Trigeminal Autonomic Cephalalgias

A Diagnostic and Therapeutic Overview

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The Trigeminal Autonomic Cephalalgias (TACs) are a group of headache disorders characterised by attacks of moderate to severe unilateral pain in the head or face, with associated ipsilateral cranial autonomic features such as lacrimation, conjunctival injection, rhinorrhoea, nasal congestion, eyelid oedema and ptosis. The syndromes vary in the duration and frequency of the attacks, with cluster headache (CH) attacks being the longest and least frequent, through paroxysmal hemicrania (PH), to the Short-lasting Unilateral Neuralgiform headache attacks, with the most frequent and shortest attacks. Hemicrania Continua has recently been included in the classification of TACs, although it shares characteristics of both migraine and the TACs.

Cluster headache

This is the commonest of the TACs, with an incidence of around 0.1%. There is a male: female predominance of 3:1. Attacks of severe to excruciating pain occur in and around the eye, retro-orbital region, and side of the head. Attacks last 15-180 minutes, and can occur once every other day, up to eight times per day.[1] The pain is associated with ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, forehead and facial sweating, miosis, ptosis end/or eyelid oedema, forehead and facial flushing, a sense of fullness in the ear, and/or with restlessness and agitation.

Characteristically the pain can wake the patient from sleep at night, often at a set time (such as 90 minutes after falling asleep). Attacks can be triggered by strong smells such as paints, perfumes or petrol fumes, and by ingestion of alcohol – which will typically induce an attack within a few minutes, as opposed to migraine attacks which are induced within hours of ingesting alcohol.

Episodic and Chronic Cluster Headache

In 85-90% of cases, CH occurs as Episodic Cluster Headache (ECH), in bouts (or 'clusters'), lasting weeks or months at a time, separated by remission periods of months or years. Patients with attacks for more than a year's duration without a remission of a month have Chronic Cluster Headache (CCH). CCH can arise de novo or can develop from ECH.

Paroxysmal Hemicrania

The attacks of Paroxysmal Hemicrania (PH) are similar to those of CH, but they are of shorter duration (2-30 minutes) and occur more frequently during the day (at least five attacks per day for more than half the time). The ipsilateral autonomic features are similar to CH. A diagnostic criterion of PH is that the attacks are abolished by Indomethacin.

Attacks can wake the patient from sleep, although much less frequently than in CH;[2] and there is less circadian and annual periodicity than in CH. Triggers to attacks included stress, relief from stress, and exercise (as with triggers to migraine), and also alcohol and neck movement.[2] As in CH, PH can occur as episodic or chronic forms, although CPH is commoner than EPH.

Short-lasting Unilateral Neuralgiform headache attacks (SUNCT and SUNA)

These syndromes have attacks of the shortest duration (1-600 seconds) and most frequent (up to hundreds of times per day). Originally known as SUNCT (Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing), it became apparent that any one or all of the full range of autonomic features could be present ipsilateral to the side of the attack; and therefore the ICHD-3 beta classification distinguishes between SUNCT and SUNA (Short-lasting Unilateral Neuralgiform headache attacks with cranial Autonomic symptoms), where either conjunctival injection, or tearing, or neither, but not both, are present.[1]

Again, SUNCT/SUNA can occur as either episodic or chronic forms (the latter is more common). There is a slight male preponderance in SUNCT. Multiple cutaneous stimuli have been reported to trigger attacks of SUNCT/SUNA, including:[3]

- Touching the face or scalp
- Bathing or showering
- Washing or brushing hair
- Shaving
- Nose blowing
- Chewing or eating
- Brushing teeth
- Talking
- Coughing
- Exercise
- Light (including sunlight and fluorescent lights)

Attacks can be of three types: single stab attacks; groups of stabs; or a saw-tooth pattern, with a group of stabs occurring in quick succession such that the pain does not return to baseline between stabs. The sawtooth attacks, made up of

