J Headache Pain (2010) 11:281–284
DOI 10.1007/s10194-010-0210-7

CASE REPORT

Different forms of trigeminal autonomic cephalalgias in the same patient: description of a case

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Received: 2 March 2010 / Accepted: 23 March 2010 / Published online: 8 April 2010

Abstract The trigeminal autonomic cephalalgias (TACs), including cluster headache, paroxysmal hemicrania and SUNCT, are characterized by the cardinal combination of short-lasting unilateral pain and autonomic phenomena affecting the head. Hemicrania continua (HC) shares many clinical characteristics with TACs, including unilateral pain and ipsilateral autonomic features. Nevertheless, HC is separately classified in the revised International Classification of Headache Disorders (ICHD-II). Here, we describe the case of a 45-year-old man presenting an unusual concurrence of different forms of primary headaches associated with autonomic signs, including subsequently ipsilateral cluster headache, SUNCT and HC. This report supports the theory that common mechanisms could be involved in pathophysiology of different primary headache syndromes.

Keywords Hemicrania continua · Cluster headache · SUNCT · TACs

Introduction

The trigeminal autonomic cephalalgias (TACs) are a group of primary headaches characterized by attacks of unilateral head pain that occurs in association with prominent ipsilateral craniofacial autonomic features, such as lacrimation, conjunctival injection or nasal symptoms [1]. TACs are listed in section III of the revised International Classification of Headache Disorders (ICHD-II) [2] that includes cluster headache (CH), paroxysmal hemicrania (PH) and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing/cranial autonomic features (SUNCT/SUNA). TACs differ in attack frequency and duration as well as in the response to therapy [3]. CH has the longest attack duration and relatively low attack frequency. On the contrary, SUNCT has the shortest duration and the highest frequency of attacks. PH has intermediate duration and attack frequency.

Hemicrania continua (HC) represents a primary headache characterized by a continuous pain with exacerbations that can include cranial autonomic symptoms as part of phenotype. Whether HC should be included in the group of TACs is moot. It entered the ICHD in 2004 being classified in the section IV (other primary headaches), rather than in the section III (TACs) [2]. Indeed, as discussed below, different evidence suggests to bring HC into the TACs group [3].

The pathophysiology of TACs has not been completely elucidated [4]. Current thinking is that the pain and the autonomic symptoms, respectively, arise as a result of activation of the trigeminal nerve and craniofacial parasympathetic nerve fibers as a consequence of the pathological activation of the trigemino-autonomic brainstem reflex [1, 4]. Neuroimaging [5–9], structural [9] and neuroendocrinological [10, 11] findings have led to the hypothesis that the trigger of the trigeminofacial reflex could be located in the hypothalamus, even if the role of hypothalamus in these disorders needs further clarification.

In this paper, we describe the case of a patient presenting three different forms of primary headaches associated with autonomic signs at different times, in the following order: first cluster headache, then SUNCT, and lastly HC. This report could be important to help understanding of common pathophysiological mechanisms of

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primary headache disorders, favoring also their correct taxonomy.

Case report

Our patient was a 45-year-old Italian man with an unremarkable family and past medical history. There was neither history of migraine nor family history of headache. The subject was referred to our outpatient headache center in January 2003, 15 days after the onset of recurrent (3–4 per day) short-lasting attacks (60–120 min) of unilateral stabbing pain localized in the right orbito-frontal region. Pain was referred with an intensity of 9/10 at the visual analogue scale (VAS) and was accompanied by marked ipsilateral autonomic signs that included lacrimation, lid edema and redness of the eye. No photophobia or phonophobia was complained. Patient reported that attacks often occurred at precise hours and frequently during the night. He was completely pain-free between the attacks, and no precipitating or aggravating factors were reported. At the time of examination, his neurological status was normal. A brain MRI with pituitary views and MRA scan was performed to rule out secondary headaches. Therefore, diagnosis of cluster headache (CH) was made according to the ICHD-II criteria. Patient underwent an electrocardiogram and a cardiological evaluation before starting symptomatic and prophylactic treatment. Given the absence of contraindications for the use of triptans, subcutaneous injections of sumatriptan 6 mg were prescribed for attack treatment. Sumatriptan showed to relieve the CH pain in a few minutes. In order to not exceed the maximal sumatriptan dose for 24 h (12 mg), we also recommended oxygen inhalation with high-flow (10 l per 10–15 min) as alternative symptomatic treatment. The calcium-channel blocker verapamil was used for the prophylactic treatment, at the full dose of 360 mg/day (120 mg per 3) with slow titration (120 mg increase every 3 days). This treatment resulted in a rapid clinical improvement with complete remission within 10 days. Two weeks after the last attack, verapamil dosage was gradually reduced and then stopped. In the three following years the CH pain usually recurred in January or February, showing a clear seasonal variation. At the beginning of each headache bout the patient started verapamil as previously prescribed with completed relief within a few weeks.

