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Trigeminal autonomic cephalalgias: a review

Trójdzielno-autonomiczne bóle głowy – przegląd piśmiennictwa

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Abstract

Trigeminal autonomic cephalalgias are a group of primary headache disorders presenting as unilateral pain in the somatic distribution of the trigeminal nerve, associated with ipsilateral cranial autonomic symptoms. This clinicopathologic group includes cluster headache, paroxysmal hemicrania, hemicrania continua and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing/cranial autonomic features, which differ mainly as regards the duration and frequency of pain as well as response to treatment. These disorders are not as rare as they were thought to be and due to the severity of the pain can substantially affect the patients' quality of life. Many other forms of primary headaches, such as migraine, trigeminal neuralgia and primary stabbing headache, as well as secondary headaches, particularly those caused by pituitary, posterior fossa, orbital, paranasal sinus and vascular pathology, need to be carefully considered in the diagnosis of trigeminal autonomic cephalalgias. Research in this field, particularly using functional neuroimaging, has resulted in a much better understanding of these disorders. Dysfunction in the nociceptive modulatory pathways in brain's pain matrix is currently thought to produce a permissive state for the occurrence of a trigeminal autonomic cephalalgia attack, with posterior hypothalamus serving as a terminator rather than the generator of the attack. The current treatment strategies include medical and surgical approaches; of the latter, neuromodulation techniques, particularly deep brain stimulation of posterior hypothalamus, have proven to be particularly effective and promising.

Key words: trigeminal autonomic cephalalgia, cluster headache, paroxysmal hemicrania, hemicrania continua, SUNCT, SUNA

Streszczenie

Trójdzielno-autonomiczne bóle głowy stanowią grupę pierwotnych bólów głowy, w których jednostronny ból w okolicy zaopatrywanej przez nerw trójdzielny związany jest z tożstronnymi objawami autonomicznymi w obrębie czaszki. Ta kliniczno-patologiczna grupa obejmuje klasterowy ból głowy, hemikranię napadową, hemikranię ciągłą i krótkotrwałe napady jednostronnego bólu głowy przypominającego nerwoból z przekrwieniem spojówek i łzawieniem/objawami autonomicznymi w obrębie czaszki. Postaci te różnią się przede wszystkim czasem trwania i częstością występowania bólu, a także odpowiedzią na leczenie. Zaburzenia te nie są tak rzadkie, jak dawniej przyjmowano, a ich nasilenie może znacząco wpływać na jakość życia pacjentów. W diagnostyce różnicowej trójdzielno-autonomicznych bólów głowy należy wziąć pod uwagę wiele innych rodzajów pierwotnych bólów głowy, takich jak migrena, neuralgia trójdzielna i pierwotny kłujący ból głowy, jak również wtórne bóle głowy, zwłaszcza te spowodowane przez patologię przysadki mózgowej, tylnego dołu czaszki, oczodołów, zatok przynosowych i naczyń. Badania na tym polu, w szczególności z wykorzystaniem neuroobrazowania funkcjonalnego, zaowocowały znacznie lepszym zrozumieniem tych chorób. Obecnie uważa się, że zaburzenia modulacyjnych dróg nocyceptywnych w macierzy bólu ośrodkowego układu nerwowego wytwarzają permisywny stan dla wystąpienia napadu trójdzielno-autonomicznego bólu głowy, przy czym tylna część podwzgórza wydaje się służyć raczej jako terminator niż generator napadu. W leczeniu tej grupy schorzeń stosuje się środki farmakologiczne, jak również techniki chirurgiczne; z tych ostatnich neuromodulacja, szczególnie głęboka stymulacja mózgu w obrębie tylnej części podwzgórza, okazała się szczególnie skuteczna i obiecująca.

Słowa kluczowe: trójdzielno-autonomiczne bóle głowy, klasterowy ból głowy, hemikrania napadowa, hemikrania ciągła, SUNCT, SUNA

INTRODUCTION

Trigeminal autonomic cephalalgias (TACs) are a group of primary headache disorders presenting as unilateral pain in the somatic distribution of the trigeminal nerve, associated with ipsilateral cranial autonomic symptoms (CASs) resulting from the activation of parasympathetic trigeminal autonomic reflex (TAR). The International Classification of Headache Disorders, 3rd edition, beta version (ICHD-3 beta) recognises four forms of TACs, mainly on the basis of the duration and frequency of pain as well as response to treatment: cluster headache (CH), paroxysmal hemicrania (PH), hemicrania continua (HC) and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing/cranial autonomic features (SUNCT/SUNA) [Headache Classification Committee of the International Headache Society (IHS), 2013]. Most of the above-mentioned types, apart from HC, are further categorised into episodic and chronic as well as probable forms. Many other forms of primary headaches, such as migraine, trigeminal neuralgia and primary stabbing headache, as well as secondary headaches, particularly those caused by pituitary, posterior fossa, orbital, paranasal sinus and vascular pathology, need to be carefully considered in the diagnosis of trigeminal autonomic cephalalgias.

