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TUTORIAL

Focus on therapy: hemicrania continua and new daily persistent headache

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Abstract Hemicrania continua (HC) and new daily-persistent headache (NDPH) represent the only two forms of chronic daily headache in Chap. IV "Other Primary Headaches" of the second edition of the International Classification of Headache Disorders. HC and NDPH are rare and poorly defined from a pathophysiological point of view; as a consequence, their management is largely empirical. Indeed, there is a lack of prospective, controlled trials in this field, and treatment effectiveness is basically inferred from the results of sparse open-label trials, retrospective case series, clinical experience and expert opinions. In this narrative review we have summarised the information collected from an extensive analysis of the literature on the treatment of HC and NDPH in order to provide the best available and up-to-date evidence for the management of these two rare forms of primary headache. Indomethacin is the mainstay of HC management. The reported effective dose of indomethacin ranges from 50 to 300 mg/day. Gabapentin 600–3,600 mg tid, topiramate 100 mg bid, and celecoxib 200–400 mg represent the most interesting alternative choices in the patients who do not tolerate indomethacin or who have contraindications to its use. NDPH is very difficult to treat and it responds poorly only to first-line options used for migraine or tension-type headache.

Keywords Hemicrania continua · New daily persistent headache · Chronic daily headache · Therapy · Management

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Background

Hemicrania continua (HC) and new daily-persistent headache (NDPH) represent the only two forms of chronic, daily headache in Chap. IV "Other Primary Headaches" of the second edition of the International Classification of Headache Disorders (ICHD-II) [1]. The chronic temporal pattern differentiates these two forms from the other types included in Chap. IV, which are episodic and/or short-lasting headache and rarely require a prolonged treatment.

Hemicrania continua (HC) and NDPH are rare and poorly defined from a pathophysiological point of view. As a consequence, the management of HC and NDPH is largely empirical. Indeed, there is a lack of prospective, controlled trials in this field, and treatment effectiveness is basically inferred from the results of sparse open-label trials, retrospective case series, clinical experience and expert opinions. The only available guidelines for the therapy of HC and NDPH are not available in English and have been released soon after the publication of ICHD-II, thus including cases mainly diagnosed with other diagnostic criteria [2].

In this narrative review we have summarised the information collected from an extensive analysis of the literature on the treatment of HC and NDPH in order to provide the best available and up-to-date evidence for the management of these two rare forms of primary headache.

Hemicrania continua

Clinical features, diagnostic criteria, epidemiology and pathophysiology

Hemicrania continua (HC) is an uncommon primary headache disorder, first described as a syndrome by Sjaastad and Spierings in 1984 [3]. Hemicrania continua is a strictly unilateral, continuous, moderate-to-severe headache that fluctuates in intensity with possible exacerbations of severe pain associated with autonomic disturbances (conjunctival injection and/or lacrimation, nasal congestion and/or rhinorrhoea, ptosis and/or miosis); it is absolutely responsive to indomethacin (Table 1, diagnostic criteria). Migrainous features and jab-and-jolt pain may also be present [4]. Hemicrania continua is usually unremitting, but rare cases of remission have been reported. It is probably less uncommon than thought in the past [4]. In the Vågå study of headache epidemiology [5], up to 1% of the individuals surveyed exhibited a clinical picture that seemed to resemble HC but the diagnosis could not be confirmed for the compliance problems of the study (difficult to assess the response to indomethacin).

Different classification systems have been proposed for HC [6, 7]. Universally accepted operational diagnostic criteria for HC are contained in the ICHD-II and include, as an obligatory criterion, an absolute response to therapeutic doses of indomethacin. However, this criterion has been criticised because HC may also respond to other drugs, although less effectively, and also because it means that HC cannot be diagnosed in patients who have never been administered this drug [7]. Very recently, Murmura et al. [8], in a retrospective study, reported that most patient with a clinical phenotype leading to a putative diagnosis of HC do not respond to indomethacin. The fact that HC is included in Chap. IV of ICHD-II, "Other primary headaches", reflects its uncertain nosological status. Indeed, the clinical phenotype of HC overlaps that of trigeminal autonomic cephalalgias and migraine, possibly because it shares a pathophysiological mechanism with these two conditions [9, 10]. The inclusion of HC among the primary chronic headache disorders (CHDs) has been criticised on the grounds that aside from the chronicity, a highly unspecific quality, HC is a headache condition showing a sharply delineated unilaterality and clear therapeutic profile [11]. From a practical point of view, it may indeed be helpful to consider HC as one of the possible causes of chronic daily headache (CDH). Early administration of the "indotest" (a diagnostic test to detect indomethacin-responsive headaches) to all cases of chronic unilateral headache may lead to the timely identification of cases of HC [4].

