various alternative drugs used in HC patients. Various drugs have been found effective in case reports or open-label studies. The COX-2 inhibitors (celecoxib and rofecoxib), piroxicam derivative and topiramate are the main drugs found to be effective in patients with HC. However, the effects of all these drugs are not uniform and consistent in each patient. It is difficult to predict which patient will respond to these drugs.

However, celecoxib and rofecoxib should be used with great precaution because of the increased risk of vascular events (myocardial infarction and strokes). Glaucoma, renal stones and depression are some problematic side effects with topiramate, and patients should be monitored for it. Melatonin can also be an option in indomethacin-tolerant patients. In a few patients, it may produce complete relief of pain. However, in other patients, addition of melatonin may allow 45% patients to reduce the dose of indomethacin.<sup>49</sup>

Table 8 included only those cases where response was either complete or excellent. However, there are several cases in the literature where these drugs were partially effective. Apart from these drugs, there are several other drugs (such as lamotrigine, lithium, naproxen and paracetamol with caffeine) that have provided marked (although partial) effect on some patients with HC. It can also be tried before subjecting the patient for interventional therapies.

We know that the reappearance of headache after skipping of indomethacin is a stronger clinical characteristic of HC. Therefore, immediate reappearance of HC will occur even with these effective drugs. A large number of patients

with HC may receive these drugs unknowingly (without a correct diagnosis of HC). In clinical practice, we note several patients with strictly unilateral headaches who complain “they got a response as long as the drugs are continued”. They may further say “headaches reappear immediately when they stop taking effective drugs”. A possibility of HC is here, as no other headache reappears so fast on withdrawal of the effective drugs.

## Surgical interventions

Several surgical approaches have been tried in patients with HC who could not tolerate indomethacin for a long term.

### Peripheral nerve block

In earlier observations, there was no positive influence of nerve block in HC patients. There was only partial response to supraorbital nerve (SON) in a few patients in Antonaci et al's<sup>50</sup> series. Only one patient (out of seven) showed complete response in Afridi et al's<sup>51</sup> series. In Cittadini and Goadsby's series, nerve block was performed in greater occipital nerve in 23 patients. Approximately one-third responded to greater occipital nerve (GON) injection.<sup>14</sup>

Recently, Guerrero et al<sup>34</sup> reported nine patients with HC who received GON, SON, trochlear nerve or a combination of SON and GON blocks. Each patient had some tenderness over the represented peripheral nerves. Injections were chosen based on the tenderness. Five patients showed a complete response, while the rest had a partial response. The response started immediately after the block and persisted from 2 to 10 months. Repetition of blocks resulted in prolonged effects. The authors suggested that peripheral nerve block will be more effective if local tenderness is considered before the block.

### Sphenopalatine ganglion (SPG) block

Very recently, Androulakis et al<sup>52</sup> have shown an effect of repetitive blocks of SPG. Initially, it was performed twice per week. This was followed by maintenance treatment every 4–5 weeks. It produced significant (not complete) improvement on each occasion.

### Radiofrequency ablation

Beams et al<sup>53</sup> have demonstrated positive effects of radiofrequency ablation of the C2 ventral ramus (one case), C2 dorsal root ganglion (two cases) and SPG (one case). The response after each radiofrequency procedure was long lasting and it persisted from 1 to 2.5 years. Weyker et al<sup>54</sup> used radiofrequency ablation of the SON in three patients

with HC. Radiofrequency ablation showed complete relief of headache at 7–12-month follow-up.

### Occipital nerve stimulation (ONS)

ONS is an effective treatment for various intractable primary headache disorders. Schwedt et al<sup>55</sup> first examined the role of ONS in a patient with HC. The patient had significant improvement in pain (although not complete). However, the patient had episodes of cranial autonomic manifestation without headache. Schwedt et al<sup>56</sup> treated two more patients by ONS. There was a marked reduction in headache frequency and pain intensity. However, both patients developed complications that include stimulator lead migration and infection.

Burns et al<sup>57</sup> treated six patients with a newer wireless stimulator device (Bion). In this crossover study design, the Bion was on for 3 months, off for the fourth month and on again during the long-term follow-up. Four patients reported substantial improvement (80%–95%) and one noted a 30% improvement. The onset of the benefit was delayed by days to weeks, and the headaches did not recur for a similar period when the device was switched off. Recently, Miller et al<sup>58</sup> treated 16 patients by ONS in an open-label prospective study. The mean monthly moderate-to-severe headache days fell by 48.9%. A favorable response (>50% reduction in monthly moderate-to-severe headache days) was observed in 50% patients.

### Vagus nerve stimulation (VNS)

Nesbitt et al<sup>59</sup> and Eren et al<sup>60</sup> assessed the effect noninvasive VNS device in patients with HC. The patients were asked to stimulate the left vagus nerve in the neck with a transcutaneous vagus nerve stimulator. There was a reduction in pain intensity immediately after the stimulation in all three patients. Some more observations are required before it could be suggested for HC.