EPIDEMIOLOGY

CH is the most studied TAC, mainly because it is the most common subtype of TACs and actually more common than previously thought. The prevalence from surveys of various populations ranges from 64 to 381 per 100,000; the mean prevalence amounts approximately to 0.1% in the general population (Costa *et al*., 2015; Eller and Goadsby, 2016; Sjaastad and Bakketeig, 2003; Tonon *et al*., 2002). A clear male predominance is evident, with a male:female ratio ranging from 2.5:1 to 7.1:1 (Bahra *et al*., 2002; May *et al*., 2006). A meta-analysis of data from different countries demonstrated a 1-year incidence of 53 per 100,000 and lifetime incidence of 124 per 100,000 (Fischera *et al*., 2008).

Since the other subtypes of TACs are less prevalent, there is less epidemiological data available on them. This could be partly due to the fact that they are often misdiagnosed as CH, migraine and trigeminal neuralgia. Also, patients are less likely to seek medical attention with these less severe forms of TACs. It has been suggested that the prevalence of PH and SUNCT is around 0.5 per 1,000 or less, quite a high figure that probably takes into account the previous points and makes up for them (Sjaastad and Bakketeig, 2003). Another study conservatively estimated the prevalence of SUNCT/SUNA at 6.6 per 100,000 and its incidence at 1.2 per 100,000 (Williams and Broadley, 2008). SUNA is also more common in women with the male:female ratio of 1:2; the opposite is true for SUNCT with the ratio of 2:1. PH, once believed to be more prevalent in women, has shown no gender preponderance in one study of a large cohort of patients.

PATHOPHYSIOLOGY

The pathophysiology of TACs has as yet not been fully elucidated. To understand the mechanism of headache in this group of disorders it is necessary to review the functional anatomy of the structures involved in pain processing and modulation. The intracranial structures capable of producing pain have long been known to include pial, arachnoid and dural blood vessels, large cerebral arteries and dural venous sinuses; the brain parenchyma itself does not produce pain (Ray and Wolff, 1940). The pain producing dura mater and cerebral blood vessels are sometimes together referred to as durovascular complex. The nociceptive stimuli from this complex (as well as head, face and neck) are conducted via unmyelinated C-fibres and thinly myelinated Aδ-fibres of the trigeminal nerve, mainly its ophthalmic division (V1), to the Gasserian ganglion. Due to the fact that they innervate intracranial vascular structures, these nociceptive neurons are collectively called trigeminovascular system (TVS) (May and Goadsby, 1999). In addition to that, pain from infratentorial/posterior fossa intracranial structures (as well as posterior head and neck) is conducted through the branches of upper cervical nerves, mainly greater occipital nerve, to the upper cervical dorsal root ganglia (C1–C3). Neurons in the Gasserian ganglion and upper cervical root ganglia constitute first order sensory neurons of the nociceptive pathway. The neurotransmitters involved in pain transmission at the level of TVS include calcitonin gene-related peptide (CGRP), substance P (SP), neurokinin A (NKA) and pituitary cyclase-activating peptide (PACAP) (Holland and Goadsby, 2007).

Trigeminal axons originating in the Gasserian ganglion synapse on the pars caudalis of the spinal trigeminal nucleus, also known as trigeminal nucleus caudalis (TNC), which extends from the obex in the medulla to the C2 cervical spinal segment. Similarly, axons of the sensory neurons in the upper cervical dorsal root ganglia (C1–C3) project to the dorsal horns of upper cervical spinal segments. Trigeminal nucleus caudalis and the C1–C3 dorsal horns contain second order sensory neurons and since they constitute one unit both anatomically and functionally, together they are referred to as trigeminocervical complex (TCC) (Bartsch and Goadsby, 2003). Trigeminocervical complex serves as the common relay station controlling the inflow of nociceptive input from intracranial pain-producing structures (as well as face, head and neck). Neurons of the TCC project via quintothalamic (trigeminothalamic) tract through the brainstem, where they decussate, to the third order sensory neurons in the thalamus, where the stimulus is further transmitted to the somatosensory cortex (SSC) posterior to the central sulcus.

