

Why is it important to diagnose hemicrania continua?

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Abstract

Hemicrania continua (HC) is an indomethacin-responsive primary headache which belongs to the trigeminal autonomic cephalalgias. Although the first description of HC was 35 years ago, there are still different views regarding the clinical course, the diagnostic criteria, and the treatment. The high clinical heterogeneity of HC, missed diagnosis, and the delay to the correct diagnosis are important in patient care. Central features of HC are continuous side-locked headaches (with superimposed exacerbations) and the response to indomethacin. We are describing the case of a 29-year-old woman who developed right-sided headache 3 weeks after the excision of a right-sided vestibular schwannoma. She tried different painkillers and also was started on a prophylactic treatment with oxcarbazepine, acupuncture, and physiotherapy. But nothing really helped. She was then admitted for an inpatient withdrawal program for medication overuse headache. Again the pain did not change. She has then been treated with indomethacin 50-mg tds, where after the headache improved rapidly within 3 days. This educational case presentation and review of the literature aims to consider HC as a possible differential diagnosis in chronic headache, especially when side-locked and shows that indomethacin maybe a quick therapeutic option before putting the patients on a long treatment odyssey with analgesics and other drugs.

Keywords

Hemicrania continua, indomethacin, continuous side-locked headaches

Introduction

Hemicrania continua (HC), according to the definition of the International Headache Society, is an indomethacin-responsive primary headache disorder classified among the trigeminal autonomic cephalalgias (TACs), along with cluster headache (CH), paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing, and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms.¹

Thirty-five years after the first description of HC, the clinical features, the clinical course, the diagnostic criteria, and the therapeutic measures are still discussed. A pathophysiological mechanism similar to the other trigeminal-autonomic cephalalgias has been suggested.²

As in others TACs, HC is defined as strictly unilateral pain in the trigeminal distribution, with cranial autonomic features on the respective side and with or without restlessness/agitation during exacerbation or attacks. In contrast to other TACs, patients with HC usually have a continuous

background headache with superimposed moderate or severe exacerbations.¹ In the last 20 years, the diagnostic criteria have been repetitively modified (see Table 1).¹ Furthermore, restlessness has been added to the criteria.¹

Prakash and Patel² found 171 articles until 2017 addressing at least one case of HC. From the total of 1002 cases with HC, more than 900 have been reported after 2001. Epidemiologically HC represents around $1.7 \pm 0.4\%$ of all headaches seen in specialized headache centers or neurology outpatient clinics. Some clinical authors suggest that HC might not be uncommon but underdiagnosed, mostly due to the variety of its pain severity and other symptoms.³

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Table 1. Diagnostic criteria of hemicrania continua (ICHD-3, 2018).

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- A. Unilateral headache fulfilling criteria B to D
 - B. Headache 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. 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
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The same authors suggest that HC might be the second most common TAC in the clinical setting.^{2,3} Overall, HC has been described to be the fourth most common cause of side-locked headache, after CH, side-locked migraine, and cervicogenic headache.⁴

Case description

A 29-year-old woman came to our neurology department with right-sided head pain of 8–9/10 NRS. It had started about 3 weeks after the excision of a right-sided vestibular schwannoma (using a retrosigmoidal extirpation approach). First manifestation was noticed about 3 weeks after the head surgery when a severe headache started in the right occipital region.

She didn't report any headache before the schwannoma surgery but had suffered from transient equilibrium issues, especially in the dark, as well as progressive hearing loss on the right. The vertigo continued to some degree also after the surgery. During the first month, the patient could control the pain using up to 800-mg ibuprofen and 500-mg acetaminophen daily. As the pain became more severe, she started to take metamizole 500 mg twice per week in addition. Later also diclofenac and oxcarbazepine were tried. The patient tried to relieve her pain by doing light exercises, walking, hiking, running, biking, without sufficient relief. Also, acupuncture and physiotherapy did not help to reduce the pain. Coffee did not help either.

Three months after the surgery the pain became much stronger and started with exacerbations. During these episodes, she had lacrimation and rhinorrhea. In the same time, she started to feel an urge to be more active, she did a lot of sport. In the next 4 months, she had alternating phases of severe and less severe headache, with a severe exacerbation after a session of swimming.

Cooling the head with cold packs was somewhat helpful. She was seen in another hospital, where the continuous throbbing headache was diagnosed as medication overuse headache. As neither the reduction of pain nor a withdrawal

of analgesics was achieved, the patient was referred to our rehabilitation clinic where she started a multimodal, interdisciplinary, headache specific rehabilitation program.⁵ Again the pain did not decrease within the first weeks of analgesic withdrawal. Assuming a diagnosis of HC, we started a treatment with indomethacin up to 50-mg tds orally. The headache improved rapidly within 3 days, and the patient became pain free.

