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Case report

Chronic paroxysmal hemicrania and hemicrania continua responding to topiramate: Two case reports

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Abstract

Chronic paroxysmal hemicrania (CPH) is a rare primary headache syndrome, which is classified along with cluster headache and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing as a trigeminal autonomic cephalalgia (TACs). Hemicrania continua (HC) was previously classified as one of the TACs, but in the recent second classification of the International Headache Society this disorder was moved to the group of *other primary headaches*.

Both CPH and HC are characterised by moderate to excruciating pain requiring pharmacological treatment; furthermore, both conditions are characterised by an absolute response to indomethacin, which represents one of the current diagnostic criteria for these two syndromes. Unfortunately, in about one-fourth of cases treatment with indomethacin may cause adverse events, mostly gastrointestinal. We report one subject with CPH and another with HC intolerant to indomethacin, who responded remarkably well to topiramate.

Keywords: Paroxysmal hemicrania; Hemicrania continua; Trigeminal autonomic cephalgias; Prophylaxis; Indomethacin; Topiramate

1. Introduction

Trigeminal autonomic cephalgias (TACs) are a group of primary headaches characterised by unilateral pain in the somatic distribution of the trigeminal nerve with ipsilateral autonomic features [1,2]. TACs, which include cluster headache, paroxysmal hemicrania (PH) and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), have been grouped into Section 3 by the recent International Classification of Headache Disorders, 2nd edition (ICHD-II) [3]. Hemicrania continua (HC) was previously included in the umbrella term of TACs [4], but was then moved into Section 4 of the ICHD-II criteria, including *other primary headaches* [3].

PH and HC have common elements, such as the presence of autonomic features and moderate to excruciating pain in the temporal-orbital region. Furthermore, both conditions are characterised by an absolute response to indomethacin, which represents one of the current diagnostic criteria for these two syndromes [3]. While PH is characterised by short-lasting severe attacks, HC is, however, a continous headache and it should be considered in the differential diagnosis of chronic daily headache [5].

Due to the high disability associated with PH and HC, these headache disorders require specific acute and preventive treatments. However, treatment with indomethacin for these conditions is limited by the potential for systemic toxicity, mostly gastrointestinal [6]. For these reasons alternative drugs, with a better-tolerated profile, have been proposed for the treatment of PH and HC [1,2,7–9]. In particular, three case reports have recently suggested the potential use of topiramate as a preventive treatment for chronic PH (CPH) [7] and HC [8,9].

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In this paper we report two patients: one with CPH and another with HC, who were effectively treated with topiramate due to intolerance to indomethacin.

2. Case report

2.1. Patient 1

A 44-year-old woman was referred to our Headache Centre for stabbing headache attacks, which had started 2 years earlier. She described excruciating, left-sided temporal and orbital headache attacks, which usually lasted for 15–20 min with a frequency of up to 20 episodes per day. On two occasions the attacks lasted for up to 1 h. The pain occurred regularly throughout the day and it was associated with ipsilateral lacrimation, nasal congestion and rhinorrhoea. During these attacks, the patient preferred to sit or lie still. The attacks were not triggered by neck movements or alcohol consumption, physical activity, lack of sleep or eating. The patient related that from the onset of her symptoms, she experienced about five pain attacks per day, but the frequency progressively increased every few months and, in the 1-year period prior to admission, they occurred almost daily with remission periods of less than 10 days.

Before coming to our centre the patient was diagnosed with cluster headache and treated with prednisone 50 mg a day and verapamil 240 mg a day with a slight effect. She had tried subcutaneous sumatriptan 6 mg once with moderate pain relief but this was immediately discontinued due to severe nausea and vomiting. Treatment with oxygen (100%, 7 l/min for 15 min) moderately relieved the attacks.