Cranial autonomic symptoms in trigeminal autonomic cephalalgias are a result of the activation of parasympathetic trigeminal autonomic reflex (TAR), also known as trigeminal parasympathetic and trigeminal facial reflex (Ailani, 2016). The afferent limb of the reflex is identical to the sensory pathway described above up to the second order sensory neurons in the trigeminocervical complex. Some neurons in this complex have a reflex connection with the superior salivatory nucleus (SSN) in the pons, where parasympathetic preganglionic fibres of the facial nerve arise from. These fibres synapse in the pterygopalatine ganglion (PPG, also known as sphenopalatine ganglion, SPG), otic ganglion and internal carotid miniganglia. The postganglionic parasympathetic neurons containing various neurotransmitters, such as vasoactive intestinal peptide (VIP), peptide histidine isoleucine (PHI), peptide histidine methionine (PHM) and other VIP-related peptides, innervate parasympathetic effectors whose activation results in parasympathetic symptoms that are ipsilateral to craniofacial pain (Holland and Goadsby, 2007). Symptoms such as miosis and ptosis, which constitute incomplete Horner's syndrome, are thought to arise from parasympathetic-induced perivascular oedema and vasodilatation of the internal carotid artery (ICA) and subsequent functional impairment of the third order sympathetic fibres running through the cavernous sinus. These fibres originate in the superior cervical ganglion and their terminals produce such neurotransmitters as neuropeptide Y (NPY), noradrenaline (NA) and adenosine triphosphate (ATP) (Holland and Goadsby, 2007).

How exactly the nociceptive and parasympathetic systems described above are activated in the course of a TAC attack has been a matter of a debate throughout the years. Two main hypotheses emerged: peripheral and central (Leone and Bussone, 2009). The former places the origin of the symptoms in the structures outside of the central nervous system (CNS), such as trigeminal nerve and intracranial arteries. The latter purports that there is a central cluster/TAC generator, located somewhere in the CNS, either directly triggering the attacks or acting as a facilitator of a permissive state for the occurrence of the attack.

The main argument supporting the first hypothesis comes from the observations that lesions located in various intra- and extracranial structures, particularly pituitary and posterior fossa, but also orbits, paranasal sinuses as well as vasculature, can cause secondary, symptomatic TACs, whose clinical presentation is indistinguishable from those of primary TACs (Berk and Silberstein, 2016; Jin *et al.*, 2016; Rigamonti *et al.*, 2007; Rojas-Ramirez *et al.*, 2016). These lesions, which can take the form of a tumour, infection, arteriovenous malformation, inflammation and trauma, are thought to directly stimulate the trigeminovascular system generating pain, but once removed, the pain ceases. Thus, the work-up for TACs should include pre- and post-contrast magnetic resonance imaging (MRI) of the brain as well as endocrine screen, comprised of insulin-like growth factor-1 (IGF-1), cortisol, follicular stimulating hormone (FSH), luteinising hormone (LH), thyroid stimulating hormone (TSH), thyroxine (T4), triiodothyronine (T3) and prolactin (PRL) testing (Eller and Goadsby, 2016). Also supporting the peripheral hypothesis is the fact that increased concentrations of CGRP in the ipsilateral jugular vein have been found during the CH attacks and that surgical resection of trigeminal nerve fibres has been described to alleviate the pain in some cases (Goadsby and Edvinsson, 1994; Jarrar *et al.*, 2003). In addition to that, sumatriptan, a drug highly effective in the termination of CH, does not cross blood-brain barrier easily and is hypothesised to exert its action peripherally, on the serotoninergic receptors in the trigeminal ganglion and blood vessel walls (Hoskin and Goadsby, 1998; Kaube *et al.*, 1993).