Early diagnosis of HC is mandatory because the condition can be highly disabling and treatment with indomethacin may help patients to achieve a pain-free state. The diagnostic indotest involves injection of indomethacin 50 mg i.m. and measurement of time for complete pain relief. In 12 HC patients, complete pain relief was achieved 2 h after this injection [12]. The test is simple and may also be helpful in identifying atypical cases [13].

Treatment

Indomethacin is the mainstay of HC management. The mechanism by which it exerts its effect on HC and other primary headaches is unclear. The reported effective dose of indomethacin for HC ranges from 50 to 300 mg a day [3, 14]. It is advisable to start with 25 mg tid. The response to

Table 1 International Headache Society diagnostic criteria for hemicrania continua

Description: persistent strictly unilateral headache responsive to indomethacin
Diagnostic criteria
A. Headache for >3 months fulfilling criteria B–D
B. All of the following characteristics
1. Unilateral pain without side shift
2. Daily and continuous, without pain-free periods
3. Moderate intensity, but with exacerbations of severe pain
C. At least one of the following autonomic features occurs during exacerbations and ipsilateral to the side of pain
1. Conjunctival injection and/or lacrimation
2. Nasal congestion and/or rhinorrhoea
3. Ptosis and/or miosis
D. Complete response to therapeutic doses of indomethacin
E. Not attributed to another disorder

From [1]

indomethacin is prompt. Most patients report complete relief of headache within 24 h. After one week, if the patient is asymptomatic, the dose should be decreased to the minimum effective dose at which the patient remains pain-free. If, on the other hand, there is no satisfactory response, the dose should be increased to 50 mg tid. Occasional patients require higher doses. Gastroprotectors are required to control gastrointestinal side effects of indomethacin and to prevent gastroduodenal ulcers. Because remitting forms have been described, after 3–6 months all patients should try to decrease the daily dose of indomethacin by 25 mg each week until discontinuation, unless the symptoms reappear.

Hemicrania continua is often a lifelong condition, raising the issue of loss of therapeutic efficacy over time and potential long-term side effects. Indomethacin does not seem to show tachyphylaxis. On the contrary, Pareja et al. [6] showed that, over time, 42% of patients were able to decrease, by up to 60%, the dose of indomethacin required to maintain a pain-free state. As regards the long-term tolerability of indomethacin, of 12 HC patients followed up for varying periods of between 1 and 11 years, 23% experienced minor side effects, mostly gastrointestinal problems relieved with gastroprotectors [4]. In the literature, more than 35% of patients receiving therapeutic dosages of indomethacin experience adverse effects and 20% have to discontinue the drug [15]. Most adverse effects are dose-related, which underlines the importance of achieving the lowest effective dose. Gastrointestinal complications, such as anorexia, nausea, vomiting, dyspepsia, abdominal pain, mucosal ulceration and diarrhoea are the most frequent adverse effects but they are not often a cause for discontinuation. Indomethacin is contraindicated in conditions, such as renal failure, gastric ulcers and bleeding disorders. The risks associated with long-term indomethacin use include gastrointestinal ulcers and renal dysfunction, such as papillary necrosis. The first described HC patient was followed up for 19 years and developed bleeding gastric ulcer, treated with gastric surgery [16].

