Hemicrania Continua

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Unilateral throbbing headaches may present similar signs and symptoms as dental pathology and are a diagnostic challenge for dental practitioners. Cases may be seen with a primary complaint of unilateral pain or referred by medical colleagues for exclusion of dental causes. In the present article the authors add a new case of hemicrania continua (HC), which is one such unilateral headache, and review the previously published cases. HC is relatively easy to treat since it responds completely to treatment with indomethacin. However, as is presented in this case, HC may masquerade as dental pain. Cases secondary to trauma, systemic disease, and nervous system pathology have been described in the literature, and the clinician must exclude these possible causes. A thorough knowledge of this entity is therefore essential.
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The International Headache Society (IHS) criteria[1] classify primary headaches as migraines, tension-type headaches, cluster headaches, paroxysmal hemicranias, miscellaneous headaches unassociated with a structural lesion, and cranial neuralgias. Since its adoption in 1988 this classification system has been central in unifying diagnostic and research criteria in the field of headache and facial pain. Recently, a revision of the IHS classification has been suggested that would further categorize daily headache.[2,3] In spite of disagreement as to whether such new classification is needed,[4] the concept of chronic daily headaches has gained wide acceptance.

The daily headaches have been grouped under primary chronic daily headache (PCDH) and include transformed migraine (TM), chronic tension-type headache (CTTH), new daily persistent headache (NDPH), and hemicrania continua (HC).[2] Although there are still nosologic differences and some disagreement on precise inclusion criteria,[3,5,6] the general consensus seems to be that TM refers to daily or nearly daily pain that must have evolved from migraine. TM may be unilateral or bilateral and ranges from moderate to severe in intensity. The diagnosis of NDPH is recommended for patients with daily headache with strictly no history of episodic migraine or episodic tension-type headache (ETTH). The diagnosis of CTTH is reserved for patients with daily bilateral headache evolved from ETTH. HC is a rare indomethacin-responsive unilateral headache characterized by fluctuating but continuous, moderate pain. This headache is discussed in detail below. Since all patients with daily pain have a tendency to abuse analgesics, the above subtypes are further divided into cases with or without drug abuse. Field-testing of the suggested criteria has

shown that they are able to accurately classify most cases of PCDH.[7,8]

Although chronic daily headache is common in pain clinics, HC is rarely encountered. In a recent study,[7] 45% of 171 patients with a primary complaint of headache were diagnosed as suffering from PCDH; 62% of them had TM, 34% had CTTH, 2.6% had NDPH, and only 1.3% were diagnosed with HC.

The first 2 cases of HC were reported in 1984.[9] Based on our literature search and 2 published reviews[10,11] we have found a total of 39 cases reported in the English-language literature.[10–23] In the present article we add 1 new case and review all 40 cases.

Case Report

History

A 30-year-old female was seen for a complaint of pain on the right side of the face and head that had begun approximately 2 years previously as a continuous headache. The intensity of the pain was usually moderate (5 to 6 on a verbal scale of 0 to 10) but the patient described occasional exacerbation of severe headache (graded as 7 or 8). The headache was present all day and the exacerbation did not have a "jabbing" quality. A throbbing, pressure-like quality was associated with the pain, which sometimes awakened her from sleep, usually in the early morning. No autonomic or systemic signs accompanied the pain. Pain was also felt unilaterally in the mouth and affected the area around the maxillary first and second molars. Dental treatment in this area had been ineffective in relieving the pain. Paracetamol in doses of 1 to 2 g provided partial relief.

The patient had undergone clinical neurologic, otolaryngologic, and dental examination, with no relevant findings. Hematologic and biochemical blood screening were within normal limits. Computerized scanning of the head, paranasal sinuses, and temporomandibular joints (TMJs) showed no pathology, and dental radiographs disclosed no relevant findings. Results of Doppler examination of carotid blood flow were normal.

Past treatments had included propranolol, diazepam, ergotamine combinations, and intensive physiotherapy, with no substantial improvement. Diclofenac sodium had initially reduced pain intensity but had become ineffective within approximately 10 days.

