Abstract
The concept of a group of headaches whose pathophysiological focus revolves around the trigeminal-autonomic reflex fills a useful gap in characterising a number of primary headache syndromes. Broadly, these syndromes involve activation of trigeminovascular nociceptive pathways with reflex cranial autonomic activation. Clinically, this physiology predicts pain with some combination of lacrimation, conjunctival injection, nasal congestion, or eyelid oedema. Several of the primary neurovascular headaches, notably cluster headache, paroxysmal hemicrania and short-lasting neuralgiform pain with conjunctival injection and tearing (SUNCT), seem to immediately fit this classification. This physiology also explains why some patients with migraine present cranial autonomic features, and the concept is thus broadly useful for clinicians seeking a pathophysiological understanding of the primary neurovascular headaches. I will deal with the broad anatomical and physiological issues and then focus on the three clinically identified trigeminal autonomic cephalgias (TACs).

Key words: Cluster headache; paroxysmal hemicrania; trigeminovascular system; trigeminal-autonomic reflex; SUNCT.

Introduction
The concept of a group of headaches whose pathophysiological focus revolves around the trigeminal-autonomic reflex fills a useful gap in characterising a number of primary headache syndromes (Goadsby and Lipton, 1997). Broadly, these syndromes involve activation of trigeminovascular nociceptive pathways with reflex cranial autonomic activation (May and Goadsby, 1999). Clinically, this physiology predicts pain with some combination of lacrimation, conjunctival injection, nasal congestion, or eyelid oedema. Several of the primary neurovascular headaches, notably cluster headache, paroxysmal hemicrania and short-lasting neuralgiform pain with conjunctival injection and tearing (SUNCT), seem to immediately fit this classification and will be the focus of this brief review. This physiology also explains why some patients with migraine present cranial autonomic features, and the concept is thus broadly useful for clinicians seeking a pathophysiological understanding of the primary neurovascular headaches. I will deal with the broad anatomical and physiological issues and then focus on the three clinically identified trigeminal autonomic cephalgias (TACs).

The Trigeminovascular System
The trigemino-cerebrovascular system (Goadsby and Duckworth, 1987) is in a unique, indeed pivotal position, in terms of cerebrovascular physiology. It is the sole sensory (afferent) innervation of the cerebral vessels and has, in addition, an efferent potential in pathophysiological settings.

Anatomy: The trigeminovascular system consists of those neurons innervating the cerebral vessels and dura mater whose cell bodies are located in the trigeminal ganglion. The ganglion contains bipolar cells, the peripheral fibre making a synaptic connection with the vessel, and other cranial structures, particularly the pain-producing large cranial vessels and dura mater (Feindel et al., 1960; McNaughton, 1938; McNaughton and Feindel, 1977), and the centrally projecting fibre synapsing in the caudal brainstem or high cervical cord (Goadsby and Hoskin, 1997; Kaube et al., 1993). Some projections have been noted to involve both cerebral (middle cerebral artery) and extracerebral (middle meningeal artery) vessels (O’Connor and van der Kooy, 1986). Activation of afferents in both the large venous sinuses (Goadsby and Hoskin, 1997) and intracranial arteries (Hoskin et al., 1999) leads to Fos production in neurons with the same anatomical distribution in the trigemino-cervical complex, trigeminal nucleus caudalis and dorsal horns of C1 and C2.

Transmitters: Several powerful vasodilator peptides are to be found in cell bodies within the trigeminal ganglion that innervate blood vessels. These substances, calcitonin gene-related peptide (CGRP), substance P (SP) and neurokinin A (NKA), are found in various combinations of neurons (Edvinsson et al., 1993) so that virtually any combination of 1, 2 or 3 may characterise any...
neuron. The functional consequences of these combinations is yet to be fully elucidated but it seems likely that the trigemino-craniovascular innervation is homogenous at least in its vasodilation actions. Certainly, both CGRP and NKA levels increase during migraine and CGRP during cluster headache (Edvinsson and Goadsby, 1998).