Patients who cannot tolerate indomethacin present a major challenge as regards the management of their headache, as no other drug has been shown to be consistently effective in HC. However, anecdotal observations suggest that drugs other than indomethacin may be helpful in HC. Sjaastad and Antonaci [17] reported a complete response to piroxicam beta-cyclodestrin 20 to 40 mg/day in 4 out of 6 patients (1 had a moderate response and 1 had no response). Selective COX-2 inhibitors, rofecoxib (50 mg/day) and celecoxib (200–400 mg bid), were found to be highly effective in 3 out of 9 patients and 3 out of 5 patients [18], respectively (1 patient receiving celecoxib and 5 of those receiving rofecoxib experienced a partial response). The COX-2 inhibitors have been proposed as an alternative to indomethacin in HC and other indomethacin-responsive syndromes [18, 19], but their long-term use has recently been associated with an increased risk of myocardial infarction and stroke, and rofecoxib has been withdrawn from the market worldwide [20]. Indeed, an increased risk of cardiovascular events exists with non-steroideal anti-inflammatory drugs in general, indomethacin included, and patients with cardiovascular disease should be informed about this risk and considered for alternative therapeutic options [21]. Rozen [22] described 3 patients responding to melatonin (9–15 mg/day), which has a similar chemical structure to indomethacin. In two cases melatonin alone was sufficient to achieve a pain-free state while in the third case it made it possible to reduce the total dose of indomethacin by 50%. Another case responding to melatonin 7 mg at bedtime was described by Spears [23], and there have recently been descriptions of five cases (two with atypical features) responding to topiramate (100 mg bid), and of a single patient with HC evolving from CH responding to valproic acid [24–27]. Very recently, Spears reported the efficacy of gabapentin in 9 HC patients who had difficulties in tolerating indomethacin [28]. Seven patients reported a 50–80% reduction of pain with doses ranging from 900 to 3,600 mg/day (two of them used other medication for pain control). One patient reported a 50% reduction of pain and one reported no effect. Four patients were pain free on gabapentin (600–1,800 mg/day).

Isolated case reports have described ibuprofen, naproxen, aspirin, paracetamol with caffeine and verapamil as effective [29, 30], but most of these drugs have been found to be ineffective in other HC cases.

Other classes of drug have not been successful in controlling HC. Antonaci et al. [31] reported a lack of efficacy of sumatriptan in 7 patients. Because HC is widely misdiagnosed, patients are prescribed many classes of drugs, often ones effective in migraine (such as analgesics, calcium-antagonists, beta-blockers, amitriptyline and other antidepressants, antiepileptics, ergot derivatives, pizotifen, methysergide) as well as others that are reported to be of no benefit in migraine [32].

Anaesthetic blockades of pericranial nerves have been found to be ineffective [33].

Very recently, Schwedt et al. and Burns et al. [34, 35] reported that occipital nerve stimulation may be a safe and effective treatment for HC (8 cases) at short- and long-term follow-up.

To review the problems linked to the misdiagnosis and mismanagement of HC patients we recently interviewed 25 consecutive HC subjects attending the Headache Clinic INI Grottaferrata [36]. Patients were asked about their use of pharmacological treatments, surgical treatments and non-pharmacological treatments for headache and to rate the effectiveness of each treatment on a four-point scale (very effective, i.e. complete and long-lasting relief; effective,

i.e. partial and/or short-lasting relief; ineffective; headache worsened). The patients had tried a mean of 3.63 ± 2.1 different classes of drug (67% prescribed, 33% unprescribed). NSAIDs had been tried by 92%. Nimesulide (a non-steroideal anti-inflammatory drug not available on the market in US and in the majority of EU countries) had been tried by 7 patients and been judged very effective by one and effective by six. Aspirin and ibuprofen had each been tried by 9 patients and were rated as effective by five and three of them, respectively. Antidepressants had been used by 8 patients (6 amitriptyline, 2 fluoxetine) but showed no effectiveness. Triptans had been used by 8 patients (5 sumatriptan s.c., 1 zolmitriptan and 2 rizatriptan) and been judged ineffective by all of them. Two patients had used rofecoxib and considered it very effective. Taken together, these HC patients had used a cumulative total of 80 different drug treatments, judging 73.7% of these medications ineffective, 22.5% partially effective (all NSAIDs) and 3.75% (rofecoxib and nimesulide) effective.