Examination

Physical intraoral and extraoral examination including neurological assessment of cranial nerves was normal. There was some mild masseter, temporalis, and suboccipital muscle tenderness ipsilateral to the pain, but there was no limitation of mouth opening or neck movement and the patient reported no other muscular dysfunction.

Treatment

Because of the combination of musculoskeletal and vascular-type features, treatment was initiated with amitriptyline, starting at 10 mg and increasing to 35 mg at bedtime. The patient was requested to fill out a daily pain diary that included assessment of intensity on a 10-cm visual analog scale (VAS). Four weeks later, the patient was seen again and reported no change in pain frequency or intensity. Further interview and analysis of the pain diary revealed features that suggested a diagnosis of HC continua. In summary, the pain was:

1. Unilateral, including half the head and face
2. Continuous, with a throbbing, sometimes pressure-like, quality
3. Fluctuating, from moderate to severe
4. Not accompanied by autonomic signs
5. Able to waken the patient

In view of this, indomethacin treatment was initiated at 75 mg daily in 3 doses, and the patient received instructions to reduce the amitriptyline to 10 mg daily. Because of past gastrointestinal upsets with non-steroidal anti-inflammatory drugs (NSAIDs), the patient was prescribed 200 mcg misoprostol with each dose of indomethacin. At her next review appointment, 3 weeks later, the patient reported considerable reduction in pain intensity (measured by VAS) and frequency on 50 mg indomethacin (she was reluctant to increase the dose to 75 mg). Relief had begun rapidly, and within 2 days she was essentially pain-free. Fig 1 summarizes the pain intensity data and shows clearly that within 1 week the mean VAS score was reduced from 6 to 2. Gastrointestinal symptoms had been avoided with the misoprostol, but since the patient's health insurance did not cover this drug, the patient was continued on omeprazole 20 mg daily. At the next review appointment, the patient had continued pain relief and reported that she had tried to reduce the indomethacin to 25 mg daily but had begun suffering headaches and had returned the

dosage to 50 mg daily. Follow-up until 18 weeks revealed continued pain relief (see Fig 1).

Discussion

General Characteristics

The following features are based on 40 published cases, summarized in Table 1.

Pain Features. Pain severity was graded as moderate by most patients and is demonstrated in the plot of mean weekly VAS ratings in our patient (Fig 1). Although the pain may be long-lasting or continuous, it is characterized by fluctuations in severity; this was noted in 30 (75%) of the cases. Exacerbation from baseline pain could result in severe pain that lasted for 5 to 10 hours but sometimes continued for 2 to 5 days. The pain was described as throbbing in 15 cases (37.5%) and could be a constant feature of the pain or appear only when pain intensity increased. Strong exacerbation of pain lasting from 30 minutes to 10 hours has also been reported.[11] Pain that awakened the patient was described by 20 subjects (50%), and some patients reported that if they were awakened for other reasons the pain was invariably present.

In addition, many patients reported a sharp pain similar to the condition of "jabs and jolts." This was reported in all the cases reviewed by Bordini et al in 1991,[10] and we found clear reports of short, sharp, stabbing pain in a further 8 patients.[11,21,24,25] It seems therefore that this is an important feature of the pain syndrome.

Temporal Pattern. Two forms of HC have been described: remitting and continuous. The remitting form is characterized by headache that can last for some days followed by a pain-free period lasting from 2 to 15 days; this was seen in 21 of the 40 subjects. Ten patients (25%) remained in the remitting form, and over time 11 had become continuous (28%). In 19 of the 40 cases (47.5%), the pain had been continuous since its onset. In the cases that had begun as remitting and transformed to continuous, the mean remitting duration was 7.8 years (range 1 month[15] to 30 years[18]). One case has been reported where a continuous form of HC transformed into the remitting type.[26] Thus, although over 50% of cases begin as remitting, the late continuous/remitting pattern ratio is 2.6:1.