**Trigeminovascular physiology**: Cerebral blood flow measured with iodoantipyrine and tissue autoradiography is not altered in the cat after trigeminal ganglion section. Indeed after unilateral section flow is identical to homologous contralateral cortex (Edvinsson et al., 1986). Furthermore, glucose utilisation is not affected by trigeminal ganglion section and thus the usual close relationship between flow and metabolism is not disturbed (Edvinsson et al., 1986). Stimulation of the trigeminal ganglion in humans by either thermocoagulation (Onofrio, 1975; Sweet and Wepsic, 1974) or injection of alcohol (Oka, 1950) can cause facial flushing usually in the division or divisions appropriate to the manipulation. In addition it has been shown that this flushing is accompanied by an increase in facial temperature of 1-2°C (Drummond et al., 1983). Corresponding with this flush there is an increase in the dilator peptides SP and CGRP in the external jugular (Goadsby et al., 1988), even if the flush is cutaneously triggered (Goadsby et al., 1992), but this change is not seen in the peripheral circulation (Schon et al., 1987). Such changes are also seen in the cat (Goadsby et al., 1988).

**Trigeminal-autonomic reflex**: In addition trigeminal ganglion stimulation in the cat (Lambert et al., 1984) or monkey (Goadsby et al., 1986) leads to a diminution of carotid resistance, with increased flow and facial temperature predominantly through a reflex mechanism. The afferent limb of this arc is the trigeminal nerve and the efferent the facial/greater superficial petrosal nerve (parasympathetic) dilator pathway (Goadsby, 1989). About 20% of the dilatation seen remains after facial nerve section and is probably mediated by antidromic activation of the trigeminal system directly. The portion running through the parasympathetic outflow traverses the sphenopalatine (pterygopalatine) and otic ganglia (Goadsby et al., 1984) and employs vasoactive intestinal polypeptide as its transmitter (Goadsby and Macdonald, 1985). This vasodilator reflex is the trigemino-parasympathetic or trigeminal-autonomic reflex (Goadsby and Lipton, 1997).

The trigeminal neural innervation of the cerebral circulation is somatotopically selective. Stimulation of the superior sagittal sinus increases cerebral blood flow as measured by laser Doppler flowmetry but does not alter carotid flow in the same manner, in contrast to the effect of trigeminal ganglion stimulation which increases both cerebral and non-cerebral cranial blood flow (Goadsby et al., 1997).

It seems likely, therefore, that primary neurovascular headache syndromes entrain these craniovascular responses in their expression and this is the physiological basis for the changes described below and so readily recognised in patients.

**Cluster headache**

Cluster headache is a rare very severe episodic primary headache that has been recognised for many years (Koehler, 1993) with among the earliest known description appearing in Gerhard van Swieten’s medical textbook (Isler, 1993):

> A healthy robust man of middle age [was suffering from] troublesome pain which came on every day at the same hour at the same spot above the orbit of the left eye, where the nerve emerges from the opening of he frontal bone : after a short time the left eye began to redden, and to overflow with tears ; than he felt as if his eye was slowly forced out of its orbit with so much pain, that he nearly went mad. After a few hours all these evils ceased, and nothing in the eye appeared at all changed.

This description fulfils the International Headache Society diagnostic criteria (Table 1) for cluster headache (Headache Classification Committee of The International Headache Society, 1988). Before the term _cluster headache_ was widely used the disease was known by a large number of names (Table 2), with perhaps the most remarkable understatement being that of Sir Charles Symons who called it _a particular variety of headache_.

**Clinical features and differential diagnosis**: Cluster headache is characterised by intermittent, repeated, brief attacks of very severe unilateral pain that is most usually reported to occur over or