As much as 36% of the patients had undergone ineffective and unnecessary surgery (dental extraction, sinus/deviated septum surgery, temporomandibular joint surgery and cervical spine surgery) for their HC. Four patients had tried acupuncture (two considering it effective) and four had tried homeopathy (deemed ineffective by all of them).

These data suggest that HC is largely mismanaged as a consequence of its misdiagnosis. Indeed, apart from NSAIDs which, as a rule, were not prescribed, patients were mainly prescribed, by physicians, medications shown to be effective in the treatment of migraine or cluster headache but ineffective for HC.

Hemicrania continua may be complicated by overuse of symptomatic drugs [8, 37] and (in this situation) differential diagnosis of HC versus transformed or chronic migraine may be difficult. An exhaustive disease history could be helpful, as it may show a pre-existing unilateral primary headache. However, the overused medication should always be withdrawn and, if the headache persists, the indomethacin response should be tested.

Figure 1 sets out a schematic approach to the management of HC.

Fig. 1 A schematic approach to the management of hemicrania continua

First choice

Indomethacin 50-300 mg

- *Start with 25 mg tid with me als and increase the dosage gradually until complete pain relief is obtained*
- *Treatment failure should be considered if a patient fails to respond to a daily dosage of 300 mg (consider alternative diagnosis)*
- *Once an effective dosage has been established for several weeks, reduce the dosage to ascertain the lowest effective dosage*
- *Prescribe gastroprotectors to prevent and manage gastrointestinal side effects*
- *Check renal function regularly*

Alternative choices (patients not tolerating or presenting contraindications to indomethacin)

- *Consider celecoxib (200-400 mg bid)*

  If not effective
- *Consider topiramate (100 mg bid) or gabapentin (600-3600 mg tid) or melatonin (7-15 mg at bedtime)*

Refractory cases

- *Consider occipital nerve stimulation*

New daily-persistent headache (NDPH)

Clinical features, diagnostic criteria, epidemiology and pathophysiology

New daily-persistent headache (NDPH) is characterised by the abrupt onset of persistent headache that generally develops over <3 days and does not remit (Table 2, diagnostic criteria). In isolated reports on this entity, NDPH has been interpreted as a post-viral syndrome [38] and described as having a spontaneously favourable outcome [39]. On the basis of retrospective clinical observations, Silberstein et al. [40] included NDPH as a separate clinical entity in their classification of CDH and provided operational diagnostic criteria for the condition [briefly, they included: (a) average headache frequency >15 days/month for >1 month, (b) average headache duration >4 h/day, if untreated, (c) no history of migraine or TTH increasing in frequency or decreasing in severity in association with the onset of NDPH, (d) acute onset—developing over 3 days—of constant unremitting headache and exclusion of secondary headache]. In ICHD-II, NDPH is included in Chap. IV, "Other primary headaches", underlining its uncertain nosological status. According to these International Headache Society diagnostic criteria, NDPH is phenotypically reminiscent of tension-type headache (TTH), i.e. a sort of de novo chronic TTH (CTTH). However, NDPH is unique in that the headache is daily and unremitting from or almost from the moment of onset, and occurs typically in individuals without a prior headache history, which suggests that the pathogenetic mechanisms in NDPH and CTTH are different.

In a recent clinic-based study conducted in a paediatric population, using a modified version of the ICHD-II criteria, NDPH was more common than CTTH and most of the subjects with NDPH did not overuse medication and commonly presented migrainous features [41].

New daily-persistent headache (NDPH) is probably a heterogeneous disorder and should therefore be regarded as a syndrome. A viral infection or other organic cause may precede the headache in more than one-third of patients [42], possibly leading to a CNS inflammation and sensitisation of nociceptive pathways [43]. In some patients, cervical spine joint hypermobility may be a factor predisposing to the development of NDPH [44]. NDPH has a wide range of secondary forms that have to be excluded after thorough diagnostic work-up [45]. In these cases the causes (e.g. spontaneous intracranial hypotension, neoplasms, pseudotumour cerebri, cervical artery dissections, cerebral venous thrombosis, Chiari I malformation and temporal arteritis) can be treated and should be carefully excluded before a headache management plan is worked out [45]. The prognosis of NDPH is highly variable, ranging from self-limiting cases that typically resolve without therapy within several months to refractory cases resistant to aggressive treatment programmes.