Demographics. Twenty-seven of the 40 cases reported were women (female:male = 2:1). The mean age of onset was 32.2 years (range 8 to 58 years; Fig 2) with a delay of nearly 10 years until diagnosis (mean age ± standard error [SEM] at presentation 41.75 ± 1.9 years). We found no significant difference in onset age between cases that had begun as remitting (mean ± SEM = 31.65 ± 2.8 years) and those that had begun as continuous (mean ± SEM = 32.8 ± 2.8 years).

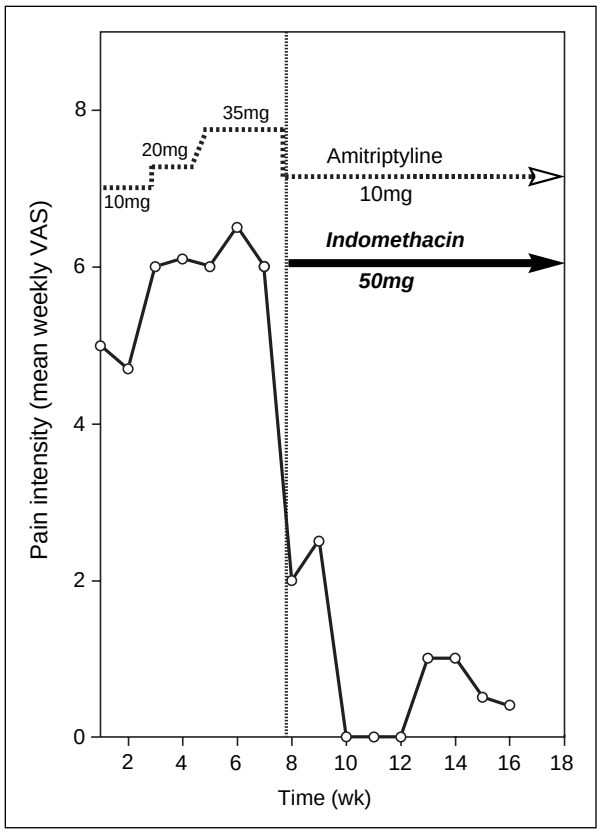

Fig 1 Data obtained from the present patient's pain diary. Daily assessments of pain with a visual analog scale (VAS) were converted to mean weekly VAS assessments. The arrows above the graph depict the drug schedule. The dotted line shows the dose of amitriptyline, which reached 35 mg daily but was totally ineffective. The bold arrow indicates treatment with indomethacin. The response was rapid, and within 48 hours of 25 mg twice daily, the patient was pain-free most of the time.

Location. The vast majority of cases have been unilateral (n = 37) with no definite side preponderance noted.[10] Only 4 cases have been reported as bilateral[11,13,15,22]; 2 of these developed from an originally unilateral pain, and pain intensity was consistently higher on the originally painful side. Although rare, pain can also change sides.[24]

Pain is generally felt in the frontal and temporal regions,[10,11] including the area around the eye. Some patients have described a distinct ocular sen-

Table 1 Diagnostic Features of Hemicrania Continua: Incidence (Shown in Parentheses) in 40 Published Cases

Pain	Moderate to severe
Laterality	Unilateral (92.5%) Changes sides rarely
Duration	Continuous: months to years (75%) Remitting: hours to days with pain-free periods (25%)
Location	Orbital/periorbital Temporal
Character	Throbbing (37.5%), sudden sharp pain (62.5%), fluctuating (72.5%), wakes patient (50%)
Triggers	Alcohol (17.5%), odors, etc (similar to migraine triggers)
Associated features	Rare Nausea (40%), phonophobia (30%), photophobia (40%), conjunctival injection (32.5%), tearing (27.5%)
Treatment response	Absolute to indomethacin Partial to other NSAIDs

