

TRIGEMINAL AUTONOMIC CEPHALGIAS

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ii19

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The trigeminal autonomic cephalgias (TACs) are a group of primary headache disorders characterised by unilateral trigeminal distribution pain that occurs in association with prominent ipsilateral cranial autonomic features.¹ The group comprises cluster headache, paroxysmal hemicrania, hemicrania continua, and short lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT syndrome). Firstly, they must be differentiated from secondary TACs, and other short lasting primary headaches (table 1), and then from each other. The concept of a short lasting headache is naturally somewhat artificial in terms of defining “short”—that said, a typical attack time is less than four hours, in contrast with the major differential diagnosis of migraine in which attacks are usually longer.² The differentiation between TACs is essential since the treatments are very different. Hemicrania continua is a continuous headache and should be considered in the differential diagnosis of relatively long lasting chronic daily headache (see page ii2).³

The TACs are relatively rare, which is likely to be why they are poorly recognised in primary care. TACs will thus be referred to neurologists eventually, offering an excellent opportunity to diagnose and treat these patients. It is noteworthy that each of the TACs has been seen in paediatric practice. The importance of recognising these syndromes is underscored by their excellent but highly selective response to treatment.

CLUSTER HEADACHE

Cluster headache (CH) is a strictly unilateral headache that occurs in association with cranial autonomic features and, in most patients, has a striking circannual and circadian periodicity. It is an excruciating syndrome and is probably one of the most painful conditions known to humans. Female patients describe each attack as being worse than childbirth.

Epidemiology

The prevalence of CH is estimated to be 0.1%,⁴ approximately the same as that of multiple sclerosis in the UK. The male:female ratio is 3.5–7:1.⁵ It can begin at any age though the most common age of onset is the third or fourth decade of life.

Clinical features

It is useful for both clinician and patient to standardise the terms used in CH. A *cluster headache* or *an attack* is an individual episode of pain that can last from a few minutes to some hours. A *cluster bout* or *period* refers to the duration over which recurrent cluster attacks are occurring; it usually lasts some weeks or months. A *remission* is the pain-free period between two cluster bouts. CH is a disorder with highly distinctive clinical features. These features are dealt with under two headings: *the cluster attack* and *the cluster bout*.

The cluster attack

The attacks are strictly unilateral, though the headache may alternate sides. The pain is excruciatingly severe. It is located mainly around the orbital and temporal regions though any part of the head can be affected. The headache usually lasts 45–90 minutes but can range from 15 minutes to three hours. It has an abrupt onset and cessation. Interictal discomfort or pain is present in some patients.⁷

The signature feature of CH is the association with cranial autonomic symptoms, and it is extremely unusual for these not to be reported. The International Headache Society (IHS) classification diagnostic criteria⁷ require these features (table 2). The autonomic features are transient, lasting only for the duration of the attack, with the exception of partial Horner's syndrome; ptosis or miosis may rarely persist, especially after frequent attacks.

Recently, there have been several descriptions of the full range of typical migrainous symptoms in significant proportions of cluster patients.^{6,8} Premonitory symptoms (tiredness, yawning) and associated features (nausea, vomiting, photophobia, phonophobia), in addition to typical aura

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Table 1 Primary short lasting headaches¹

Prominent autonomic features	Sparse or no autonomic features
Cluster headache	Trigeminal neuralgia
Paroxysmal hemicrania	*Idiopathic stabbing headache
SUNCT syndrome	Cough headache
	Benign exertional headache
	Headache associated with sexual activity
	Hypnic headache

*Likely to be renamed primary stabbing headache when the International Headache Society classification² is revised.⁹

symptoms, have all been described in relation to cluster attacks. However, in pronounced contrast to migraine, the majority of CH sufferers (> 90%) are usually restless and irritable with the attack, preferring to move about in the hope of finding a movement or posture that may relieve the pain.⁶

The cluster attack frequency varies between one every alternate day to three daily, although some have up to eight daily. The condition can have a striking circadian rhythmicity, with some patients reporting that the attacks occur at the same time each day.

