Clinical Case Seminar

Chronic paroxysmal hemicrania in an adult responding to valproate: a case report

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Abstract

Chronic paroxysmal hemicrania (CPH) is a rare primary headache syndrome classified as a trigeminal autonomic cephalalgia. It is characterized by repeated attacks of severe, strictly unilateral and short-lasting pain occurring with cranial autonomic features. The absolute response to indomethacin represents the diagnostic key. Unfortunately, often, treatment with indomethacin may cause adverse events, mostly gastrointestinal. We report the case of a 53-year-old male affected by CPH responding to indomethacin, which had to be withdrawn because of gastric side effects. He had a subsequent good and prolonged response to valproate. Our observation suggests the potential use of valproate as a treatment option in patients with CPH with contraindications or intolerance to indomethacin.

KEYWORDS: Chronic paroxysmal hemicrania; indomethacin; valproate

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Introduction

Chronic paroxysmal hemicrania (CPH) is a rare primary headache syndrome, classified along with cluster headache (CH), short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and Hemicrania continua (HC), as a trigeminal autonomic cephalalgia (TAC). The criteria require: relatively short-lasting (2–30 min) episodes of severe unilateral orbital, supraorbital or temporal pain, accompanied by cranial autonomic symptoms with a typical attack frequency of more than 5 per day (1). The episodes are prevented completely by therapeutic doses of indomethacin. However, this treatment is limited by the potential for systemic toxicity, mostly gastrointestinal (2). For these reasons, other classes of medications with a better-tolerated profile have been shown to be effective (3). We report a patient affected by CPH responding to indomethacin, which had to be withdrawn because of gastric side effects. He had a subsequent good and prolonged response to valproic acid (VPA).

Case Report

A 53-year-old man was referred to our Headache Centre for stabbing headache attacks, which had started about 25 years earlier. He described excruciating, right-sided temporal and orbital
headache attacks, which usually lasted for 15–20 min with a frequency of up to 5 episodes per day. The pain occurred regularly throughout the day, especially during sleep, always waking him up at the same time of the night. It was associated with ipsilateral lacrimation, nasal congestion and rhinorrhea. The pain was not triggered by neck movements or alcohol consumption, physical activity, lack of sleep or eating. The episodes occurred almost daily. The patient was previously diagnosed in another Hospital with chronic CH and he was treated with lithium carbonate 300 mg per day, prednisone 50 mg per day, verapamil 240 mg per day and lamotrigine 200 mg per day, with no benefits. Treatment with oxygen (100% 7 L/min for 15 min) and zolmitriptan 5 mg nasal spray did not relieve the attacks.

Family history and past medical history were negative. Physical and neurological examinations were normal. Routine blood tests, electrocardiogram, brain Magnetic Resonance Imaging (MRI) with gadolinium and angio-MRI were unremarkable. He 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 per day was also prescribed. The clinical picture and response to indomethacin confirmed a diagnosis of CPH, based on ICHD-3 BETA criteria (1).

After 5 months, he discovered megaloblastic anemia due to erosive gastropathy, so we attempted to slowly withdraw indomethacin, with pain reappearance within a few days. Thus, he was subjected to several different treatments, such as topiramate 100 mg/ day, pizotifen 1.5 mg/ day and carbamazepine 600 mg/ day, without benefits and persistence of up to 4 attacks per day. Then, he underwent transitional anesthetic block of the greater occipital nerve (GON) using bupivacaine and methylprednisolone with slight effects.

Thereafter, he was started on VPA with slow titration to 600 mg with complete pain remission after 3 weeks. After 6 months we attempted to slowly withdraw VPA, but when the patient had reached a dose of 200 mg per day, the pain recurred and VPA was gradually titrated to the previous dose, which rendered him completely pain-free in about 20 days. At 2-year follow-up, he still has good control of his episodes. He has reported no adverse effects from VPA.

Discussion

The main differential diagnosis of CPH is CH because pain site and associated autonomic phenomena are similar in both headaches. Furthermore, there is a considerable overlapping between the diagnostic criteria for CPH and CH, mostly concerning headache duration (from 15 to 30 min) and attack frequency (from 5 to 8), thus complicating the differential diagnosis. The higher frequency of the attacks, their shorter duration and the absolute response to indomethacin
may help in distinguishing CPH from CH. Furthermore, if attack duration and frequency can
make the diagnosis more difficult, the absolute response to indomethacin represents the
diagnostic key for CPH (indotest) (1).
Our patient was previously diagnosed in another Hospital with chronic CH but the episodes
occurred almost daily, and usually lasted for 15–20 min with a frequency of up to 5 per day (from
5 to 7). Moreover, treatment with oxygen and zolmitriptan did not relieve the attacks, while they
were prevented completely by indomethacin, leading to the diagnosis of CPH.
At therapeutic doses, 35% to 50% of patients experience unpleasant adverse effects dose-related,
and 20% may need to discontinue treatment (2). Alternative therapies have been proposed for the
preventive treatment of CPH, such as topiramate, acetazolamide, verapamil (3). Tarantino et al.
described two children with typical CPH features and a positive response to VPA therapy (4). To
our knowledge, no other cases of adult CPH treated with VPA have been previously reported.
VPA, a branched short-chain fatty acid, is one of the most frequently used anti-epileptic drugs
and it is now being effectively used in the prophylactic treatment of migraine without aura,
chronic migraine and CH. Its major mechanism of action is to enhance γ-aminobutyric acid
(GABA)-ergic neurotransmission and to increase intracellular potassium concentrations with
consequent hyperpolarization of membranes at rest (5).
GABA modulates the transmission of painful sensory information to the cortex when the
trigeminovascular nociceptive system is active and VPA is able to inhibit trigeminal nociceptive
transmission in the ventroposteromedial nucleus through GABA_A receptor mechanisms (6).
Furthermore, the existence of trigemino-hypothalamic connections could lead to the disinhibition
of the trigeminal-autonomic reflex (7). In fact, activation of the superior salivatory nucleus, by
the posterior hypothalamic, or through the trigeminal-autonomic reflex results in an increased
firing of parasympathetic fibers and thus in ipsilateral autonomic signs (8).
So, we could hypothesize that VPA, inhibitor of GABA_A in the central nervous system, might
exert his therapeutic effect by inhibiting posterior hypothalamic neurons, responsive to trigeminal
imputs.
Herein, our observation suggests the potential use of VPA as an alternative option in adult
patients with CPH with intolerance to indomethacin. We are aware that the effects of a treatment
in a single case can be due to several factors, so our findings need to be confirmed collecting a
higher number of cases suffering from this uncommon but not extremely rare disease.

Conflicts of Interest: There is no potential conflict of interest, and the authors have nothing to disclose.
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References


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