Neuromodulatory Approaches to the Treatment of Trigeminal Autonomic Cephalalgias (TACs)

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Introduction

Trigeminal Autonomic Cephalalgias (TACs) is a grouping of headache syndromes including cluster headache, paroxysmal hemicrania and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) [1]. These syndromes share two major clinical pictures: trigeminal distribution of pain and ipsilateral cranial autonomic symptoms [2]. These features are consistent with cranial parasympathetic activation and sympathetic hypofunction (ptosis and miosis) representing a neurapraxic effect of carotid swelling with cranial parasympathetic activation [3, 4]. The distinction between TACs and other headache syndromes is the degree of cranial autonomic activation, not its presence alone, since other primary or secondary headaches show this type of activation [5–8].

Positron emission tomography (PET) studies in cluster headache and paroxysmal hemicrania and functional magnetic resonance imaging (MRI) studies in SUNCT have demonstrated ipsilateral posterior hypothalamic activation which seems to be specific to these syndromes and not present in other types of migraine. There are direct hypothalamic-trigeminal connections [9] and the hypothalamus is known to have a modulatory role on the nociceptive and autonomic pathways, specifically trigeminovascular nociceptive pathways [10].

Summary of Background Data and State of Today's Knowledge

Cluster Headache (CH)

A CH attack is an individual episode of pain that can last from a few minutes to some hours. A cluster bout or period usually lasts from some weeks to months. Pain is excruciatingly severe and is mainly located around the orbital and temporal regions and usually lasts 45 to 90 min, with an abrupt onset and cessation. The distinctive feature of CH is the association with autonomic symptoms such as conjunctival injection, lacrimation, miosis, ptosis, eyelid edema, rhinorrhoea, nasal blockage, forehead or facial sweating. In contrast to migraine, CH sufferers are usually restless and irritable, move about and look for a movement or posture that may relieve the pain. Alcohol, nitroglycerin, exercise and elevated environmental temperature are precipitants of acute attacks. Most patients have 1 or 2 annual cluster periods, each lasting between 1 and 3 months. It is a lifelong disorder in the majority of patients.

Pharmacological Treatment. Abortive agents are administered parenterally or by the nasal route. They are represented by sumatriptan, zolmitriptan, oxygen inhalation, intranasal dihydroergotamine and subcuta-

neous octreotide [11–16]. For prevention of attacks, the main stay treatments are high-dose verapamil [17, 18], lithium [19], methysergide [20], melatonin [21], prednisolone [22] and topiramate [23]. Nerve blocks by means of the local injection of anesthetics and corticoids around the greater occipital nerve has yielded inconsistent results [24–26].

Surgery. Destructive procedures may be employed as a last-resort measure in patients resistant to pharmacological treatment and exclusively with unilateral headache. The main procedures employed are the interruption of the trigeminal sensory or autonomic pathways, trigeminal sensory rhizotomy via a posterior fossa approach, radiofrequency trigeminal gangliorhizolysis and microvascular decompression of the trigeminal nerve with or without microvascular decompression of the nervus intermedius. All these techniques bring with them several complications.

Neuromodulation. Franzini et al. [27] and Leone et al. [28] reported favorable lasting results in a cohort of patients with chronic CH treated with deep brain stimulation (DBS). Suboccipital nerve stimulation is also being investigated in CH [28, 29].

SUNCT

SUNCT syndrome manifests as a unilateral headache which occurs in association with cranial autonomic features. In contrast to other TACs, attacks have a very brief duration, can occur very frequently and the prominent feature is represented by conjunctival injection and lacrimation [30, 31]. This syndrome is rare, has a male predominance (sex ratio: 2.1:1) and the onset is between 40 and 70 years. Pain is usually maximal in the ophthalmic distribution of the trigeminal nerve (orbital and peri-orbital regions, forehead and temple) and is typically unilateral. It is of moderate to severe intensity and attacks last between 5 and 250 seconds [32] although attacks lasting up to 2 hours have been described [33–35]. Attacks are always accompanied by ipsilateral conjunctival injection and lacrimation, while other autonomic symptoms are less commonly reported.

The majority of patients can precipitate attacks by touching trigger zones innervated by trigeminal nerve. SUNCT must be differentiated from trigeminal neuralgia, primary (idiopathic) stabbing headache and paroxysmal hemicrania.

Pharmacological Treatment. Several categories of drugs used in other headache syndromes such as non-

steroidal anti-inflammatory drugs (including indomethacin), paracetamol, 5-HT agonists (triptans, ergotamine and dihydroergotamine) beta-adrenergic blockers, tricyclic antidepressants, Ca-channel blockers (verapamil, nifedipine), methysergide, lithium, prednisolone, phenytoin, baclofen and i.v. lignocaine have proved to be ineffective in SUNCT [34]. Intravenous lignocaine has been shown to be effective in the acute suppression of SUNCT [37].

Prevention of attacks may be obtained with carbamazepine [33, 34, 36, 38, 39], lamotrigine [40–44], gabapentin [45–47] and topiramate [34].

Surgery. Several surgical approaches have been tried in SUNCT syndrome, but none has a follow up sufficient to reach reliable conclusions. Destructive procedures are therefore at the moment not recommended.

Neuromodulation. Leone et al. [48] have recently reported excellent results in SUNCT after stimulation of posterior hypothalamus.

Future Directions

Neuromodulation appears to be a promising new approach to treatment of both CH and SUNCT syndromes refractory to other treatments.

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