Alcohol, nitroglycerine, exercise, and elevated environmental temperature are recognised precipitants of acute cluster attacks. Alcohol induces acute attacks, usually within an hour of intake, in the vast majority of sufferers, contrasting with migraine sufferers who generally have headache some hours after alcohol intake. Alcohol does not trigger an attack during a remission. Allergies, food sensitivities, reproductive hormonal changes,⁶ and stress do not appear to have any significant role in precipitating attacks.

The cluster bout

CH is classified according to the duration of the bout. Some 80–90% of patients have *episodic cluster headache* (ECH), which is diagnosed when they experience recurrent bouts, each with a duration of more than a week and separated by remissions lasting more than two weeks. The remaining 10–20% of patients have *chronic cluster headache* (CCH) in which either no remission occurs within one year or the remissions last less than two weeks. The time window to differentiate episodic and chronic CH will be increased to four weeks after the IHS classification is revised.⁹

Most patients with ECH have one or two cluster periods annually, each lasting between 1–3 months. Often, a striking circannual periodicity is seen with the bouts occurring in the same month of the year. Although the duration of the cluster and remission periods varies between individuals, these periods remain relatively consistent within the same individual.

Differential diagnosis

In spite of the rather characteristic clinical picture, the differential diagnosis may be difficult in some cases as each of the features of CH can be mimicked by other headaches. The main differential diagnoses to consider are: secondary causes of CH, other TACs, migraine, and hypnic headache.

Before a diagnosis of CH can be made, secondary headache disorders that mimic CH need to be excluded. Symptomatic CH has been described after infectious, vascular, and neoplastic intracranial lesions. Any atypical features in the history or abnormalities on neurological examination (with the exception of partial Horner's syndrome) warrant further investigations to search for organic causes.

Table 2 Diagnostic features of cluster headache modified from the International Headache Society² with the proposed changes*

- Cluster headache has two key forms:
- ▶ Episodic: occurs in periods lasting 7 days to 1 year separated by pain-free periods lasting one month*
 - ▶ Chronic: attacks occur for more than one year without remission or with remissions lasting less than one month*
- †Headaches must have each of:
- ▶ Severe unilateral orbital, supraorbital, temporal pain lasting 15 minutes to 3 hours
 - ▶ Frequency: 1 every second day to 8 per day
 - ▶ Associated with 1 of:
 - lacrimation
 - nasal congestion
 - rhinorrhea
 - forehead/facial sweating
 - miosis
 - ptosis
 - eyelid oedema
 - conjunctival injection
- Or
- sense of restlessness or agitation during headache*

†No reasonable secondary cause.

Unilaterality of pain and presence of migrainous and autonomic symptoms are features common to both migraine and CH, and differentiating between them can be difficult in some cases. The features that can be useful in distinguishing CH from migraine include: relatively short duration of headache; rapid onset and cessation; circadian periodicity; precipitation within an hour, rather than several hours, by alcohol; behaviour during an attack; and clustering of attacks with intervening remissions in ECH.

Hypnic headache typically occurs in aged persons and predominates in females. Patients are awakened from sleep by headaches that are frequently bilateral but may be unilateral and, typically, not associated with autonomic features. The headaches are brief, lasting 5–180 minutes, and can occur up to three times per night. Effective treatments include bedtime doses of lithium, indomethacin or caffeine.¹⁰

Investigations

The diagnosis of CH is made entirely on the basis of a good clinical history and a detailed neurological examination. However, it is very difficult to clinically dissect CH mimics from primary CH. A magnetic resonance image (MRI) scan of the brain is a reasonable screening investigation.

Treatment

The management of CH includes offering advice on general measures to patients, treatment with abortive and preventative agents, and rarely surgery.

General measures and patient education

Patients should be advised to abstain from taking alcohol during the cluster bout. Otherwise, dietary factors seem to have little importance in CH. Anecdotal evidence suggests that patients should be cautioned against prolonged exposure to volatile substances, such as solvents and oil based paints. Patients should be advised to avoid afternoon naps as sleeping can precipitate attacks in some patients.

Abortive agents

The pain of CH builds up very rapidly to such an excruciating intensity that most oral agents are too slowly absorbed to cure the pain within a reasonable period of time. The most efficacious abortive agents are those that involve parenteral or pulmonary administration.