At the 1-year follow-up, she still reported an absence of headaches on a daily dose of 150 mg of indomethacin. She did not have any adverse events from the treatment. A trial to reduce the dose by 25 mg resulted in a slight increase of half-sided head pain on the right side.

Discussion

A missed diagnosis or a delay toward the correct diagnosis may be pivotal in patient care. Mainly this is due to a high heterogeneity of HC. A mean delay of 8 ± 7.2 years with a range between 1.3 years and 21 years has been reported.⁶ Continuous background headaches (with superimposed exacerbations) and the response to indomethacin are the central features of HC. It looks like ignoring the continuous background headache and focusing on the exacerbation—sometimes even with migrainous features—may be an important reason for HC misdiagnosis.¹ Seventy percent of patients may fulfill diagnostic criteria for migraine during exacerbations.² The “migrainous features” include nausea, vomiting, photophobia, and phonophobia. They may be common in HC with a mean prevalence of 56% (at least one feature), with a range between 17% and 90%.⁶ There is a slight preference for the right side 53% versus 45% for the left side, and very few patients (2%) report a side-shift, which seems to be located mostly in the first trigeminal branch (V1).⁶ The pain character and the intensity of pain might play a very important role in the diagnostic evaluation and may include dull background pain (similar to tension-type headache). Some patients report throbbing (pulsating) or stabbing pain characteristics, more compatible with migraine. Background pain intensity was found to be mild to moderate, that is, 3 to 5 on a 0–10 numeric rating scale.² Only few patients report severe headaches, with intensities greater than 7/10. The pain during exacerbations was on average 9/10, with a range from 5/10 to 10/10. Many patients (49%) considered this pain as the “most painful condition they had ever experienced,” and compare it to childbirth, a fractured bone, toothache, or burns. Duration and frequency do not follow any specific pattern and may indeed vary considerably from one exacerbation to the next. The mean duration of exacerbation is around 30 min but may vary from a few seconds up to 2 weeks. Nocturnal exacerbations are common in HC.

During the exacerbation, the ipsilateral cranial autonomic signs (CAS) are more prominent and may include lacrimation, conjunctival injection, rhinorrhea, nasal congestion, eyelid edema, and ptosis. The mean

prevalence of at least one of these features is 74% in HC, varying in different studies between 59% and 100%. Tearing was the most common cranial autonomic feature with a range of 36–77%.^{3,6} The presence of CAS is often denied by the patients and only observed in objective assessments. Another important and specific feature of HC is the sensation of a foreign object in the eye (“sand in the eye” or “itching”).⁶

Of course, indomethacin may have an unspecific effect on pain and any other primary or secondary headache. One could also argue that the phenotype of persistent headache after craniotomy may be variable.⁷ Still, in our case, other unspecific NSAIDs did not touch the pain, and the analgesics were even thought to be the cause rather than the consequence of the pain. Technically, the headache does not fulfill the criteria of a persistent headache after craniotomy, as the start was not within 7 days. However, this may be disputable from a pathophysiological point of view. All in all, the phenotype was rather typical for hemicranias continua, fulfilling all the criteria, including a total response to indomethacin.

From the pharmacological point of view, indomethacin belongs to the group of NSAIDs. Compared to ibuprofen and naproxen, it has the highest rate of penetration through the blood brain barrier, which may help to explain its specific efficacy in this type of headache. The difference in the mechanism of action of indomethacin as compared to other NSAIDs is still unknown. There are some indications that indomethacin might inhibit the vasodilation induced by nitric oxide. Ackerman et al. reported a more pronounced effect of indomethacin in dural vasodilation as compared to ibuprofen and naproxen, in a concentration resulting from doses typically used for HC therapy.⁸ The property of indomethacin to directly inhibit the NO production in rat microglia has been reported.⁹ This could be seen as a potential protective anti-headache mechanism within the nociceptive structures of the head (trigeminovascular system).¹⁰

Some authors recommend the INDOTEST with 50–100 mg indomethacin i.m. in blinded application as a useful tool in the diagnosis of HC and CPH.¹¹ In this study, the headache disappeared on average within 73 ± 66 min after a dose of 50-mg indomethacin with a pain free period of about 13 ± 8 h and within 13 ± 10 h after an injection of 100 mg.¹¹ It has been suggested that the use of 50-mg indomethacin may be the best suited for HC diagnosis purposes and that the difference in dosage and response time for pain relief might be less important being influenced by the “bioavailability and individual sensitivity.”¹²

HC should be considered in side-locked chronic headaches, and indomethacin might be tried prior to other analgesics or prophylactics. Also in other headache diagnoses, such as chronic migraine with or without medication overuse, HC might be an underestimated differential diagnosis that should be kept in mind.

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