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**Table 1**

<table>
<thead>
<tr>
<th>Diagnostic features of cluster headache modified from the International Headache Society (Headache Classification Committee of The International Headache Society, 1988) with the proposed change*</th>
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<tbody>
<tr>
<td>Headaches must have each of :</td>
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<tr>
<td>• Severe unilateral orbital, supraorbital, temporal pain lasting 15 minutes to 3 hours ;</td>
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<tr>
<td>• Frequency : 1 every second day to 8 per day ;</td>
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<tr>
<td>• Associated with 1 of :</td>
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<tr>
<td>– lacrimation</td>
</tr>
<tr>
<td>– nasal congestion</td>
</tr>
<tr>
<td>– rhinorrhea</td>
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<tr>
<td>– forehead/facial sweating</td>
</tr>
<tr>
<td>– miosis</td>
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<tr>
<td>– ptosis</td>
</tr>
<tr>
<td>– eyelid oedema</td>
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<tr>
<td>– conjunctival injection</td>
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<tr>
<td>Or</td>
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<tr>
<td>Headache is associated with a sense of restlessness or agitation*</td>
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behind one eye. There are usually associated autonomic features such as, lacrimation, nasal congestion, conjunctival injection and either a full or partial Horner’s syndrome (Headache Classification Committee of The International Headache Society, 1988). By these criteria each attack may last from 15 minutes to 3 hours and the frequency of attacks varies from one every other day to eight per day. Recent large series demonstrate the utility of the feature of agitation or restlessness in more than 90% of cluster headache patients (Bahra et al., 2000b). Moreover, typical migraine aura clearly can be seen in a substantial proportion of patients with cluster headache (Bahra et al., 2000b; Silberstein et al., 2000). The IHS classification to some extent provides arbitrary rules, since they are phenomenologically-based not biologically determined. Human biology will break phenomenologically based rules from time to time; when broken a more refractory clinical problem may be emerging.

Most patients with cluster headache have them in a bout or cluster that may last from 6 weeks to several months and are thus designated episodic cluster headache (ECH). Some 10-15% of patients have no substantial breaks and are classified as chronic cluster headache (CCH). The latter group can be the most challenging of cases being frequently resistant to simpler treatments and consuming large amounts of medicine regularly.

It is important to differentiate cluster headache from similar conditions, which most often consist of shorter more frequent attacks (Goadsby and Lipton, 1997), and to be aware of the rare but recognised causes of secondary cluster headache (Table 3) as they guide logical investigation. It can be both diagnostically profitable and clinically reassuring to the patient to investigate or even re-investigate the most refractory patients. It is certainly conceivable that they may harbour a secondary headache, since secondary cluster can respond to routine treatments, and it certainly can be difficult to differentiate on clinical grounds. In terms of re-investigation this should certainly not be done routinely but when there are atypical features, such as length of attack or other emergent clinical signs.

**MANAGEMENT OF CLUSTER HEADACHE**

Many medical treatments in cluster headache can be used in both episodic and chronic cluster headache patients. In general the acute medications may be used in both settings although in chronic cluster headache long-term safety issues make the use of the medicines sometimes problematic. Key issues in difficult cluster headache include: providing acute treatment when there are several attacks a day, finding a drug or combinations of drugs that are useful in preventing attacks, and making decisions about the place and timing of surgery.

<table>
<thead>
<tr>
<th>Primary headaches</th>
<th>Secondary headaches</th>
<th>Secondary Cluster Headaches</th>
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</thead>
<tbody>
<tr>
<td>Migraine</td>
<td>Tolosa-Hunt syndrome</td>
<td>meningioma of the lesser wing of sphenoid (Hannerz, 1989)</td>
</tr>
<tr>
<td>Paroxysmal hemicrania</td>
<td>Maxillary sinusitis</td>
<td>vertebral artery dissection (Cremer et al., 1995) or aneurysm (West and Todman, 1991)</td>
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<tr>
<td>SUNCT syndrome*</td>
<td>Temporal arteritis</td>
<td>giant cell arteritis (Jimenez-Jimenez et al., 1998)</td>
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<tr>
<td>Hypnic headache</td>
<td>Raeder’s paratrigeminal neuralgia</td>
<td>medullary infarct (Cid et al., 2000)</td>
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<tr>
<td>Trigeminal neuralgia</td>
<td></td>
<td>high cervical meningioma (Kurtzky, 1984)</td>
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<tr>
<td>Idiopathic stabbing headache</td>
<td></td>
<td>cervical spinal cord infarction (de la Sayette et al., 1999)</td>
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<td></td>
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<td>head or neck injury (Hunter and Mayfield, 1949)</td>
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<td></td>
<td></td>
<td>pituitary adenoma (Tfelt-Hansen et al., 1982)</td>
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<td>occipital lobe AVM (Mani and Deeter, 1982)</td>
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<td></td>
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<td>facial trauma (Lance, 1993)</td>
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<td></td>
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<td>multiple sclerosis (Leandri et al., 1999)</td>
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<td></td>
<td></td>
<td>orbital-sphenoidal aspergillosis (Heidegger et al., 1997)</td>
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<td></td>
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<td>pseudoaneurysm of intracavernous carotid a. (Koenigsberg et al., 1994)</td>
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* SUNCT, Short-lasting Unilateral Neuralgiform headaches with Conjunctival injection and Tearing.
PREVENTATIVE TREATMENT