Triptans

Subcutaneous sumatriptan 6 mg is the most effective in abortive treatment of a cluster attack. It has a rapid effect and high response rate.¹¹ In CH, unlike in migraine, subcutaneous sumatriptan can be prescribed at a frequency of twice daily, on a long term basis if necessary without risk of tachyphylaxis or rebound.^{12–14} However, in this era of a cost conscious National Health Service (NHS) some practitioners are reluctant to prescribe this relatively expensive drug. We feel, given the devastating morbidity associated with this excruciating pain syndrome, that it is unethical to withhold treatment for cost reasons. Nasal sumatriptan may be used, but it is considerably less efficacious than the subcutaneous formulation.¹⁵ There is no controlled evidence to support the use of oral sumatriptan in CH. Sumatriptan 100 mg three times daily taken before an anticipated onset of an attack or at regular times does not prevent the attack and, therefore, it should not be used for CH prophylaxis.¹⁶

Zolmitriptan provides meaningful pain relief after oral administration of 5 mg in the majority of patients with episodic CH, but not in chronic CH. However, its efficacy is modest and does not approach the efficacy or speed of subcutaneous sumatriptan or oxygen.¹⁷

Oxygen

Inhalation of 100% oxygen, at a rate of 7–12 l/min, is rapidly effective in relieving pain in the majority of sufferers.¹⁸ It should be inhaled continuously for 15–20 minutes via a non-rebreathing facial mask. Patients need to be informed that they should cover any apertures on the facemask. A major problem in the UK is that the high flow rate oxygen regulator is not available on the NHS, and low flow oxygen is generally unhelpful. Thus, this treatment is an option only if the patient can afford to buy the high flow rate regulator. The regulator and the facemask can be purchased from BOC Medical Gases (numerous branches throughout the UK). The BOC specifications are “Multiflow regulator code 888842” and “Face mask (variable) (005) code 888845”.

Topical lignocaine

Lignocaine solution 20–60 mg, given as nasal drops (4–6% lidocaine solution) or a spray deep in the nostril on the painful side, results in mild to moderate relief in most patients, though only a few patients obtain complete pain relief.¹⁹ Therefore, intranasal lignocaine serves as a useful adjunct to other abortive treatments but is rarely adequate on its own.

Ergotamine

Oral or rectal ergotamine is generally too slow in onset to provide meaningful relief in a timely manner.

Analgesics

Opiates, non-steroidal anti-inflammatory drugs and combination analgesics generally have no role in the acute management of CH in most patients.

Preventative treatments

The aim of preventative treatment is to produce a rapid suppression of attacks and to maintain that remission with minimal side effects until the cluster bout is over, or for a longer period in patients with chronic CH. Preventative treatments can be divided into short term preventatives, suitable for rapidly controlling the attack frequency but not for prolonged use; and long term treatments that are required for prolonged medical management of CH.

Table 3 Preventative management of cluster headache

Short term prevention Episodic cluster headache	Long term prevention Episodic cluster headache— prolonged Chronic cluster headache
▶ Prednisolone	▶ Verapamil
▶ Methysergide	▶ Lithium
▶ Daily (nocturnal) ergotamine	▶ Methysergide
▶ Verapamil	▶ Valproate*
▶ Greater occipital nerve injection*	▶ Pizotifen*
▶ Pizotifen*	▶ ?Topiramate
	▶ ?Gabapentin
	▶ ?Melatonin

*Limited data, such as pizotifen,⁶⁹ or negative controlled data, such as valproate.⁷⁰
? Unproven but promising

Short term prevention

Patients with either short bouts, perhaps in weeks, or in whom one wishes to control the attack frequency quickly, can benefit from short term prevention. These medicines are distinguished by the fact that they cannot be used in the long term and thus may require replacement by long term agents in many patients.

Steroids

Corticosteroids are highly efficacious and the most rapid acting of the preventative agents.^{20–21} However, caution has to be exercised in their use because of the potential for serious side effects. Treatment should be limited to a short intensive course of 2–3 weeks in tapering doses. We start patients on oral prednisolone 1 mg/kg, to a maximum of 60 mg once a day for five days, and thereafter decrease the dose by 10 mg every three days. Unfortunately, relapse almost invariably occurs as the dose is tapered. For this reason, steroids are used as an initial treatment in conjunction with preventatives, until the latter are effective.