### Botulinum toxin

There are a total of three case reports or series in the literature.<sup>61–63</sup> In the first case, the patient showed marked improvement (not complete) in headache days by trimestral injections. However, episodes of cranial autonomic occurred even in the absence of pain.<sup>61</sup> Khalil and Ahmed<sup>62</sup> reported another patient with HC, where the response was complete that persisted for ~10–12 weeks. Recently, Miller et al<sup>63</sup> reported nine patients with HC who were treated with multiple sessions of onabotulinumtoxin A injection. Five subjects had a response of ≥50% reduction in moderate-to-severe headache days to mild headache days or pain-free state. The median reduction

in total headache days was 90% and in moderate-to-severe headache days 80%. The median duration of response of the five responders was 11 weeks. However, more studies are necessary before it could be recommended for HC.

## Future perspective

Wide heterogeneity in clinical features and marked variability in therapeutic responses to various drugs in patients with HC suggest that several things are still to be explored. There are no uniformly accepted diagnostic criteria for HC. No case studies have yet been published based on the recent ICHD-3β criteria (2013).

Migraine and TTH have alternative criteria in the appendix section of ICHD-3β. There is a need for alternative diagnostic criteria even for the most controversial primary headache disorder (HC), so that its various aspects can be explored in different clinical and epidemiological settings. We have suggested more accommodating type criteria for appendix section.<sup>14</sup>

Cranial autonomic features, agitation and response to indomethacin are three important issues in the diagnostic criteria. Agitation was not the part of earlier criteria. It was first included in Cittadini and Goadsby criteria (2010)<sup>14</sup> and later on in Prakash and Golwala criteria (2012)<sup>29</sup> and now in ICHD-3β criteria (2013).<sup>1</sup> In ICHD-3β criteria, agitation and cranial autonomic features have been put together and only one of these two features is required for diagnosis purpose.

The most debated issue is about the response to indomethacin. It was “not a must” in the Goadsby and Lipton criteria (1997).<sup>64</sup> However, since ICHD-2 (2004), it is a “must” feature.<sup>4</sup> Several cases of indomethacin-resistant HC had been published before 2004. However, there was a sudden quietness in the reporting of indomethacin-resistant HC in the literature after 2004 till Marmura et al<sup>65</sup> and Prakash and Golwala<sup>29</sup> reported several cases with HC phenotype but with no or minimal response. In a review, we noted underreporting (or no reports) of indomethacin-resistant HC.<sup>66</sup> There are several authors who in principle accept a possibility of indomethacin-resistant HC.<sup>66</sup> Moreover, the word “complete” is also debatable. There are several cases with marked/excellent response to indomethacin. But it cannot be classified as HC according to current criteria. Chronic painful conditions, including chronic daily headache, are known for their refractoriness (or partial response to various drugs).

We suggested (Prakash–Golwala criteria; Table 9) that the presence of any two of the following is enough to make a diagnosis of HC: 1) cranial autonomic features, 2) a sense

**Table 9** Prakash and Golwala criteria (modified) for HC

| A Headache for >3 months fulfilling criteria B–D |   |
|--|---|
| B  | All the following characteristics:  |
| 1  | Unilateral orbital, supraorbital or temporal pain without side shift  |
| 2  | Daily and continuous, without pain-free periods   |
| 3  | Moderate intensity, but with exacerbations of severe pain   |
| C  | At least two of the following:  |
| 1  | At least one of the following autonomic features occurs during exacerbations and ipsilateral to the side of pain: |
| 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  |
| h)   | Feeling of sand in eye  |
| 2  | A sense of restlessness or agitation, or aggravation of the pain by movement                                      |
| 3  | Headache resolves or greatly improves to therapeutic doses of indomethacin  |
| D  | Not better accounted for by another ICHD-3 $\beta$ diagnosis  |

**Note:** Copyright ©2012. Sage Journals. Adapted from Prakash S, Golwala P. A proposal for revision of hemicrania continua diagnostic criteria based on critical analysis of 62 patients. *Cephalalgia*. 2012;32(11):860–868.<sup>29</sup>

**Abbreviations:** HC, hemicrania continua; ICHD-3 $\beta$ , International Classification of Headache Disorder, third edition.

of restlessness during exacerbations and 3) a response to indomethacin.

ICHD-3 $\beta$  criteria for HC did not mention the site of pain.

As sites of pain in HC are comparable to that of CH, PH and SUNCT/SUNA, it should be included even for HC.

As suggested earlier, feeling of foreign body sensation in the eye (or sand in eye sensation or itching eye) is very specific and a common CAS. We suggest to include it in the diagnostic criteria of HC as a part of CAS.

We think that current ICHD-3 $\beta$  criteria are still restrictive. As clinical features, therapeutic options and many other aspects are still to be defined in patients with HC, we suggest more accommodating and broader criteria (at least in the appendix section of ICHD-3 $\beta$ ; Table 9). Broader criteria will inspire clinician/researchers to study such type of headaches, and it would provide a broader view of HC and HC-like headaches. We suggest large prospective or retrospective studies from multiple centers to validate the different criteria proposed for HC.

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## Author contributions

SP and PP were involved in the conception and design of the review. SP and PP were involved in the acquisition of data. SP

was involved in the manuscript preparation. PP was involved in revising the draft for intellectual content. Both authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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