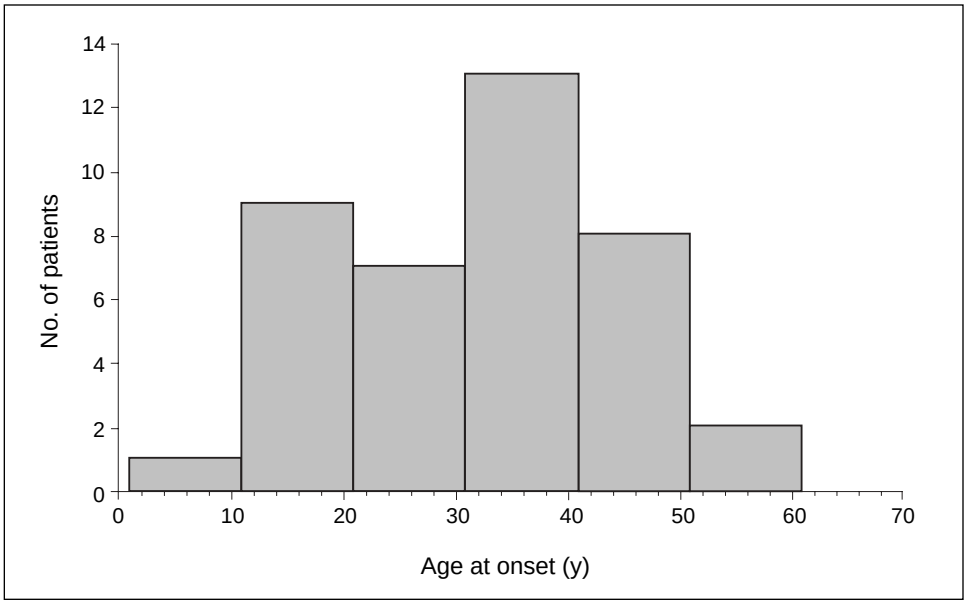

Fig 2 Distribution of onset age in 40 cases of HC. Peak onset is between the ages of 30 to 40 years.

sation, mimicking a foreign body (eg, sand), that may accompany[10] or precede the headaches.[21] Although in the first review[10] this phenomenon was noted in almost one-third of patients, we found only 7 of 40 cases (17.5%) with a clear reference to ocular discomfort.

Accompanying Phenomena. There is usually an absence of autonomic signs that accompany the continuous pain. However, during exacerbation, signs commonly appear singly or in various combinations, but are usually mild. Based on this observation, it has been suggested that activation of autonomic signs is dependent on pain severity.[20] The most common signs are photophobia (40%), nausea (40%), conjunctival injection (32.5%), phonophobia (30%), and tearing (27.5%). More rarely, nasal stuffiness or rhinorrhea (17.5%), vomiting (15%), or ptosis (15%) may be reported.

Precipitating or Aggravating Factors. A variety of factors, such as bending over,[9] menses,[10,14] strong odors,[18] physical activity,[23] and stress,[17] have been reported to provoke or worsen the pain. These are reminiscent of migraine triggers but are not a consistent feature of HC. Seven patients (17.5%) clearly identified alcohol as a provoking or aggravating factor.[10,14,16,22,24,27]

Physical and Laboratory Findings. HC is not usually accompanied by notable pathology or other abnormalities[10,11] and is exemplified by our patient. As in other published cases of primary

HC, computerized scanning of the head, neurologic and other physical examination, hematology, and serum biochemistry were within normal limits. However, the clinician must be aware that cases of HC secondary to pathology or systemic disease have been reported. These are reviewed below.

Pathophysiology

The relative rarity of HC has made it difficult to study its pathophysiology, which is incompletely understood. The sporadic appearance of autonomic features and the throbbing pain quality suggest that HC, at least partly, may share some mechanisms of vascular-type pains.[20] The possible roles of neurogenic inflammation and autonomic activation in vascular-type headaches and facial pains have been reviewed extensively,[20,28,29] so we will describe these only briefly. There is unequivocal evidence for the existence of sensory axons innervating cephalic blood vessels. Together they have been termed the trigeminovascular system.[30] Moskowitz has proposed that migraine pain is most often transmitted by these axons, especially intracranial perivascular sensory axons.[31] These trigeminal axons relay nociceptive information to the central nervous system, and when stimulated antidromically, promote a neurogenic inflammation. This occurs following the release of vasoactive peptides at the nerve endings by a calcium-dependent mechanism. These neuropeptides include substance P (SP), calcitonin gene-related peptide (CGRP), and neurokinin A; the most potent vasodilator is CGRP. The fibers releasing these neuropeptides are characteristic of C-fibers. Once released, the neuropeptides initiate a cascade of events, including mast cell degranulation and platelet aggregation. In the dura these events may be the cause of headache.[32] Such pain mechanisms are possible in other craniofacial pain syndromes. Thus, the pain in cluster headache may be associated with a perivascular inflammatory process of the internal carotid artery in its bony canal or, as supported by findings of increased intraocular pressure, within the confines of the eye.[33]