Methysergide

Methysergide is a potent prophylactic agent for the treatment of CH.²² It is an ideal choice in patients with short cluster bouts that last less than 4–5 months. Doses up to 12 mg daily can be used if tolerated. Patients are started on 1 mg once a day and the daily dose then increased by 1 mg every three days (in a three times daily regimen) until the daily dose is 5 mg; thereafter, the dose is incremented by 1 mg every five days. Prolonged treatment has been associated with fibrotic reactions (retroperitoneal, pulmonary, pleural, and cardiac) though these are rare.²³ Though occasionally used in CCH, a drug holiday after every six months of treatment is necessary, and neurological supervision entirely appropriate.

Ergotamine

Ergotamine is an effective preventative agent that is particularly useful in short term management of ECH when attacks occur predictably during the day or at night.²⁴ Ergotamine 1–2 mg orally or rectally can be taken at bedtime or about an hour before the attack is due. It is rarely suitable for use in CCH. Concomitant use of sumatriptan is contraindicated.

Long term prevention

Some patients with either long bouts of episodic CH or chronic CH will require preventative treatment over many months, or even years. Verapamil and lithium are particularly useful in this setting (table 3).

Verapamil

Verapamil is the preventative drug of choice in both episodic and chronic CH.^{25–27} Clinical experience has clearly shown²⁸ that higher doses than those used in cardiological indications are needed. Dosages commonly employed range from 240–960 mg twice daily in divided doses. Verapamil can cause heart block by slowing conduction in the atrioventricular node. Observing for PR interval prolongation on the electrocardiogram (ECG) can monitor potential development of heart block, although it is a coarse measure. No formal guidelines are available. We perform a baseline ECG, and patients are usually started on 80 mg three times daily, and thereafter the total daily dose is increased in increments of 80 mg every 10–14 days. An ECG is performed before each increment. The dose is increased until the cluster attacks are suppressed, side effects intervene or the maximum dose of 960 mg daily is achieved.

Lithium

Lithium is an effective agent for CH prophylaxis, though the response is less robust in ECH than CCH.^{26, 29, 30} Renal and thyroid function tests are performed before initiation of treatment. Patients are then started on 300 mg twice daily and the dose titrated using the protocol outlined in the British National Formulary, aiming for a serum lithium concentration in the upper part of the therapeutic range. Many patients will benefit from dosages between 600–1200 mg daily. The concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs), diuretics, and carbamazepine is contraindicated.

Other drugs

Though sodium valproate, pizotifen, topiramate, gabapentin, and melatonin are often used, they are of as yet unproven efficacy.

Surgery

Surgery is a last resort measure in treatment resistant patients and should only be considered when the pharmacological options have been exploited to the fullest. Patients must be carefully selected. Only patients whose headaches are exclusively unilateral should be considered for destructive surgery, as patients whose attacks have alternated sides are at risk of a contralateral recurrence after surgery. A number of procedures that interrupt either the trigeminal sensory or autonomic (parasympathetic) pathways can be performed, though few are associated with long lasting results while the side effects can be devastating. The procedures that have been reported to show some success include trigeminal sensory rhizotomy via a posterior fossa approach,³¹ radiofrequency trigeminal gangliorhizolysis,³² and microvascular decompression of the trigeminal nerve with or without microvascular decompression of the nervus intermedius.³³ Complete trigeminal analgesia may be required for the best results. Complications include diplopia, hyperacusis, jaw deviation, corneal anaesthesia, and anaesthesia dolorosa. Aggressive long term ophthalmic follow up is essential. Recently, Leone and colleagues reported the novel treatment of posterior hypothalamic neurostimulation.³⁴ This non-destructive modality demands study.