In March 2007, the patient came back to our observation reporting a change in the clinical picture in terms of frequency and duration of the headache attacks. About 3 weeks before, he began to complain an episodic unilateral short-lasting (30–60 s) stabbing headache (9/10 at VAS) recurring 20–30 times a day, that he always referred to the right orbito-frontal region. The pain was associated with the same ipsilateral autonomic symptoms he experienced in the previous years: lacrimation, conjunctival injection and lid edema. At the beginning of the symptoms the patient started by himself the treatment with verapamil (previously prescribed for CH) without clinical benefit. On the clinical examination, there were no physical signs of nervous system involvement. Patient also underwent a new MRI of the brain which resulted unchanged when compared to the previous evaluation. Therefore, meeting the clinical criteria for SUNCT, patient started lamotrigine at dosage of 100 mg/day that ameliorated headache after 2 weeks and completely aborted it in 4 weeks.

About 6 months later, in September 2007, the patient was seen again at our clinic because the headache again exhibited different features. Indeed, the patient described a constant, widely distributed right-side head pain that started at least 1 month before while he continued the prophylactic treatment with lamotrigine. The pain was mild to moderate, waxing and waning without disappearing completely. The patient also frequently experienced clinical exacerbations, lasting about 6–8 h, characterized by more severe hemicranial pain (7/10 at VAS) and ipsilateral lacrimation and conjunctival injection. Since the clinical picture resembled that of HC, lamotrigine was stopped and a trial with indomethacin (100 mg/day) was performed. Indomethacin completely aborted pain in less than 48 h, thus allowing to support the diagnosis of HC. The drug was stopped 10 days later and headache recurred within a few days, it again settled rapidly when indomethacin was restarted. Since the topiramate has been successfully used for the treatment of HC [12], to avoid the side-effects of chronic intake of indomethacin, patient was shifted to prophylactic treatment with topiramate (50 mg bid), that he maintained until 6 months ago with complete remission of symptomatology.

Discussion

Our case seems to establish a link between different forms of TACs and HC, pointing toward common pathophysiological mechanisms of these headaches. Diagnosis of CH, SUNCT and HC was made in accordance with the ICHD-II, with the exception of criterium A (headache for >3 months) for HC. The excellent and highly selective treatment response may represent a further diagnostic proof. To our knowledge, this is the first case described in which CH, SUNCT and HC coexist in the same patient. Contrarily, various cases with coexisting TACs and HC [13–19] and two cases in which CH and SUNCT concurred [20, 21] have been described.

The clinical course of the patient suggests that CH, SUNCT and HC have a common pathophysiological

mechanism including hyperactivation of the trigeminovascular reflex, while the central pathway acting as pain trigger could be different. It is interesting to note that the side-location of pain and the autonomic symptoms remained unchanged in the attacks of different types, supporting the notion that they were tightly related.

One could suggest a shift in the pain generator to explain the clinical transition from CH to SUNCT to HC. Conversely, another intriguing explanation could be that a shift in mechanisms regulating the duration of an attack could have been responsible for the change in the clinical picture. This hypothesis seems in line with recent observations suggesting that the posterior hypothalamus likely plays a part in terminating rather than triggering attacks, thereby regulating the duration of an attack, giving rise to the different TACs that are principally distinguished by attack duration [4, 22]. Recent experiences with deep brain stimulation of posterior hypothalamus used in the treatment of TACs provide further support to this concept [30].

Neuroimaging studies have confirmed clinical and other data (e.g., neuroendocrinological) indicating hypothalamic involvement in CH and other TACs [23, 24], showing hypothalamic gray matter activation during attacks in patients affected by CH [5, 25], PH [7], SUNCT [6, 26, 27], and also HC [28]. Moreover, this hypothalamic activation was found in a patient with both SUNCT-like and cluster-like attacks, further supporting the overlap of TACs in terms of the clinical presentation as well as in terms of brain activation patterns [21]. Nevertheless, hypothalamic activation has also been reported in migraine and in non-headache pain disorders [29, 31], suggesting that this event is not specific to TACs and could represent a pain-induced epiphenomenon rather than a pain generator [4].

In line with previous reports, our case also suggests a pathogenic relationship between TACs and HC, supporting the proposal, first advanced by Goadsby [1], to reclassify TACs including HC into the TACs group. Among this latter, considerations that emphasize the similarities existing between HC and TACs are: (1) the presence of prominent cranial autonomic symptoms as consequence of the overexpression of a trigeminal autonomic reflex in both TACs and HC [3]; (2) the activation of the posterior hypothalamic gray in HC [3, 28], similar to that seen in CH, PH and SUNCT/SUNA; (3) the finding of pituitary region disorders as important secondary triggers to TAC-like headaches also apply to HC [3]; (4) the high susceptibility of HC to indomethacin, which is similar to that of PH [3].

Our report and other similar cases provide evidence of both the possible concurrence of multiple primary headaches in individual patients and the transformation between types over time, including intermediate forms such as HC, so supporting the hypothesis that the various combination of a small number of fundamental pathophysiological mechanisms could be responsible for the different manifestations of all primary headaches [32].

In agreement with this theory are also the symptomatic and therapeutic overlaps existing between different form of TACs [4, 33], and the clinical overlap between TACs and migraine [34, 35].

These considerations, taken together, lead to the hypothesis of a continuum in the spectrum of primary headache syndromes, defined by the parameters of headache intensity, frequency and duration of attacks, and trigeminal autonomic features [32]. Nevertheless, further clinical studies and larger case series are necessary to confirm this hypothesis.

Conflict of interest None.

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