To investigate the possible role of the cranial vasculature in HC, orbital phlebography was performed in 6 diagnosed HC patients.[34] In only 1 HC case suffering from unilateral headache was an abnormality detected. In this case, narrowing of the ophthalmic vein occurred bilaterally and therefore is not specific to the painful side.

Other pathophysiologic possibilities have been investigated in HC. The role of the pain control system in a limited and mixed group of HC patients was studied by measuring pressure-pain thresholds, sural nerve reflexes, blink reflexes, and corneal reflexes.[35] A lowered pain threshold was found in HC patients compared to controls but may have been a result rather than a cause of long-standing headaches. At the trigeminal level (blink and corneal reflex), no differences were found. The authors concluded that, due to the small number of patients examined, the results should be viewed as non-conclusive.

Various autonomic parameters have been studied in cases of HC.[36,37] The major finding was a lack of pupillary dilation following instillation of tyramine (tyramine test), and did not differentiate between HC and chronic paroxysmal hemicrania (CPH) patients. In 1 HC patient the anisocoria (a condition in which the pupils are not of equal size) was prevented when the patient took indomethacin. These findings may indicate a subclinical ipsilateral sympathetic dysfunction. The heat and pilocarpine-induced sweating patterns in HC and CPH patients were symmetric between symptomatic and non-symptomatic sides.[38] The lack of experimental autonomic abnormalities supports the paucity of clinical autonomic signs.

Differential Diagnosis

Cluster Headache/Paroxysmal Hemicrania. Our patient suffered from unilateral, continuous, moderate, fluctuating pain not accompanied by autonomic signs. Cluster headache is usually an episodic excruciating headache with intense autonomic activation. Even when compared with the more similar remitting form of HC, the clinical characteristics and the absolute indomethacin response seen in HC should differentiate it from cluster headache. Moreover, cluster headache occurs predominantly in men (female:male = 1:5), while HC occurs mostly in women (female:male = 2:1).

An absolute indomethacin response is seen also in paroxysmal hemicrania (PH), also a unilateral headache seen mainly in women.[39] PH is a shorter headache (up to 30 minutes) that is more intense and accompanied by more autonomic signs than HC. Undoubtedly this is a difficult differential diagnosis and is based on a thorough knowledge of clinical signs and symptoms of both entities.

Cervicogenic Headache. Cervicogenic headache is a unilateral headache that originates in the neck or back of the head and spreads anteriorly to the frontotemporal area. Pain in cervicogenic

headache is usually episodic but may become chronic and accompanied by mild autonomic signs.[40] These clinical signs are similar to those seen in HC. However, in cervicogenic headache there are additional signs referable to the neck; these include restricted motion, occipital nerve tenderness, and radiologic signs of neck pathology that follow a history of trauma (eg, whiplash). A case was reported with typical indomethacin-responsive HC that required consistently high doses (225 to 275 mg/day) of indomethacin.[41] The patient finally underwent neck surgery for disc protrusion, which was causing C7 nerve compression; this resulted in a dramatic reduction in indomethacin requirements. This case stresses the similarities between the 2 headache types, but since the HC continued after surgery we assume both headaches occurred concomitantly. High indomethacin requirements should alert the physician to underlying pathology.

The clinical similarities between HC and cervicogenic headache[40,42] led to a therapeutic trial of anesthetic blockade of pericranial nerves (this usually relieves pain in cervicogenic headache) in HC.[43] No effect on pain was noted following greater or minor occipital nerve blocks, but a marginal effect was noted following supraorbital nerve block. This is the area where many HC patients feel pain, but further large studies will be needed to validate and then explain this finding.

