Cluster headache: what has changed since 1999?

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Abstract The peripheral and central origin of pain in cluster headache (CH) and trigeminal autonomic cephalgias (TACs) has been matter of debate. In the last decade, a number of information came from both animal and human studies. This paper briefly highlights main data from these studies. Taken together, there is now sufficient body of evidence indicating that CH and TACs can be regarded as a unique headache spectrum–syndrome, due to involvement of specific brain areas.

Keywords Cluster headache · Treatment · Neurostimulation · Hypothalamus

Until 1988, cluster headache (CH) was classified together with migraine under the section of “vascular headaches” [1]. For the first time in 1988 the International headache society (IHS) classification separated CH from migraine [2]. In the second IHS classification [2] CH was grouped together with other two primary headache forms: paroxysmal hemicrania (PH), and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) [3]. This group was named the trigeminal autonomic cephalalgias (TACs) and is characterised by

attacks of unilateral head pain associated with ipsilateral craniofacial autonomic manifestations. Attack duration is the main feature that distinguishes the three TAC forms. The term TAC was first introduced by Goadsby and Lipton [4] in 1997 because of the simultaneous activation of trigeminal and parasympathetic craniofacial nerves both in these headache forms. The contemporary activation of these nerves could be due to pathological activation of the trigeminofacial brainstem reflex [4].

The peripheral and central origin of pain in TACs, mainly in CH has been matter of debate. Orbital phlebographies in CH and other headaches did not reveal differences and systemic signs of inflammation have never been reported in CH [5], thus excluding inflammation of the cavernous sinus as a source of the pain in CH.

Vasodilation seems not to be the cause of pain in CH: intracranial vasodilation is not specific to CH as it is observed in experimental forehead pain [6]. In addition, CH can occur even if vasodilation is blocked by trigeminal nerve section [7].

Sumatriptan efficacy is due to the antagonistic effect on peripheral 5-HT_{1D} (at trigeminal nerve endings) and 5-HT_{1B} receptors (on the walls of intracranial blood vessels) [8]. Thanks to these effects on peripheral 5-HT_{1D} and 5-HT_{1B} receptors, sumatriptan could control CH pain by reducing the increased concentrations of calcitonin gene-related peptide in the ipsilateral jugular vein during CH attacks [9].

A peripheral origin of pain in CH and TACs also comes from secondary forms of these headaches: under such circumstances the clinical characteristics of CH and TACs are rather often difficult to differentiate the primary forms [10]. In many cases, the lesions are located in the sella turcica or the sinus cavernosus [10], and surgical removal leads to resolution of the pain.

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Other observations indicate that activation of trigeminal nerve endings alone cannot explain the pain of CH (and other TACs). Other factors probably in the brain play a role in pain generation. Vasodilators such as alcohol, nitroglycerine [11], and the 5-HT_{2B} agonist *m*-chlorophenylpiperazine [12], can precipitate CH attacks but only during the bouts. These observations point to a central permissive state allowing vasodilation being perceived as painful.

In a PET study, peripheral trigeminal activation occurs in CH [13] without provoking CH pain attacks; in addition, surgical lesioning of the trigeminal nerve does not always resolve the pain in CH as well as other TACs [14, 15]. It is of interest to note that sumatriptan retains its ability to stop CH attacks after complete trigeminal nerve section [7], indicating that its effect is not at peripheral level but in the brain. Other data also suggest that the trigeminal nerve is not crucial in CH and TACs pain. In a large study on CH patients, 48 % reported the headache outside the trigeminal distribution [16]. In PH pain can occur in various non-trigeminal areas, occipital (42 %), neck (32 %), ear (13 %), ipsilateral shoulder (10 %), and arm (10 %) [17]. In SUNCT pain can occur in the back of the head and neck in 31 % and in the ear in 6 % [18].