Natural history

Although there is a paucity of literature on the long term prognosis of CH, the available evidence suggests that it is a lifelong disorder in the majority of patients. In one study, about 10% of patients with ECH evolved into CCH whereas a

Abbreviations

CCH: chronic cluster headache
CH: cluster headache
CPH: chronic paroxysmal hemicrania
ECG: electrocardiogram
ECH: episodic cluster headache
EPH: episodic paroxysmal hemicrania
HC: hemicrania continua
IHS: International Headache Society
MRI: magnetic resonance imaging
NSAID: non-steroidal anti-inflammatory drugs
PH: paroxysmal hemicrania
SUNCT: Short lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing
TAC: trigeminal autonomic cephalgia

third of patients with CCH transformed into ECH.³⁵ An encouraging piece of information for CH sufferers is that a substantial proportion of them can expect to develop longer remission periods as they age.³⁶

PAROXYSMAL HEMICRANIA

Paroxysmal hemicrania (PH), like CH, is characterised by strictly unilateral, brief, excruciating headaches that occur in association with cranial autonomic features. PH differs from CH mainly in the higher frequency and shorter duration of individual attacks, though there is a considerable overlap in these characteristics. However, unlike CH, PH responds in a dramatic and absolute fashion to indomethacin, thereby underlining the importance of distinguishing it from CH. PH has both episodic and chronic forms that will be defined in exactly the same way as is done for CH (see above) in the revision of the IHS classification.

Clinical features

The attack profile of PH is highly characteristic.^{37, 38} The headache is strictly unilateral. The maximum pain is most often centred on the ocular, temporal, maxillary, or frontal regions; less often, the pain is centred on the neck, occiput or the retro-orbital regions. The pain is typically excruciating in severity and described as a throbbing, aching or boring sensation. The headache usually lasts 10–30 minutes, but can range from 2–45 minutes. It has an abrupt onset and cessation. Interictal discomfort or pain is present in up to one third of the patients.³⁷

Attacks of PH invariably occur in association with ipsilateral cranial autonomic features. The IHS classification criteria for chronic paroxysmal hemicrania² require the attacks to be accompanied by at least one of the following, which have to be present on the pain side: conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, ptosis or eyelid oedema. Photophobia and nausea may accompany some attacks though vomiting and phonophobia are rare. During episodes of pain, approximately half the sufferers prefer to sit or lie still while the other half assume the pacing activity usually seen with CH.³⁷

In PH the attacks occur at a high frequency. Typically, patients have more than five attacks daily though the frequency of attacks shows a considerable fluctuation, ranging from 1–40 daily. The attacks occur regularly throughout the 24 hour period without a preponderance of nocturnal attacks as in CH.³⁹

Table 4 Differential diagnosis of short lasting headaches

Feature	Cluster headache	Paroxysmal hemicrania	SUNCT*	Idiopathic stabbing headache	Trigeminal neuralgia	Hypnic headache
Sex (male:female)	5:1	1:2	2:1	F>M	F>M	5:3
Pain						
Type	Boring	Boring	Stabbing	Stabbing	Stabbing	Throbbing
Severity	Very severe	Very severe	Severe	Severe	Very severe	Moderate
Location	Orbital	Orbital	Orbital	Any	V2/V3>V1	Generalised
Duration	15–180 mins	2–45 mins	15–120 s	<30 s	<1 s	15–30 mins
Frequency	1–8/day	1–40/day	1/day–30/hour	Any	Any	1–3/night
Autonomic	+	+	+	–	–†	–
Trigger	Alcohol, nitrates	Mechanical	Cutaneous	None	Cutaneous	Sleep
Indomethacin	?	+	–	+	–	+

*Short lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.
†Cranial autonomic activation may be seen in first division trigeminal neuralgia.

While the majority of attacks are spontaneous, approximately 10% of attacks may be precipitated mechanically, either by bending or by rotating the head. Attacks may also be provoked by external pressure against the transverse processes of C4–5, C2 root, or the greater occipital nerve. Alcohol ingestion triggers headaches in only 7% of patients.³⁷

Differential diagnosis

The differential diagnoses that need to be considered are secondary causes of PH and other TACs (table 4). PH is rare and warrants, even when clearly indomethacin sensitive, further investigations, including brain imaging. Mistaking PH for CH is problematic since, generally, treatments for CH are not effective for PH. The clinical features that distinguish PH from CH include: the female preponderance; higher frequency and shorter duration of the attacks; and exquisite response to indomethacin. The utility of sex of patients, and duration and frequency of the attack to distinguish PH from CH is limited by the considerable overlap of these characteristics in the two syndromes. Hence, a trial of indomethacin is the only definitive test. It could be advocated that all patients diagnosed with TACs, who do not have a contraindication to the use of NSAIDs, should have a trial of indomethacin at the start of treatment to detect the indomethacin sensitive group, at least until a reliable biological marker becomes available. The disadvantage of this approach is that the diagnostic yield will be low (as PH is comparatively rare) and will delay appropriate treatment by 2–3 weeks in CH patients. The alternative approach is to consider the indomethacin trial only in patients with a high likelihood of having PH; we routinely perform a trial of indomethacin in TAC patients having more than five attacks daily, or attacks lasting less than 30 minutes, or both.