Preventative treatments in cluster headache can be used to either arrest a bout of episodic cluster headache, short-term prevention, or to ameliorate symptoms in patients with chronic cluster headache, long term prevention. This division nicely partitions medicines that are useful in the short-term but problematic in the longer term. The division is a little artificial as some patients with ECH have rather long bouts; I will apply it for the purpose of discussion bearing mind that some treatments for CCH will be useful for longer bouts of ECH.

Short-term prevention: Oral ergotamine may be useful as a regular night-time dose to avoid nocturnal attacks (Ekbom, 1947) and at a dose of 1-2 mg nightly can be very useful. Ergotamine is at its best when given well before the attacks and is ideal for the patient with predictable nocturnal attacks and a short bout. It is problematic in patients with vascular disease although, in contrast to migraine sufferers, ergotamine-induced headache seems relatively uncommon in patients with episodic cluster headache. Another useful strategy can be daily or even bd dihydroergotamine (1 mg) which can suppress attacks very effectively. The author has found both the injectable and nasal formulations of dihydroergotamine useful.

A short burst of oral corticosteroids has been recommended for some years (Jammes, 1975) and is certainly effective. The problem of osteonecrosis of the femoral head (ON), and the other common sites, femoral condyles, head of humerus, scaphoid, lunate and talus needs to be considered (Mirzai et al., 1999). The shortest course of prednisolone reported to be associated with osteonecrosis of the femoral was a 30-day course of 16 mg/day (Fischer and Bickel, 1971). Furthermore, courses of adrenocorticotropic hormone (Good, 1974) have produced ON after 16 days and dexamethasone at 16 mg per day after 7 days (Anderton and Helm, 1982). Mirzai and colleagues (1999) have taken the view that dexamethasone was, therefore, more problematic, and that an inter-use interval of less than 12 months was also a problem. Taken together 21-28 day courses of oral prednisolone seem entirely reasonable and safe.

Methysergide can be an extremely effective anti-cluster agent and, because the bouts are usually short the exposure can be limited. Patients may require up to 6 or even 9 mg daily but usually response reasonably quickly and in up to 70% of cases (Curran et al., 1967). The dose can be adjusted every 3-4 days as tolerated. In the short term leg cramps can be an irritating side effect for the patients and the problem of retroperitoneal fibrosis can be avoided (Graham, 1967; Graham et al., 1966).

Long term prevention: The first line treatment now for long term prevention in chronic cluster headache, and in the episodic variety for more prolonged bouts, is verapamil. In an open trial employing large doses of 240-720 mg daily in episodic cluster and 120-1200 mg daily in chronic cluster headache, an improvement of more than 75% was noted in 69% of 48 patients treated with verapamil (Gabai and Spierings, 1989). Since this early report verapamil has been established as among the most effective preventative agents in cluster headache and is at least equal to lithium (Bussone et al., 1990). It is generally true that the regular verapamil preparation is more useful than the slow-release preparations and that the upper limit of dosing relates to side effects, particularly cardiac conduction problems. It is remarkable how many otherwise intractable cases will have improvement if they can tolerate the very high doses required (Olesen and Goadsby, 1999). This author has found that slow introduction in chronic cluster headache coupled with advice about constipation and postural hypotension can be a successful combination in a number of patients.

Lithium carbonate has been reported to be useful in up to 40% of patients (Carolis et al., 1988; Kudrow, 1977) and its use requires careful monitoring. Unfortunately its most recent study was limited by practical problems and came to no clear conclusions on the drug’s efficacy (Steiner et al., 1997). More recently both the anticonvulsants valproate (Hering and Kuritzky, 1989) and gabapentin (Ahmed, 2000) have been suggested to be useful in prevention of cluster headache. Both require proper study. A recent very promising report of the use of topiramate in cluster headache (Wheeler and Carrazana, 1999) again suggests the need for a controlled study.