Further pathophysiological and clinical characterisation of this syndrome is necessary so that the management of NDPH can be based on a clear rationale and on specific treatment options and general recommendation can be given. Empirical evidence on NDPH therapy is poor and based on the application of treatments that have proved to be effective in migraine or TTH. No prospective, placebo-controlled trial has been conducted in this field and the effectiveness of treatment can only be inferred, from the results of a few open-label trials, retrospective case reviews, anecdotal observations, expert opinions and generalisations from the literature on episodic migraine and TTH.

Table 2 International Headache Society diagnostic criteria for NDPH

Description
Headache that is daily and unremitting from very soon after onset (within 3 days at most). The pain is typically bilateral, pressing or tightening in quality and of mild to moderate intensity. There may be photophobia, phonophobia or mild nausea
Diagnostic criteria
A. Headache that, within 3 days of onset, fulfils criteria B-D
B. Headache is present daily, and is unremitting, for >3 months
C. At least two of the following pain characteristics
1. Bilateral location
2. Pressing/tightening (non-pulsating) quality
3. Mild or moderate intensity
4. Not aggravated by routine physical activity such as walking or climbing stairs
D. Both of the following
1. No more than one of photophobia, phonophobia or mild nausea
2. Neither moderate or severe nausea nor vomiting
E. Not attributed to another disorder

From [1]

Treatment

The largest uncontrolled study investigating the effectiveness of drug therapy and the prognosis of NDPH diagnosed according to the ICHD-II criteria was conducted in Japan by Takase et al. [46]. In 30 NDPH patients (17 males) the authors first administered muscle relaxants. If no effect was observed, tricyclic antidepressants (23 patients), valproic acid (9 patients), SSRIs (12 patients) and beta-blockers (2 patients) were subsequently administered. Drug treatment was rated as very effective by 27% of patients, moderately effective by 3%, mildly effective by 20% and ineffective by 50%. The authors concluded that NDPH has a poor prognosis and is highly resistant to currently available treatments.

Meineri et al. [47] retrospectively evaluated the effectiveness of drug therapy in 18 NDPH patients (the authors used both ICHD-II and Silberstein-Lipton's criteria). Sixteen patients tried amitriptyline, seven tried fluoxetine and seven tried valproic acid. The authors reported that no drug was effective.

In a small American case series of NDPH patients diagnosed according to the Silberstein and Lipton criteria, the following drugs were reported to be effective: gabapentin (1 case, 2,700 mg/day), topiramate (1 case, 150 mg/day), venlafaxine (1 case, 75 mg/day) and nortriptyline (1 case, 100 mg/day) [48]. In these cases the therapeutic effectiveness was achieved after the patients had tried many first-line drugs for migraine and CTTH. Marmura et al. [49] recently reported 3 patients with NDPH (two of which were overusing symptomatic drugs) who experienced significant improvement with mexiletine (1,050–1,200 mg) after having failed on multiple appropriate preventive treatments. All of these patients experienced side effects, such as nausea, fatigue, tremor and dizziness, which were reported to be dose-dependent. An isolated report has documented the effectiveness of botulinum toxin A [50].

Like other chronic daily headaches, NDPH may be complicated by medication overuse. Physicians are advised to ascertain a patient's complete medication history before starting any therapy. If medication overuse is diagnosed, drug withdrawal is necessary before other therapeutic options can be tried even though no prospective study has specifically investigated the effect of medication overuse in the worsening and maintenance of NDPH or in the determining of a resistance to therapy.

In summary, NDPH seems to be difficult to treat and to respond only poorly to first-line options used for migraine or TTH. Well-designed, targeted clinical trials considering the heterogeneity of this clinical entity, are needed so that an evidence-based therapy can be developed for this poorly characterised clinical syndrome.

Conflict of interest None.

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