Physical and neurological examinations on admission were normal. Routine blood tests, ECG and a brain MRI with gadolinium were unremarkable. Past medical history was negative; a family history showed that her mother suffered from migraine. She was started on indomethacin with slow titration to 50 mg three times per day with maximum effectiveness 2 days after initiating the effective dose; a gastroprotective therapy with omeprazole 20 mg a day was also prescribed. The clinical picture and response to indomethacin confirmed a diagnosis of CPH, based on ICHD-II criteria [3]. After 2 months she developed dyspepsia and we attempted to slowly withdraw indomethacin with pain reappearance within a few days. After a further 1-month period, indomethacin was withdrawn because of the increasing epigastric pain that on some occasions was associated with severe vomiting. Thus, she was started on topiramate with slow titration to 100 mg twice a day, with complete pain relief after few days of initiating the effective dose. After 3 months, she developed moderate leg paraesthesia and we attempted to slowly withdraw topiramate with pain recurrence at the dose of 50 mg twice a day. Thereafter, an intermediate dose of 75 mg twice a day daily was reached with a substantial reduction of the sensory symptoms and complete pain relief. Three months later, we gradually discontinued topiramate, reducing it by 25 mg a week. After a further 6 months the patient no longer experienced attacks and there were no adverse effects from topiramate.

2.2. Patient 2

A 39-year-old man was referred to our Headache Centre, having experienced daily persistent headaches for 6 months. He had a 4-year history of remitting headache lasting weeks to months, with long-lasting remissions. There were no precipitating factors. He described a strictly unilateral, right-sided, non-pulsatile, pressing headache, which started in the frontal region and the orbit with radiation to the parietal region. The headache was usually of moderate intensity with exacerbations of severe pain. The attacks had a throbbing quality and were associated with ipsilateral lacrimation and conjunctival injection but not with other autonomic features or migraine accompanying symptoms, such as nausea, vomiting, photo- or phonophobia. The headache was not triggered by neck movements or exacerbated by alcohol consumption, physical activity, lack of sleep or eating. Past medical history was negative with the exception of *Helicobacter pylori*-negative gastric ulcers, diagnosed on gastroscopy, treated with gastroprotective agents and attributed to NSAID 3 years prior to admission. There was no family history of headache, he was a non-smoker and drank no more than one glass of red wine a day.

The patient was taking ibuprofen 600 mg tablets twice a day for moderate pain with a partial response but other NSAID were totally ineffective during exacerbations of severe pain, which required intramuscular ketorolac 30 mg twice a day with some relief. He had previously tried other NSAID (i.e., aspirin, naproxen, piroxicam, rofecoxib), corticosteroids, benzodiazepines, and tricyclic antidepressants to no effect.

Physical and neurological examinations on admission were normal. Routine blood tests, ECG and a brain MRI with gadolinium were unremarkable. He was started on indomethacin 25 mg three times per day with a total headache relief within 24 h. We also prescribed a gastroprotective therapy with omeprazole 20 mg a day. The clinical presentation and response to indomethacin confirmed a diagnosis of HC based on ICHD-II criteria [3]. The patient was pain-free for 2 weeks and after this period he developed severe epigastric pain, thereby necessitating cessation of indomethacin, which led to the recurrence of the headache within 3 days. Thereafter, he was started on topiramate with slow titration to 50 mg twice a day, with complete pain remission after 2 weeks. After 6 months we attempted to slowly withdraw topiramate. One day after the patient had reached a dose of 25 mg twice a day, pain recurred and topiramate was gradually titrated to the previous dose, which rendered him completely pain-free in about 15 days. At 1-year follow-up, he still has good control of his episodes. When he reduces the dose, the episodes return. He has reported no side-effects from topiramate.

3. Discussion

We have reported two patients who fulfil the ICHD-II criteria [3] for CPH and HC, intolerant to indomethacin, who fully responded to topiramate. The dose of topiramate required for complete pain relief was somewhat less than that usually needed for the antiepileptic effect of the drug for all patients [10], but similar to that previously described for the treatment of CPH and HC [7–9]. Of interest, both patients responded to treatment with topiramate incurring relatively few side effects. Furthermore, patient 1 – suffering from CPH – experienced persistent pain relief after topiramate withdrawal.

CPH and HC cause patients considerable disability and the severe nature of the pain requires the use of effective combinations of acute and preventive treatment from the outset. Indomethacin, the specific preventive treatment for both PH and HC [3], in about 25% of treated patients may cause adverse gastrointestinal effects [6], similar to those which appeared in our cases.

