Trigeminal Autonomic Cephalalgias

A Diagnostic and Therapeutic Overview

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, rhinorrhea, 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 (SU.N.C.T and SU.N.A), 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, rhinorrhea, 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 00:00 hours 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 (CHC). CHC 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, 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.1 As in CH, PH can occur as episodic or chronic forms, although CPH is uncommon than EPH.

Short-lasting Unilateral Neuralgiform headache attacks (SU.N.C.T and SU.N.A)

These syndromes have attacks of the shortest duration (1-600 seconds) and most frequent (up to hundreds of times per day). Originally known as SU.N.C.T (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 SU.N.C.T and SU.N.A (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, SU.N.C.T/SU.N.A can occur as either episodic or chronic forms (the latter is more common). There is a slight male preponderance in SU.N.C.T Multiple cutaneous stimuli have been reported to trigger attacks of SU.N.C.T/SU.N.A, including:1

- 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
The TACs are generally thought of as primary due to posterior fossa or pituitary lesions. However there are an increasing number of reports of TAC mimics and periaqueductal grey matter. Interestingly, functional imaging studies have shown activation of the region of the posterior hypothalamus significantly inhibited light and facial-skin evoked activity of neurons in the trigeminal caudalis and upper cervical regions, 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. 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.

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 20 mg intranasal spray, which can be taken a maximum of twice a day. An alternative is sumatriptan 20 mg intranasal spray, which can be taken a maximum of two to three times a day.

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

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**Table 1: Differential Diagnoses of the TACs**

<table>
<thead>
<tr>
<th>Headache Syndrome</th>
<th>Differential Diagnoses</th>
<th>Distinguishing Features</th>
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</thead>
<tbody>
<tr>
<td>CH</td>
<td>Migraine with prominent autonomic features</td>
<td>Agitation usually present in CH; also cicardian and circannual periodicity</td>
</tr>
<tr>
<td>PH</td>
<td>CH</td>
<td>PH responds absolutely to indomethacin</td>
</tr>
<tr>
<td>SUNCT/SUNA</td>
<td>Trigeminal Neuralgia (TN)</td>
<td>Autonomic features and agitation are more prominent in SUNCT/SUNA, plus no refactorory period between attacks as in TN</td>
</tr>
<tr>
<td></td>
<td>CH or PH (groups of stabs of SUNCT/SUNA)</td>
<td>Cutaneous triggering common in SUNCT/SUNA; also characterisation of the attack - stab/group of stabs/sawtooth</td>
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<tr>
<td>HC</td>
<td>CH with background pain</td>
<td>HC responds absolutely to indomethacin</td>
</tr>
<tr>
<td></td>
<td>migraine with chronic background pain</td>
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HC, which shares clinical features of both migraine and TACs, has activation in both hypothalamus and brainstem structures.

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. 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.

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, which further imply the role of the hypothalamus in trigeminal pain syndromes.
**Table 2. Treatment Options for TACs**

<table>
<thead>
<tr>
<th>Non-pharmacological</th>
<th>CH</th>
<th>PH</th>
<th>SUNCT/SUNA</th>
<th>HC</th>
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<tbody>
<tr>
<td><strong>Abortive therapies</strong></td>
<td>Oxygen</td>
<td>Sumatriptan sc</td>
<td>Sumatriptan in</td>
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<tr>
<td><strong>Short-term preventive</strong></td>
<td>Prednisolone</td>
<td>—</td>
<td>Intravenous lidocaine</td>
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<tr>
<td><strong>Preventive therapies</strong></td>
<td>Indomethacin</td>
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<tr>
<td></td>
<td>Verapamil</td>
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<tr>
<td></td>
<td>Other calcium channel antagonists</td>
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<tr>
<td></td>
<td>Topiramate</td>
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<td></td>
<td>Lithium</td>
<td>++</td>
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<td></td>
<td>Lamotrigine</td>
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<tr>
<td></td>
<td>Gabapentin</td>
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<tr>
<td></td>
<td>Amitriptyline</td>
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**GON blockade**

- **ONS**
- **SUNCT/SUNA**
- **HC**

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**Indirect Effects**

- **Hemicrania Continua**
- **Paroxysmal Hemicrania**

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**Non-pharmacological treatments**

**Greater Occipital Nerve (GON) injection**

Intracranially to the head and face, from the trigeminal and upper cervical afferents, converge at the trigeminocervical complex. Modulation of this system, either by blockage or stimulation, can abolish or reduce pain on the ipsilateral side. Injection of a local anesthetic 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. 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.

**Occipital Nerve Stimulation (ONS)**

Occipital nerve stimulation (ONS) has been employed to good effect in patients with SUNCT/CH and HC. 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.

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**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. 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.
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.

REFERENCES