MANAGEMENT OF ACUTE ATTACKS OF CLUSTER HEADACHE

Perhaps the over-riding problem in acute cluster headache is that the attacks come on rapidly and reach a peak very quickly so that therapy to be of any value must be rapid in onset and thus oral preparations used in migraine may not be effective. Inhalation of 100% (10-12 l/min) for 15 minutes has been clearly shown to be of benefit in arresting attacks (Fogar, 1985; Kudrow, 1981). Parenteral dihydroergotamine (1mg intramuscularly) which when self-administered is effective for some, but not all patients. Dihydroergotamine (1 mg) intranasally which has been clearly shown to be effective for some, but not all patients. Dihydroergotamine which when self-administered is effective in approximately 4-6% of patients (Kitelle et al., 1985; Robbins, 1995) or injection of the ipsilateral greater occipital nerve (Anthony, 1987).
Sumatriptan, a 5-HT1B/1D receptor agonist developed for the treatment of migraine (Humphrey et al., 1991), has proved highly efficacious and rapid in onset of action (Hardebo, 1993) in the treatment of acute attacks of cluster headache (Ekbom and The Sumatriptan Cluster Headache Study Group, 1991). It is no exaggeration to state that sumatriptan has been a spectacular development in cluster headache more so than in migraine. It has been shown that increasing the dose from 6mg to 12mg does not result in either more responders or a quicker effect (Ekbom et al., 1993). It is important clinically that the response is not diminished with time (Ekbom et al., 1992) and the side effect profile is modest as it for migraine (Goadsby, 1994). Pre-emptive treatment with sumatriptan in a regimen of 100mg three times daily does not alter either the timing or frequency of headaches (Monstad et al., 1995). These data are in accordace with published data for migraine with aura that has shown pre-treatment of patients prior to headache does not prevent headache (Bates et al., 1994). Sumatriptan nasal spray has been studied in an open label fashion and had modest effects (Hardebo and Dahlof, 1998). Recently, it was shown that patients with episodic but not chronic cluster headache responded to zolmitriptan 5mg orally (Bahra et al., 2000a). Although the response was modest the difference was clear from placebo and augurs well for the development of non-injectable options for the management of acute cluster headache.

**Primary headache with similarities to cluster headache**

In recent years a number of disorders which have many similarities to cluster headache have been recognised more fully. The differential considerations are substantially listed in Table 4. These headaches have been recently reviewed in detail (Goadsby and Lipton, 1997). An important issue is to recognise these problems because many are treatable.

**Paroxysmal hemicrania**

Sjaastad et al. (1980) first reported eight cases, 7 of whom were female, of a frequent unilateral severe but short-lasting headache without remission coining the term Chronic Paroxysmal Hemicrania (CPH). An episodic form has been reported, and the use of a division rather like cluster headache seems appropriate.

The mean daily frequency of attacks in Sjaastad’s cases (1980) varied from 7 to 22 with the pain persisting from 5 to 45 minutes on each occasion. The site and associated autonomic phenomena were similar to cluster headache, but the attacks of CPH were suppressed completely by indomethacin. A subsequent review of 84 cases showed a history of remission in 35 cases whereas 49 were chronic (Antonacci and Sjaastad, 1989). CPH usually begins in adulthood at the mean age of 34 years with a range of 6 to 81 years. Children with CPH have been reported (Broeske et al., 1993; Gladstein et al., 1994; Kudrow and Kudrow, 1989), although at least one case has been considered to be cluster headache (Solomon and Newman, 1995). The author has seen a 4-year child with an otherwise typical indomethacin-sensitive case. A typical case responding to acetazolamide has been reported (Warner et al., 1994).

By analogy with cluster headache the patients with remission have been referred to as episodic paroxysmal hemicrania (Kudrow et al., 1987). Pareja (1995) has recorded attacks which swap sides, just as is known for cluster headache, and attacks of autonomic features without pain. This has been observed in cluster headache after trigeminal nerve section, by this author and others, and is excellent evidence for a primarily CNS disorder.
Event-related potentials which have been reported to be abnormal in migraine (Wang and Schoenen, 1998) are normal in CPH (Evers et al., 1997) as is cognitive processing (Evers et al., 1999).