The main evidence for the existence of the central cluster/TAC generator comes from the functional neuroimaging studies. Those studies have shown a consistent pattern of ipsilateral posterior hypothalamic activation in the course of the attack; this activation is ipsilateral to pain in CH, contralateral in PH and HC and ipsilateral, contralateral, bilateral or absent in SUNCT/SUNA (Matharu *et al.*, 2006; May *et al.*, 1999, 1998; Sprenger *et al.*, 2005). The involvement of hypothalamus in the origin of the pain is further supported by the fact that hypothalamic deep brain stimulation (DBS) proved to be a successful therapeutic option in medically refractory, intractable CH cases (Clelland *et al.*, 2014; Piacentino *et al.*, 2014). Apart from hypothalamus, other CNS structures believed to be involved in pain processing and modulation are anterior cingulate cortex (ACC), insula, thalamus, amygdala, supplementary motor area (SMA), posterior parietal cortex (PPC), prefrontal cortex (PFC), primary and secondary SSC, basal ganglia and cerebellar cortex as well as certain brainstem areas, such as nucleus tractus solitarius (NST), rostral ventromedial medulla (RVM), periaqueductal gray matter (PAG) and nucleus raphe magnus (NRM). Together, they constitute brain's pain matrix or, in a broader sense, salience network involved in pain processing, modulation and integration of sensory discriminative and affective/cognitive components of nociception (Costa *et al.*, 2015; Legrain *et al.*, 2011).

Further supporting the central hypothesis is the fact that CH attacks exhibit a remarkable circadian and circannual periodicity, with diurnal recurrence of pain and seasonal recurrence of clusters, which is thought to be related to the biological clock, suprachiasmatic nucleus (SCN) located in the hypothalamus (Pringsheim *et al.*, 2002). Also, sensory TCC neurons are modulated by the hypothalamus through the neurotransmitters of the orexinergic system, such as orexin A and B (Holland and Goadsby, 2007). Posterior hypothalamus also modulates parasympathetic and sympathetic system via connections with SSN and second-order sympathetic neurons in the C8–Th2 intermediolateral columns, respectively (Amonoo-Kuofi, 1999; Haane *et al.*, 2011). Dysfunction in these modulatory pathways

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is currently thought to produce a permissive state for the occurrence of a TAC attack. Posterior hypothalamus, once thought to function as a cluster generator, may actually act as a terminator of the attacks, thus influencing the duration of the attack, one of the main distinguishing features between different TACs (Leone *et al*., 2010a; Leone and Bussone, 2009; Leone and Proietti Cecchini, 2017; May *et al*., 1998).

CLINICAL PRESENTATION

As a clinicopathologic group, these disorders share some important qualities. In all of them, the pain is described as sharp, stabbing, throbbing or boring, although the first two denominators are more often used in connection with SUNCT/SUNA and the last two more typically associated with the longer-lasting forms, CH and PH. The most common location of the pain is in the distribution of the first division of the trigeminal nerve, although it can occur anywhere in the head. The severity of the pain is marked, less often moderate. On the other hand, the main characteristics in which these TACs differ from each other are the duration and frequency of pain as well as response to treatment [Headache Classification Committee of the International Headache Society (IHS), 2013] (Tab. 1).

According to the ICHD-3 beta, the pain in cluster headache lasts from 15 minutes to 3 hours with a frequency from one every other day to 8 per day. Characteristically, attacks occur in clusters lasting for weeks to months separated by remission periods usually lasting months

	Cluster headache	**Paroxysmal hemicrania**	**Hemicrania continua**	**SUNCT/SUNA**
Number of attacks	≥5	≥20	Persistent	≥20
Severity	Severe or very severe	Severe	Any	Moderate or severe
Location	Unilateral orbital, supraorbital and/or temporal	Unilateral orbital, supraorbital and/or temporal	Unilateral	Unilateral orbital, supraorbital, temporal and/or other trigeminal distribution
Duration	15 to 180 minutes	2 to 30 minutes	Persistent	1 to 600 seconds
Frequency	One per 2 days to 8 per day	≥5 per day	Present for >3 months, with exacerbations of moderate or greater intensity	≥1 per day
Abortives	Oxygen, parenteral triptans	Indomethacin	Indomethacin	Intravenous lidocaine
Preventives	Verapamil, lithium, topiramate			Lamotrigine, topiramate, gabapentin
Additional features	1. Either or both of the following: a) At least one of the following symptoms or signs, ipsilateral to the headache: • conjunctival injection and/or lacrimation • nasal congestion and/or rhinorrhoea • eyelid oedema • forehead and facial sweating • forehead and facial flushing • sensation of fullness in the ear • miosis and/or ptosis b) A sense of restlessness or agitation 2. Attacks occur in series lasting for weeks or months (so-called cluster periods) separated by remission periods usually lasting months or years	1. At least one of the following symptoms or signs, ipsilateral to the headache: a) conjunctival injection and/or lacrimation b) nasal congestion and/or rhinorrhoea c) eyelid oedema d) forehead and facial sweating e) forehead and facial flushing f) sensation of fullness in the ear g) miosis and/or ptosis 2. Attacks are prevented absolutely by therapeutic doses of indomethacin	1. Either or both of the following: a) At least one of the following symptoms or signs, ipsilateral to the headache: • conjunctival injection and/or lacrimation • nasal congestion and/or rhinorrhoea • eyelid oedema • forehead and facial sweating • forehead and facial flushing • sensation of fullness in the ear • miosis and/or ptosis b) A sense of restlessness or agitation, or aggravation of the pain by movement 2. Responds absolutely to therapeutic doses of indomethacin	1. At least one of the following symptoms or signs, ipsilateral to the headache: a) conjunctival injection and/or lacrimation: • both in SUNCT • only one or neither in SUNA b) nasal congestion and/or rhinorrhoea c) eyelid oedema d) forehead and facial sweating e) forehead and facial flushing f) sensation of fullness in the ear g) miosis and/or ptosis 2. Cutaneous triggerability without a refractory period