Investigations

A good clinical history, a detailed neurological examination, and a therapeutic trial of indomethacin are all that are necessary to make a diagnosis of PH. As a relatively high number of symptomatic cases have been reported, an MRI scan of the brain should be routinely performed in all patients with PH.

The therapeutic trial of oral indomethacin should be initiated at 25 mg three times daily; if there is no or a partial response after 10 days, the dose should be increased to 50 mg three times daily for at least 10 days; if the index of suspicion is high then the dose should be further increased to 75 mg three times daily for 10 days.

Management

The treatment of PH is prophylactic. Complete resolution of the headache with an appropriate dose of indomethacin is

prompt, usually occurring within 1–2 days of initiating the effective dose. The typical maintenance dose ranges from 25–100 mg daily, but doses up to 300 mg daily are occasionally required. Dosage adjustments may be necessary to address the clinical fluctuations seen in PH. Skipping or even delaying doses may result in the prompt reoccurrence of the headache. In patients with EPH, indomethacin should be given for slightly longer than the typical headache bout and then gradually tapered. In patients with CPH, long term treatment is usually necessary; however, long lasting remissions have been reported in rare patients following cessation of indomethacin, hence drug withdrawal should be advised at least once every six months.

Gastrointestinal side effects secondary to indomethacin may be treated with antacids, misoprostol, histamine H₂ receptor antagonists, or proton pump inhibitors and should always be considered for patients who require long term treatment.

The mechanism behind the absolute responsiveness to indomethacin is unknown. It appears to be independent of indomethacin's effect on prostaglandin synthesis, since other NSAIDs have little or no effect on PH.

For patients who cannot tolerate indomethacin one faces a difficult challenge. No other treatment is as consistently effective. We, and others, have tried COX-2 inhibitors and verapamil with limited success.

SUNCT SYNDROME

Short lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), like the other TACs, manifests as a unilateral headache that occurs in association with cranial autonomic features. The features that distinguish it from the other TACs are: very brief duration of attacks that can occur very frequently, and the presence of *prominent* conjunctival injection and lacrimation, both of which are present in the vast majority of patients.

Epidemiology

The prevalence or incidence of SUNCT syndrome are not known though the extremely low number of reported cases suggests that it is a very rare syndrome. The disorder has a male predominance (31 males, 15 females) with a sex ratio of 2.1:1. The typical age of onset is between 40–70 years, though this ranges from 10–77 years (mean 50 years).

Clinical features

The pain is usually maximal in the ophthalmic distribution of the trigeminal nerve, especially the orbital or periorbital

regions, forehead, and temple. The attacks are strictly unilateral. The severity of pain is generally moderate to severe. The pain is usually describing as stabbing, burning, pricking or electric shock-like in character. The individual attacks are very brief, lasting between 5–250 seconds (mean duration 49 seconds),⁴⁰ although attacks lasting up to two hours each have been described.^{41–42} The paroxysms begin abruptly, reaching the maximum intensity within 2–3 seconds; the pain is maintained at the maximum intensity before abating rapidly.⁴³ Most patients are completely pain-free between attacks, although some report a persistent dull interictal discomfort.⁴²

The temporal pattern is quite variable, with the symptomatic periods alternating with remissions in an erratic manner. Symptomatic periods generally last from a few days to several months and occur once or twice annually. Remissions typically last a few months, though can range from one week to seven years.

The attack frequency during the symptomatic phase varies immensely between sufferers and within an individual sufferer. Attacks may be as infrequent as once a day or less to more than 30 attacks an hour. Most SUNCT attacks occur during the daytime, tending to show a bimodal distribution with morning and afternoon/evening predominance. Nocturnal attacks are seldom reported.