Some recent cases have broadened our understanding of paroxysmal hemicrania. Boes and colleagues reported otalgia and an interesting sensation of fullness of the external auditory meatus responding to indomethacin (Boes et al., 1998). There has been some interesting speculation from Dodick about extra-trigeminal pain in episodic paroxysmal hemicrania (Dodick, 1998), and I doubt that the full clinical dimensions of these syndromes have been defined.

The essential features of paroxysmal hemicrania as it is now understood are:

- female preponderance;
- unilateral, usually fronto-temporal, very severe pain;
- short-lasting attacks (2-45mins);
- very frequent attacks (usually more than 5 a day);
- marked autonomic features ipsilateral to the pain;
- robust, quick (less than 72 hour), excellent response to indomethacin, generally.

Other issues: The therapy of CPH has been discussed in relation to its responses to triptans. The issue is not clearly settled and may be both variable and dependent on the length of the attacks (Antonaci et al., 1998; Dahlof, 1993; Pascual and Quijano, 1998). Greater occipital nerve injection is not useful in CPH (Antonaci et al., 1997). Piroxicam has been suggested to be helpful (Sjaastad and Antonaci, 1995), although again not as effective as indomethacin. By analogy with cluster headache verapamil has been used in CPH (Shabbir and McAbee, 1994), although the response is not spectacular and higher doses require exploration. CPH can co-exist with trigeminal neuralgia (Caminero et al., 1998; Hannerz, 1993; Hannerz, 1998), just as does cluster headache (Pascual and Berciano, 1993; Watson and Evans, 1985). Similarly, secondary CPH has also been reported with a syndrome like Tolosa-Hunt (Foerderreuther et al., 1997) and patients with a pituitary microadenoma and a maxillary cyst (Gatzonis et al., 1996).

Short-lasting Unilateral Neuralgiform headache with Conjunctival injection and Tearing (SUNCT)

This condition was first described by Sjaastad et al. (1989) and its basis has been the subject of speculation, although we have recently observed posterior hypothalamic activation with BOLD contrast fMRI (May et al., 1999), suggesting a disorder of the central nervous system. The patients are mostly males (Pareja and Sjaastad, 1994) with a gender ratio of approximately 4 to 1 (Pareja and Sjaastad, 1997). The paroxysms of pain usually last between 5 and 250 seconds (Pareja et al., 1996b) although longer duller interictal pains are recognised, as have attacks up to 2 hours in two patients (Pareja et al., 1996a). This author has certainly witnessed an attack of otherwise typical SUNCT that last 30 minutes. Patients may have up to 30 episodes an hour although more usually would have 5-6 per hour. The frequency may also vary in bouts. A systematic study of attack frequency demonstrated a mean of 28 attacks per day with a range of 6 to 77 (Pareja et al., 1996a). The conjunctival injection seen with SUNCT is often the most prominent autonomic feature and tearing may also be very obvious. Other less prominent autonomic symptoms include sweating of the forehead or rhinorrhea. The attacks may become bilateral but the most severe pain remains unilateral.

Secondary SUNCT and associations: There have been several reported patients with SUNCT syndromes secondary to homolateral cerebellopontine angle and brainstem arteriovenous malformations diagnosed on MRI (Bussone et al., 1991; De Benedittis, 1996). One patient had a cavernous hemangioma of the cerebellopontine angle seen only on MRI (Morales et al., 1994), so that MRI of the brain should be part of the investigation of this syndrome when it is recognised.

Management

Unlike some of the other short-lasting headache syndromes, such as the paroxysmal hemicranias that are highly responsive to indomethacin, SUNCT is remarkably refractory to treatment, including indomethacin (Pareja et al., 1995). The relationship between trigeminal neuralgia and SUNCT remains unclear (Sjaastad et al., 1997). There is a single report of a patient with trigeminal neuralgia who developed a SUNCT syndrome (Bouhassira et al., 1994) and a case said to be trigeminal neuralgia with cranial autonomic symptoms (Benoliel and Sharav, 1998). These patients may respond to carbamazepine in a partial sense. Our recent experience suggests that topiramate may be the treatment of choice.

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