Dental/Orofacial Pain. Pain that radiates to structures within the mouth is common in primary vascular-type pains.[39,44] Furthermore, the combination of throbbing pain that wakens the patient is highly suggestive of dental pain. The literature suggests that a high proportion (15% to 50%) of cases of primary vascular-type pain are confused with dental pain.[39,44–47] Our case had undergone dental treatment in an attempt to relieve the pain, and interestingly 1 HC patient who suffered severe pain described it as similar to toothache.[13] Although both HC and dental pain may be throbbing, dental pain is usually evoked. Even continuous dental pains such as occurs in dental abscesses, are aggravated by mastication, and have clear signs. Thorough clinical and radiologic dental evaluation will eliminate a dental cause in these cases.

One case described pain that referred to the jaw, ear, and mastoid[25] and could be confused with pain arising from temporomandibular disorders (TMD). However, although HC and TMD are both continuous, TMD rarely wake the patient from sleep or are throbbing in character.

Secondary Hemicrania Continua. *Pathology.* As in all headache patients, the clinician must be aware of the possibility of central or peripheral tumors inducing pain. A case that seemed a typical primary HC has been described that was successfully treated with indomethacin and then diagnosed as secondary to a mesenchymal tumor.[48] The tumor, located in the sphenoid bone, was inoperable and was treated with cytotoxics, inducing pain relief postoperatively for more than 2 years.

Medication Overuse. Three cases of HC complicated or caused by medication abuse have been reported.[49,50] In the first 2 cases, patients abused ergotamine (1 mg daily orally and 2 to 3 mg rectally) and acetaminophen (3 to 4 g/day).[50] Following cessation of the drugs, headaches were reduced but not eliminated, and indomethacin provided relief. However, in the third case the HC was clearly linked to analgesic abuse, and cessation brought resolution of HC.[49] As mentioned previously, medication abuse is common in chronic pain patients and the clinician must rapidly obtain control. At the very least, drug control will alleviate symptoms and reduce indomethacin requirements but potentially may eradicate the headaches.

Systemic Disease. Headaches in systemic disease are common. In a population of 115 HIV-infected patients, headache was found in 38% (44), and 66% (29) of these were primary.[51] In 13 patients with primary headache, the patients developed chronic daily headache, although this was not further classified. In a recent report, a patient with diagnosed HIV infection presented with typical HC that responded to therapy with indomethacin.[52] It seems, therefore, that daily headache is common in HIV-infected patients, and these may take the form of HC.

Macro-trauma. In 22% of the cases reviewed by Bordini et al in 1991,[10] there was a history of mild to moderate head trauma, and we found a further case of HC following mastoid resection.[24] Recently, 4 cases of HC appearing immediately after head trauma have been reported.[53] The patients met the IHS criteria for chronic post-traumatic headache and displayed clinical signs typical of HC. Furthermore, treatment with indomethacin, with doses up to 200 mg daily, was successful in all cases. However, in studies of post-traumatic headaches, HC has not been extensively reported,[54] suggesting that the secondary form of HC is as rare as its primary counterpart. In light of these recent cases[53] and the findings of Bordini et al,[10] post-traumatic HC should be included in the differential diagnosis of post-traumatic headaches.

Treatment

Indomethacin is usually totally effective in HC[10,11] and has been included as part of its definition[10] in spite of some cases being resistant. The results are usually very dramatic, with a rapid onset of relief[10,11] occurring within hours or 1 to 2 days.[55] This was seen clearly in our case (Fig 1). Due to previous gastrointestinal problems with NSAIDs, our patient began with 50 mg indomethacin daily and had such dramatic relief that she did not increase the dose any further. This may explain the slight fluctuation seen in weeks 13 and 14. A dose response was observed in our case: when the patient attempted to reduce the indomethacin dose to 25 mg daily, there was a rapid resumption of headaches.