The clockwork regularity of CH attacks and the seasonal recurrence of CH led to the hypothesis that a biological clock in the hypothalamus was involved in CH [11]. In the same direction go the observations that attacks can be provoked by napping [11], and the shift to their regular times after changing time zone [11]. Neuroendocrinological abnormalities have been documented in CH substantiating hypothalamic involvement in CH [19].

CH and TACs should be regarded as a syndrome, with a central component predominating in primary forms and a peripheral component predominating in secondary forms.

Neuroimaging findings, clinical characteristics and neuroendocrinological abnormalities in CH and in the other TACs pointed to a hypothalamic involvement, prompting the idea that this brain area could act cluster generator [20].

In animals, a direct connection between the posterior hypothalamus and the trigeminal nucleus caudalis through the trigemino-hypothalamic tract has been demonstrated [21]. Sensory information from trigeminally innervated territories is conveyed to the hypothalamus via the trigemino-hypothalamic tract [21]. On the contrary, stimulation of the posterior hypothalamus modulates the activity of trigeminal nucleus caudalis neurons: this effect is mediated by a number of substances, such as orexins [22]. In a H₂¹⁵O PET study conducted in patients with chronic CH under hypothalamic stimulation [13], hypothalamic stimulation induced activation in both the ipsilateral hypothalamic grey and the ipsilateral trigeminal system documenting for the first time a connection between the hypothalamus and the trigeminal system in humans. In this study, activation of

the trigeminal nerve and ganglion did not produce any headache nor head sensation suggesting that trigeminal activation is not sufficient to fully explain CH pain [13]. Taking together data from animals and humans, there is now sufficient body of evidence indicating that the posterior hypothalamus plays a role in head pain modulation.

High-frequency hypothalamic stimulation to treat chronic drug-resistant CH was introduced in 2000 to inhibit hyperactivity of this brain area previously detected by PET [23].

So far, experience from more than 60 patients with drug-resistant chronic CH treated with hypothalamic stimulation shows a remarkable improvement in about 60 % of cases [24]. Hypothalamic stimulation is also effective in SUNCT [25–27] and in PH [28].

Acute stimulation does not improve ongoing CH attacks [29], and stimulation must continue for weeks or months before there is benefit [30].

Taken together, these observations suggest that the mechanism of action of hypothalamic stimulation is not the mere result of inhibition of hypothalamic neurons [30]. The increased threshold for cold pain in first trigeminal branch on the stimulated side in patients under chronic hypothalamic stimulation suggested modulation of the antinociceptive system [31].

Hypothalamic stimulation affects major pain-matrix areas: activation has been recorded in the thalamus, somatosensory cortex, precuneus, and anterior cingulate cortex, whereas deactivation occurs in the middle temporal gyrus, posterior cingulate cortex, and insula [13]. This suggests that it restores normal function of pain network in CH patients. The original hypothesis that the hypothalamus is the so-called CH generator was appealing, but recent neuroimaging findings and the accumulated experience with hypothalamic stimulation indicate other interpretations.

If the posterior hypothalamus was the CH generator, one would expect hypothalamic stimulation to trigger CH pain attacks, but this is not the case [30]. An alternative explanation about the role of the posterior hypothalamus in CH and TACs is that its activation leads to attack termination, thus regulating the duration of an attack [32]; this ability could explain the different attack durations in the various TAC forms.

Data accumulated in the last years, led to move beyond the search of a single trigger zone as previously thought in CH. Brain areas involved in a CH attack [20] are almost the same of those traditionally regarded as the pain matrix; moreover, these areas show a huge overlap with brain areas modified by hypothalamic stimulation [13]. These areas play a major role also in autonomic, cognitive and affective functions. A derangement in one or more of these areas, or alternatively a deficit in their interactions, could be the cause of a permissive state leading to disinhibition of the

hypothalamo-trigeminal pathway that in turn may start a pain attack.

Conflict of interest We certify that there is no actual or potential conflict of interest in relation to this article.

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