Acute headache episodes in SUNCT syndrome are accompanied by a variety of associated symptoms. The attacks are virtually always accompanied by both ipsilateral conjunctival injection and lacrimation. Ipsilateral nasal congestion, rhinorrhoea, eyelid oedema, ptosis, miosis, and facial redness or sweating are less commonly reported. These cranial autonomic symptoms, particularly conjunctival injection and lacrimation, are typically very prominent in SUNCT syndrome. Nausea, vomiting, photophobia, and phonophobia are not normally associated with SUNCT syndrome. Unlike in CH, restlessness is not a feature of SUNCT syndrome.⁴³

The majority of patients can precipitate attacks by touching certain trigger zones within trigeminal innervated distribution and, occasionally, even from an extratrigeminal territory. Precipitants include touching the face or scalp, washing, shaving, eating, chewing, brushing teeth, talking, and coughing. Neck movements can also precipitate attacks, although some patients can lessen or abort attacks by continuously rotating their neck.⁴³ Unlike in trigeminal neuralgia, most patients have no refractory period.

Differential diagnosis

The differential diagnosis of very brief headaches includes: SUNCT (primary and secondary forms); trigeminal neuralgia; primary stabbing headache, and PH. Secondary SUNCT has been reported in seven patients, all of whom have had posterior fossa abnormalities. Any patient diagnosed with SUNCT should have an MRI of the brain. PH can be readily differentiated by a trial of indomethacin (as described above).

Differentiating SUNCT from trigeminal neuralgia can be challenging in some cases, as there is a considerable overlap in the clinical phenotypes of the two syndromes. Both headaches are short lasting, can have a high frequency of attacks, and display clustering of attacks. Both are principally unilateral headaches and the trigger zones behave similarly. The usual onset is during middle or old age in both. However, there are a number of striking differences between these two syndromes (table 5), awareness of which can aid in their differentiation.^{44–45}

Primary stabbing headache (currently known as idiopathic stabbing headache) refers to brief, sharp or jabbing pain in the

Table 5 Differentiating features of SUNCT and trigeminal neuralgia

Feature	SUNCT	Trigeminal neuralgia
Sex ratio (male: female)	2.1:1	1:2
Site of pain	V1	V2/3
Severity of pain	Moderate to severe	Very severe
Duration (seconds)	5–250	<1
Autonomic features	Prominent	Sparse or none
Refractory period	Absent	Present
Response to carbamazepine	Partial	Complete

head that occurs either as a single episode or in brief repeated volleys. The pain is usually over the ophthalmic trigeminal distribution while the face is generally spared. The pain usually lasts a fraction of a second but can persist for up to one minute, thereby overlapping with the phenotype of SUNCT, and recurs at irregular intervals (hours to days). These headaches are generally easily distinguishable clinically as they differ in several respects:

- ▶ in primary stabbing headache there is a female preponderance
- ▶ the site and radiation of pain often varies between attacks
- ▶ the majority of the attacks tend to be spontaneous
- ▶ cranial autonomic features are absent
- ▶ the attacks commonly subside with the administration of indomethacin.⁴⁶

Treatment

Until recently, SUNCT was thought to be highly refractory to treatment. Several categories of drugs used in other headache syndromes—NSAIDs (including indomethacin), paracetamol, 5-hydroxytryptamine agonists (triptans, ergotamine, and dihydroergotamine), β blockers, tricyclic antidepressants, calcium channel antagonists (verapamil and nifedipine), methysergide, lithium, prednisolone, phenytoin, and baclofen—have proved to be ineffectual.⁴⁷ Partial improvement with carbamazepine has been observed in several patients.^{41–47–49}

Recently, lamotrigine has been reported to be highly efficacious in seven patients.^{50–52} Lamotrigine, given in an open manner at 100–200 mg daily, induced a complete remission in five patients and produced about an 80% improvement in the other two patients. Although the ultimate confirmation of the utility of lamotrigine in the treatment of this debilitating syndrome should come from a randomised, double blind, placebo controlled clinical trial, for now it is the treatment of choice.