Tab. 1. Trigeminal autonomic cephalalgias [adapted from Headache Classification Committee of the International Headache Society (IHS), 2013, with changes]

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to years. Single attacks demonstrate circadian rhythm, frequently experienced at the same times of the day. Analogously, the clusters of attacks exhibit circumannual rhythm, often encountered during the same month or season of the year. The location of the pain is unilateral orbital, supraorbital, temporal or any combination of these sites, but it may spread to other regions; the pain is usually side-locked during an individual cluster period. The intensity of the pain is excruciating, in the description of patients often exceeding that of labour, renal colic and long bone fractures. Patients are usually unable to lie down, and restlessly pace the floor. The unique feature of CH is responsiveness to high-flow oxygen; parenteral and intranasal triptans are also effective, although the latter to a lesser extent. At least one CAS needs to be present, such as conjunctival injection, lacrimation, periorbital oedema, rhinorrhoea, nasal congestion, aural fullness, facial flushing and diaphoresis, miosis and ptosis. Photo- and phonophobia as well as nausea and vomiting can also occur in the course of the attack, but never as pronounced as in the case of migraine.

The duration and frequency of PH attacks is intermediate. The pain is severe, unilateral orbital, supraorbital or temporal and lasting generally from 2 minutes to half an hour. Attacks have the frequency of above 5 per day with a mean of 11 per day reported in one series and they need to be accompanied by at least one CAS. Migrainous features, such as photo- and phonophobia as well as nausea and vomiting can also occur, possibly confounding the diagnosis. The important diagnostic feature of PH is the fact that the attacks are absolutely prevented by the therapeutic doses of indomethacin. This, as well as prominent lateralisation of CASs, photo- and phonophobia helps to differentiate this disorder from migraine (Goadsby *et al.*, 2010). Presence for at least 3 months with exacerbations of moderate or greater intensity and a sense of restlessness, agitation or aggravation of the pain by movement are a feature of the continuous form of the disease, hemicrania continua.

SUNCT/SUNA probably represent a spectrum of one disorder. These conditions are characterised by the shortest duration of the attack, ranging from 1 second up to 10 minutes. These attacks need to come about at least once a day, but they often reach the frequency upwards of a hundred per day. The pain in these subtypes of TACs occurs as single stabs, series of stabs or in a saw-tooth pattern, in which the pain does not fully resolve between the stabs. The severity of the pain, which is often triggered by cutaneous stimuli, is moderate or marked and the location unilateral orbital, supraorbital, temporal or other trigeminal distribution. Obviously, as the name implies, at least one CAS needs to be present ipsilaterally to the symptoms. Large series of cases have proved that pain can actually develop anywhere in the head, although the most common location is in the distribution of the ophthalmic division of the trigeminal nerve. This, as well as the presence of CASs and triggerability without a refractory period, helps to differentiate this type of primary headache from trigeminal neuralgia and primary stabbing headache (VanderPluym and Richer, 2015). However, clinical and radiological data from recent studies indicate that SUNCT/SUNA and trigeminal neuralgia might actually constitute a continuum of one disorder (Lambru and Matharu, 2014).

MANAGEMENT

The treatment for this group of disorders, as often is the case with primary headaches, is further divided into abortive and preventive. The abortive treatment is used for acute attacks with the aim to terminate them. The preventive treatment attempts to suppress the headaches and is instigated when the attacks reach a frequency that considerably affects the patient's quality of life.