Table 1: Differential Diagnoses of the TACs

Headache Syndrome	Differential Diagnoses	Distinguishing Features
CH	Migraine with prominent autonomic features	Agitation usually present in CH; also circadian and circannual periodicity
PH	CH	PH responds absolutely to indomethacin
SUNCT/SUNA	1)Trigeminal Neuralgia (TN)	Autonomic features and agitation are more prominent in SUNCT/SUNA, plus no refractory period between attacks as in TN
	2) CH or PH (groups of stabs of SUNCT/SUNA)	Cutaneous triggering more common in SUNCT/SUNA; also characterisation of the attack- stab/group of stabs/sawtooth
HC	1)CH with background pain 2)migraine with chronic background pain	HC responds absolutely to indomethacin

many single attacks of SUNCT/SUNA, can endure for minutes or hours, and can often be mistaken for longer-lasting TACs.[3] Figure 1 depicts the three different types of attacks of SUNCT/SUNA.

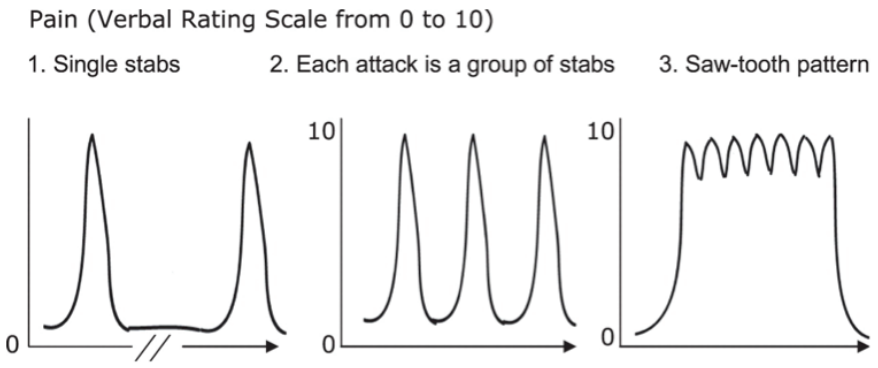

Figure 1. The different types of attacks in SUNCT/SUNA. Reproduced with permission from OUP 2006 (Cohen A S et al. Brain 2006;129:2746-2760).

Hemicrania Continua

Hemicrania Continua (HC) is a syndrome of continuous unilateral head or facial pain, without a moment's break, for at least three months' duration. There is a background constant pain with exacerbations up to moderate or severe intensity that can last for hours or days. The exacerbations are associated with ipsilateral cranial autonomic symptoms, as in the other TACs, and also agitation or restlessness. The symptom of itching or grittiness in the eye has been often cited as an identifying feature of HC, but a recent case series suggested that it was in fact another autonomic symptom referable to all the TACs.[4] However HC also shares some features of migraine, with some patients reporting aggravation of the pain by movement. Migrainous symptoms such as photophobia and phonophobia can be seen in all the TACs,[5] but are more common in HC.

Hemicrania continua is usually unremitting, but can occur in the remitting subtype where there are pain free periods lasting at least a day without treatment.

Differential diagnosis of the TACs

Table 1 outlines the differential diagnoses of the TACs, and suggests some clinical points to differentiate between them.

Symptomatic TACs secondary to structural lesions

The TACs are generally thought of as primary headache disorders. However there are an increasing number of reports of TAC mimics due to posterior fossa or pituitary lesions. In particular, SUNCT and SUNA are disproportionally over-represented in headaches due to pituitary micro- or macroadenomata.[3,6]

Pathophysiology of the TACs

Functional imaging studies have shown activation of the region of the posterior hypothalamus in CH,[7] SUNCT[8] and PH.[9] As recently reviewed in ACNR, the areas involved in migraine are the dorsal pons, locus ceruleus and periaqueductal grey matter.[10] Interestingly, HC, which shares clinical features of both migraine and TACs, has activation in both hypothalamus and brainstem structures.[11]