There is one case report of a SUNCT patient who consistently responded completely to gabapentin at 1800–2700 mg daily.⁵³ We have recently reported on a patient who responded completely to topiramate 50 mg daily.⁵⁴ These observations clearly need to be confirmed in other cases. Nonetheless, given the debilitating nature of this headache, gabapentin and topiramate are reasonable second line agents in patients who fail a trial of lamotrigine.

Several surgical approaches have been tried in SUNCT syndrome. Anaesthetic blockades of pericranial nerves have been reported to be ineffective.⁴⁷ There are three reports of apparently successful treatment of SUNCT syndrome with surgical procedures: two with the Jannetta procedure^{55–56} and one with percutaneous trigeminal ganglion compression. In addition, there is one report of a partial response with local opioid blockade of the superior cervical ganglion.⁵⁷ However, follow up in these patients was limited to less than 18 months,

which makes it difficult to assess the actual effectiveness of the procedures given the episodic nature of the syndrome. We have managed two patients who had failed to demonstrate a persistent response following trigeminal thermocoagulation and microvascular decompression (unpublished observations). Given the uncertain efficacy of trigeminal procedures together with the potential for complications, surgery should only be considered as a last resort and only when the pharmacological options have been exploited to the fullest.

Natural history

The natural history of SUNCT syndrome is poorly understood yet. In a series of 21 patients, the average duration of symptoms was 11.8 years. In 10 of these patients the duration of SUNCT exceeded 10 years. The longest reported duration of SUNCT was 48 years.⁴³ It appears to be a lifelong disorder once it starts, though more prospective data are needed. The syndrome itself is not fatal and does not cause any long term neurological sequelae.

PATHOPHYSIOLOGY OF TACS

Any pathophysiological construct for TACs must account for the two major clinical features characteristic of the various conditions that comprise this group: trigeminal distribution of pain and ipsilateral autonomic features. The pain producing innervation of the cranium projects through branches of the trigeminal and upper cervical nerves to the trigeminocervical complex from whence nociceptive pathways project to higher centres. This implies an integral role for the ipsilateral trigeminal nociceptive pathways in TACs. The ipsilateral autonomic features suggest cranial parasympathetic activation (lacrimation, rhinorrhoea, nasal congestion, and eyelid oedema) and sympathetic hypofunction (ptosis and miosis). Goadsby and Lipton have suggested that the pathophysiology of the TACs revolves around the trigeminal–autonomic reflex.¹ There is considerable experimental animal literature to document that stimulation of trigeminal efferents can result in cranial autonomic outflow, the trigeminal–autonomic reflex.⁵⁸ In fact, some degree of cranial autonomic symptomatology is a normal physiologic response to cranial nociceptive input and patients with other headache syndromes often report these symptoms.⁵⁹ The distinction between the TACs and other headache syndromes is the degree of cranial autonomic activation.⁴⁵

The cranial autonomic symptoms may be prominent in the TACs because of a central disinhibition of the trigeminal–autonomic reflex.⁴⁵ Supporting evidence is emerging from functional imaging studies: positron emission tomography studies in CH^{60–61} and a functional MRI study in SUNCT syndrome⁶² have demonstrated ipsilateral hypothalamic activation. Hypothalamic activation is specific to these syndromes and is not seen in migraine^{63–64} or experimental ophthalmic trigeminal distribution head pain.⁶⁵ There are direct hypothalamic–trigeminal connections^{66–67} and the hypothalamus is known to have a modulatory role on the nociceptive and autonomic pathways.⁶⁸ Hence, CH and SUNCT syndrome are probably caused by an abnormality in the hypothalamus with subsequent trigeminovascular and cranial autonomic activation.

There are several issues that remain unresolved in the understanding of the pathophysiology of the TACs. Further studies need to seek the anatomical or functional basis of the variations in patterns of expression of pain and autonomic symptoms in the different TACs. As in CH and SUNCT, the central locus of abnormality in PH and hemicrania continua

(HC) needs to be identified. The nature of the hypothalamic abnormality in CH and SUNCT needs to be elucidated. Finally, the mechanism of action of indomethacin needs to be unravelled. Advances in the pathophysiological understanding of these conditions is likely to lead to better treatments for these devastatingly painful syndromes.

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