The treatment of choice in an acute CH attack is a parenteral triptan (Becker, 2013). Typically, this is subcutaneous sumatriptan, but it can also be intranasal sumatriptan and zolmitriptan. High-flow oxygen is also effective, usually 7 to 15 L/min for 10 to 30 minutes, administered through a non-rebreathing mask. Short taper of oral corticosteroids, e.g. prednisone, taken at the beginning of a cluster can help terminate it and often acts as a bridge to preventives. The most common drug currently used to that end is verapamil (Blau and Engel, 2004; Tfelt-Hansen and Tfelt-Hansen, 2009). This drug has a potential to cause atrioventricular conduction delay that can manifest as first, second or even third degree heart block as well as other bradyarrhythmias. Thus, an ECG is required after two weeks of dose change. The maximum dose is 480 mg per day in three divided doses, although dosages as high as 960 or even 1200 mg per day have been described. Other preventive treatment options include lithium and topiramate (Láinez *et al.*, 2003; Stochino *et al.*, 2012). It is important to monitor the lithium plasma concentrations, however toxicity, which can include catastrophic renal and CNS complications, can occur even at therapeutic levels. Monitoring involves checking lithium levels 12 hours post-dose at least every three months and during any acute illness. The side effects of topiramate include weight loss and depressed mood.

Responsiveness to a non-steroidal anti-inflammatory drug indomethacin is the sine qua non condition for the diagnosis of PH and HC (VanderPluym, 2015). The starting dose is usually 75 mg per day in three divided doses, which is increased within a couple of days to 150 mg per day. The response should come promptly within 48 hours, but occasionally it takes longer. Treatment is usually maintained at the doses between 12.5 to 300 mg per day. The most common side effect of chronic indomethacin use is peptic ulcer disease, so prophylaxis with proton pump inhibitor should be commenced at the same time. Lack of response to therapeutic doses of indomethacin should

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prompt a clinician to reconsider the diagnosis. Coxibs, selective cyclooxygenase-2 inhibitors, as well as verapamil and topiramate have also been shown to be effective in some cases (Goadsby *et al.*, 2010).

In the acute treatment of severe SUNCT/SUNA attacks, intravenous lidocaine was found to alleviate both the pain and CASs (Arroyo *et al.*, 2010; Matharu *et al.*, 2004). The dose is 1 to 4 mg per kg per hour by infusion. This is done ideally in a monitored setting as serious cardiovascular side effects, such as hypotension and dysrhythmias as well as seizures can occur. In the preventive treatment of this disorder, lamotrigine was shown to be particularly effective (Rosselli and Karpinski, 2011). The usual dose is 100 to 300 mg per day, however, this needs to be titrated from small doses to avoid potentially serious dermatologic complications, including Stevens–Johnson syndrome. Topiramate, gabapentin, carbamazepine and oxcarbazepine have also been tried with some success (Pomeroy and Nahas, 2015).

Finally, for medically refractory TACs, nerve blocks and neuromodulation have demonstrated effectiveness. Greater occipital nerve (GON) injections with anaesthetic and/or corticosteroid are helpful in alleviating pain in those difficult cases (Gantenbein *et al.*, 2012; Lambru *et al.*, 2014). This has also been attempted with mixed results on other nerves, such as auriculotemporal, supraorbital and supratrochlear (Blumenfeld *et al.*, 2013). Neurostimulation, particularly DBS of posterior hypothalamus, has gained a lot of interest recently, with very promising results in pharmacologically resistant cases (Clelland *et al.*, 2014; Fontaine *et al.*, 2010; Leone *et al.*, 2010a, 2010b). Peripheral nerve stimulation, including occipital nerve stimulation (ONS) has also been used (Leone *et al.*, 2016). These techniques have been shown to bring substantial relief to patients who have exhausted medical treatment options.

CONCLUSION

Trigeminal autonomic cephalalgias are primary headache disorders that seem to share a common underlying pathologic mechanism (Charleston, 2015). They are not as rare as they were thought to be and – due to the severity of the pain – they can substantially affect the patients' quality of life. Research in this field, particularly using functional neuroimaging, has resulted in a much better understanding of the disorder. The current treatment strategies include medical and surgical approaches; of the latter, neuromodulation techniques have proven to be particularly effective and promising.

Conflict of interest

The authors do not report any financial or personal relationships with other persons or organisations, which could adversely affect the content of the publication and lay claim to this publication.

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