A striking feature of the TACs is the autonomic component accompanying each attack of pain. This is mediated by the trigeminal autonomic reflex, where stimulation of trigeminal efferents can result in cranial autonomic outflow.[12] Thus, some degree of autonomic symptomatology is a normal physiological response to cranial and facial pain, and can be present in other headache syndromes such as migraine, especially in the paediatric population.[13]

However in the TACs the autonomic symptoms are more prominent, in addition to agitation during an attack (especially in CH and SUNCT), which suggest a common pathophysiological link. It is suggested that a central disinhibition of the trigeminal-autonomic reflex, as well as hypothalamic direct modulation of the trigeminovascular nociceptive pathways, are responsible. Experimental results suggest that stimulation of the posterior hypothalamus significantly inhibited light and facial-skin evoked activity of neurons in the trigeminal caudalis and upper cervical regions,[14] which further imply the role of the hypothalamus in trigeminal pain syndromes.

Epidemiology of the TACs

Although rare disorders, the TACs and CH specifically may have a genetic preponderance. Genetic epidemiological surveys have shown that first-degree relatives of CH patients are more likely to have CH than in the general population.[15] The HCRTR2 1246G > A and the ADH4 925A > G polymorphisms have been associated with CH. Pharmacogenetic studies have suggested that the GNB3 825C > T polymorphism may modify treatment response to triptans among CH patients by altering the signal transduction cascade via G protein-coupled receptors.[16]

Treatment of the TACs

CH is the only TAC for which an acute (abortive) therapy is indicated to treat an individual attack. The other TACs are too short and too frequent for abortive therapy to be of any practical use, and therefore the mainstay of treatment is preventive therapy. Short-term preventive therapies are useful in CH and SUNCT, in order to allow a pain-free window for titration of preventive medications.

Cluster headache

Abortive therapies in CH include Sumatriptan 6mg to be given subcutaneously at the start of the attack, and this should abort an attack within a few minutes. This can be taken a maximum of twice a day. An alternative is Sumatriptan 20mg intranasal spray, which can be taken a maximum of three times a day.

Oxygen in high dose and high flow (12L/min for 15 mins) taken at the start of the

Table 2. Treatment Options for TACs

	CH	PH	SUNCT/SUNA	HC
Abortive therapies	Oxygen Sumatriptan sc Sumatriptan in	—	—	—
Short-term preventive	Prednisolone	—	Intravenous lidocaine	—
Preventive therapies				
Indomethacin	—	+++	—	+++
Verapamil	+++	+	—	+/-
Other calcium channel antagonists	—	+	—	—
Topiramate	++	+	+	+
Lithium	++	—	—	—
Lamotrigine	—	—	+++	—
Gabapentin	—	—	++	+
Amitriptyline	—	—	—	+
Non-pharmacological				
GON blockade	++	+/-	++	++
ONS	++	+	++	++

attack has been proven effective in a recent placebo-controlled trial.[17]

Preventive medications for CH are outlined in Table 2. In Episodic CH the preventive medications should be taken only during the bout, and are of no benefit if taken during the remission period. For patients with short bouts (six weeks or less) then verapamil is of less practical use, as the dose may only be titrated up every two weeks, thus taking a longer time to achieve a therapeutic dose.

Verapamil should be started at 80mg tds, and increased every two weeks by 80mg, to a maximum of 960mg tds, or at whichever dose supresses the attacks, or until side effects intervene. An ECG should be performed prior to commencement of verapamil, and also at every two weeks prior to each dose increase, in order to prevent the side effect of first degree heart block.[18]

In terms of short-term preventive therapy, intravenous methylprednisolone has been used as a short-term regimen in order to induce clinical remission,[19] and thus allow the upward titration of preventive medications during the pain-free period. Oral prednisolone at doses of 40mg daily or higher, have for many years been known to effect a short-term remission in CH.[20] Current practice is to give 60mg/day for three days, then to reduce by 10mg every three days, to zero.