When 50 mg indomethacin was given intramuscularly in 12 HC patients, complete pain relief occurred within 73 minutes and, interestingly, lasted for 13 hours.[56] The authors[56] suggested that this test be used diagnostically as the "Indotest." However, the occurrence of indomethacin-resistant HC is a possibility. Four cases have been reported (2 men, 2 women) where typical cases of HC did not respond to indomethacin.[57] However, the maximum dosage used was 100 mg of indomethacin daily, and the possibility remains that higher doses may have provided benefit, as has been reported in other cases.[11] We have adopted the following recommendations for a treatment schedule in HC[11]: Therapy should be initiated with indomethacin 25 mg 3 times daily. If no response is obtained within 7 days, the dose should be gradually increased to 50 mg 3 times daily. Higher doses are rarely required and may be a sign of underlying pathology.[41] Due to indomethacin's high rate of gastrointestinal side effects, concomitant misoprostol or an H2-receptor blocker is recommended.

Other NSAIDs such as aspirin,[10,16–18] ibuprofen,[58] piroxicam-beta-cyclodextrin,[25] and diclofenac (our case) have provided partial but sometimes adequate relief. Our patient also reported partial relief with the use of paracetamol, an observation that has been previously reported.[15] Following the case that responded well to piroxicam-beta-cyclodextrin,[25] an open study on 6 patients with HC was performed.[59] In 4 patients complete relief was observed, and although the authors concluded that piroxicam-beta-cyclodextrin is inferior to indomethacin in HC, the better tolerability of piroxicam-beta-cyclodextrin may offer a good alternative for selected cases.

Due to the similarities between HC and other vascular-type headaches (eg, cluster headache), treatment with serotonin agonists has been attempted. An open trial on 7 HC patients using 6 mg of subcutaneous sumatriptan has shown partial but clinically doubtful efficacy.[60]

Indomethacin Profile. Untoward symptoms are very common with the use of indomethacin. At therapeutic doses, 35% to 50% of patients experience unpleasant side effects (dose-related) and 20% may need to discontinue treatment. Short-term effects include gastrointestinal symptoms (anorexia, nausea, and abdominal pain). Dizziness and severe frontal headache occur in many patients (20% to 50%) on long-term therapy and therefore prevent its prolonged use.[61] Indomethacin is also relatively contraindicated in patients with asthma, anemia, and impaired hepatic or renal function.

Current knowledge of HC's possible pathophysiology has been reviewed above, and it is clear that due to its rarity the available data are scarce. However, we will briefly re-examine the possible mechanisms while drawing on indomethacin's effects and examining what is known about migraine and cluster headache, which are more documented and researched headache entities. The mechanism underlying indomethacin's absolute effect is poorly understood, but it seems that its efficacy is a result of more than the inhibition of cyclo-oxygenase. Other NSAIDs with effective antiprostaglandin actions are less effective in HC.[59] Indomethacin has inhibitory effects on the central nociceptive system[61,62] and may induce analgesia in headaches via this mechanism. Moreover, it has also been shown that indomethacin can reduce cerebral blood flow in experimental animals[63] and in humans by 25% to 35%.[64] Based on theories linking vasodilatation to vascular headaches,[31] it is likely that the therapeutic outcome of indomethacin in HC is also through this effect. Further in vitro research has demonstrated that indomethacin inhibits neuropeptide-induced vasodilation[65] and enhances endothelin-1-induced vasoconstriction.[66] These effects were less marked than that seen for aspirin, a drug that has not proven effective in HC, and therefore brings into question the exact role of vasodilatation in the pathophysiology of HC. Moreover, there is evidence that vascular-type headaches and vasodilatation are not always tightly coupled.[67,68] Therefore, dilatation need not be the cause of the pain.[68] Stimulation of sensory fibers projecting to intracranial vessels induces the release of vasodilating neuropeptides, which may then cause sec-

ondary vasodilation.[31,69] In this model the vasodilation is secondary to sensory neurogenic activation; therefore, effective antimigraine drugs may also act primarily by blocking neurotransmission. This effect has been shown for sumatriptan and ergot alkaloids,[70–73] but we have found no literature describing such an effect for indomethacin. In summary, there are as yet no proven pathophysiologic mechanisms associated with HC, and the absolute effect of indomethacin still remains to be elucidated.

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