For these reasons alternative therapies, with favorable pharmacokinetic properties and side effects – such as the newer antiepileptic drugs – have been proposed for the preventive treatment of CPH and HC [1,2,7–9]. In particular, one case with CPH [7] and four cases with HC [8,9], responding to topiramate, have been described. Our results confirm and extend previous reports, thereby suggesting the potential use of topiramate in CPH and HC in those patients who are intolerant to indomethacin. Indeed, the drug has also been proved to be effective as a preventive treatment of migraine [11]. Furthermore, it has been used to treat chronic tension-type headache [12] and hypnic headache [13]. Lastly, topiramate has been reported to be beneficial in cluster headache [14] and SUNCT [15], both disorders included in the umbrella term of TACs.

Summarizing our cases and previous case reports [7–9] specifically focused on the preventive treatment with topiramate of CPH and HC, some suggestions can be made (see Table 1): (a) the mean effective topiramate dose for CPH is at least 200 mg/day. However, with this or higher doses there is a possibility of adverse effects, thus reaching a dose of approximately 150 mg/day could safely control both adverse effects and headache attacks; (b) the mean effective topiramate dose for HC ranges from 100 to 200 mg/day. This dose appears to be well-tolerated in young adults, while using a 200 mg/day dose in adult-to-elderly subjects may cause severe adverse effects, leading to topiramate withdrawal.

Considering the high placebo response reported in clinical trials on preventive medications in TACs [16], these considerations should be interpreted with caution. However, the persistence of the therapeutic effect of topiramate after the suspension of treatment, as shown by the patient with CPH in the present study and described in the two HC cases reported by Brighina et al. [9], it can hardly be attributed to a purely placebo effect.

Topiramate is a derivative of the monosaccaridhe D-fructose that has demonstrated antiepileptic activity [10]. Its multiple action mechanisms include: voltage-sensitive, sodium channel blockade; calcium channel inhibition; increase of potassium conductance; γ-aminobutyric-acid-mediated chloride current increment; glutamate-mediated neurotransmission inhibition; and carbonic anhydrase isoenzyme inhibition [10]. It is not known on which of these mechanism(s) topiramate acts as a prophylactic treatment for various headache syndromes. The direct inhibition of the trigeminocervical complex or the modulation of neurons that regulate sensory input have been proposed to be plausible mechanisms for the topiramate action as a preventive treatment for TACs and migraine [17,18]. Of interest Goadsby et

Table 1
Summary of subjects with chronic paroxysmal hemicrania and hemicrania continua who have been treated with topiramate

Authors	Age (years), sex	Mean effective dose (mg/day)	Overall response	AEs	Recurrence on withdrawal	Withdrawal because of AEs
Paroxysmal hemicrania						
Cohen et al. [7]	42, man	200–350	100% remission	Cognitive slowing, dry mouth and weight loss	Yes	No (reduction to 150 mg/day with substantial pain control)
Patient 1 of this study	44, woman	200	100% remission	Mild paraesthesias	Yes	No (reduction to 150 mg/day with substantial pain control)
Hemicrania continua						
Matharu et al. [8]	40, woman	100	100% remission	No	Yes	NA
	64, man	200	100% remission	Cognitive slowing, behavioural problems and paraesthesias	Yes	Yes
Brighina et al. [9]	30, woman	200	100% remission	No	No	NA
	46, woman	200	100% remission	No	Yes	NA
Patient 2 of this study	39, man	100	100% remission	No	Yes	NA

AEs: adverse effects.

al. [19] have previously suggested that the pathophysiology of TACs and HC revolves around the trigeminal-autonomic reflex. In particular, the cranial autonomic symptoms prominent in TACs and HC may be due to a central disinhibition of the trigeminal-autonomic reflex by the hypothalamus, possibly through direct hypothalamic-trigeminal connections [20]. This hypothesis is further strengthened by recent findings of a posterior hypotalamic activation both in TACs and HC [21].

According to our observations, topiramate would be an interesting alternative option in patients with CPH and HC with contraindications or intolerance to indomethacin. Our observations need to be confirmed by controlled clinical trials.

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