Paroxysmal Hemicrania and Hemicrania Continua

Indomethacin is the gold standard treatment for these conditions, and in fact can be used as a diagnostic tool in the form of the modified Indotest.[21] Oral doses start at 25mg tds, increasing to 50mg tds, and subsequently to 75mg tds in partial or non-responders. If there is no response after 10 days at the highest dose, then the diagnosis of PH should be reconsidered.

If indomethacin is not tolerated, or in a subset of patients for whom indomethacin is not entirely beneficial, then a second line option would be an alternative NSAID or a COX II inhibitor such as rofecoxib or celecoxib, although with the caveats of the known side effects of these drugs. Topiramate has been reported of benefit, as has verapamil or other calcium channel antagonists such as flunarizine and nicardipine.

SUNCT/SUNA

Intravenous lidocaine, infused at 1.5-3.5 mg/kg/hour, for up to a period of seven days, has been shown to be benefical in case series, and is useful for patients with severe exacerbations, also with severe cutaneous triggering that render them unable to eat or drink. The beneficial effect of the lidocaine can last for weeks or even months after cessation of the infusion, and is therefore useful as an interim measure in order to titrate up the dose of oral medications.[21]

In terms of oral agents, lamotrigine has been reported as benefical in a number of case series, as has gabapentin. Topiramate may also be useful.

Hemicrania Continua

As in PH, the gold standard of treatment in HC is indomethacin. If indomethacin is poorly tolerated, options include other NSAIDS, COX-2 inhibitors, and topiramate. There are small series showing benefit in 66% of patients with amitriptyline, 20% on gabapentin, and 10% on topiramate.[22]

Non-pharmacological treatments

Greater Occipital Nerve (GON) injection

Nociception in the head and face, from the trigeminal and upper cervical afferents, converge at the trigeminocervical complex. Modulation of this system, either by blockade or stimulation, can abolish or reduce pain on the ipsilateral side. Injection of a local anaesthetic and/or steroid into the region of the greater occipital nerve has proven beneficial in many headache syndromes, including migraine, CH, HC, and new daily persistent headache.[23] The evidence for PH is less clear, and comes from single case reports. There is a case series for patients with SUNCT and SUNA who responded well to injections of 2% lidocaine and 80mg depomedrone, with pain-free times ranging from one week to six months.[8]

Occipital Nerve Stimulation

Occipital nerve stimulation (ONS) has been employed to good effect in patients with SUNCT[24] CH[25] and HC.[26] Again the evidence for ONS in PH is limited.

Other sites for stimulation in CH include the hypothalamus and sphenopalatine ganglion; the latter being the only one to have an acute abortive effect.[27]

Hypothalamic Deep Brain Stimulation (DBS)

As the region of the posterior hypothalamus is implicated in the pathophysiology of the TACs, there have been case series of deep brain stimulation to the region of the posterior hypothalamus with some success in CH and SUNCT, and a single case report in PH.[28] However the European Headache Foundation has suggested that these procedures should only be used in patients with medically intractable syndromes from tertiary headache centres, either as part of a valid study, or which have shown to be effective in such controlled studies with an acceptable side effect profile.

Summary

The TACs include Cluster Headache, Paroxysmal Hemicrania, Short lasting Unilateral Neuralgiform Headache attacks, and recently including Hemicrania Continua. The syndromes vary according to the severity and duration of the attacks (aside from HC which by definition is a continuous

headache). The pathophysiology is suspected to involve the region of the posterior hypothalamus, which by direct hypothalamic-trigeminal connections, and by modulating the trigeminal-autonomic reflex, can result in pain and ipsilateral autonomic symptoms. Medical treatments are specific to each syndrome, apart from greater occipital blockade or stimulation, which may be beneficial in most of the TACs. ◆

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