Advances in the Treatment of Cluster Headache

a report by

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DOI:10.17925/ENR.2008.03.01.115

Cluster headache (CH) is one of the trigeminal autonomic cephalalgias (TACs), which are primary headache disorders characterised by unilateral head pain occurring in association with prominent ipsilateral cranial autonomic features, such as lacrimation, conjunctival injection or nasal symptoms.[1,2] TACs include paroxysmal hemicrania (PH) and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) or short-lasting unilateral neuralgiform headaches with cranial autonomic symptoms (SUNA). Whether hemicrania continua (HC) should be included is moot.[3] Currently, TACs are grouped into section three of the revised International Classification of Headache Disorders (ICHD-III).[4] TACs differ in attack duration and frequency, as well as response to therapy: CH has the longest attack duration and relatively low attack frequency; PH has intermediate duration and intermediate attack frequency; SUNCT has the shortest attack duration and the highest attack frequency; and HC is marked by continuous pain with exacerbations, which can include cranial autonomic symptoms as part of the phenotype. In this article, recent advances in CH will be set against the importance of first making the diagnosis and the distinction from other TACs, and then in terms of recent developments in therapy.

General Diagnostic Matters Concerning Trigeminal Autonomic Cephalalgias

Recently, some important diagnostic matters have arisen around TACs. These concerns include the clinical features at presentation, which greatly facilitate diagnosis, the investigation of the disorders and considerations that complicate the diagnosis.

The Attacks

At presentation the clinical features of the TACs are highly characteristic when typical (see *Table 1*). Large cohorts of patients with CH have been published,[5,6] and we have supplemented this with our growing personal experience of more than 900 cases. Carefully characterised substantial cohorts are now available for PH[7] and for SUNCT/SUNA.[8] Drawing on this, material patterns have emerged, some of which run counter to the current International Headache Society (IHS) criteria[4] in their detail. While these do not attempt to overturn the largest part of the criteria, they offer some clinical pointers. First, there is no typical form of pain in these syndromes: it may be throbbing, sharp or stabbing, and this may even vary from bout to bout and, indeed, between attacks. Second, while usually involving the ophthalmic division of the trigeminal nerve, the pain may also involve any part of the head and occasionally may not involve the ophthalmic division at all. Third, each of these syndromes produces what patients describe as severe pain, and for both CH and PH it is most commonly described as severe pain. CH patients whose diagnosis is safe will routinely describe the attack pain as their worst ever experience. Many PH patients say the same thing, and so do a number of SUNCT/SUNA patients. The concept that pain character, distribution or severity exclusively defines these syndromes does not stand up in practice, so clinicians need to keep a broad view.

While attack frequency is a reasonable pointer to the diagnosis, there is considerable overlap. Although typical CH patients have one to two attacks a day, typical PH patients experience 10 and typical SUNCT/SUNA patients suffer 50, there is a marked skew that favours a lower attack frequency in each of these conditions. Thus, having 20 CH attacks in a day is most exceptional, while having one to two PH attacks is less common but recognised.[7] This fact suggests that, for example, clinicians need a low threshold for indomethacin testing in TACs. Another feature of attacks that is emerging in importance is the lateralisation of photophobia and phonophobia. In a cohort of consecutive patients, fewer than 5% of patients with unilateral migraine referred their photophobia or phonophobia to the side of the pain, whereas for TACs up to 10 times that proportion will say their photophobia or phonophobia, or both, is located ipsilateral to the pain.[9] This can be a useful clinical pointer.

Interparoxysmal Pain and Allodynia in Trigeminal Autonomic Cephalalgias

While for HC it is clear that there is pain between attacks, this is now well recognised also in mainstream TACs. In a cohort of 52 patients with SUNCT/ SUNA, 22 had interparoxysmal pain.[8] Most patients in that cohort who had interparoxysmal pain also had a personal or family history, or both, of migraine. Similarly, in a cohort of 31 PH patients, 18 had pain between attacks.[7] This has been also been reported in smaller series[10] and in 28 out of 84 patients in a retrospective series.[11] Eight of the 18 in our series had medication overuse, and again the majority had a personal or family history, or both, of migraine. We have seen allodynia and hyperalgesia in each of the TACs, and again the largest group of affected patients have had migraine or a family history of migraine, or both. For CH, allodynia has been reported both to occur[12] and not to be seen[13] in small cohorts. Our belief is interparoxysmal pain

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Table 1: Comparison of Trigeminal Autonomic Cephalalgias

		Cluster Headache	Paroxysmal Hemicrania	SUNCT/SUNA
Sex		3M to 1F	M = F	1.5M to 1F
Pain				
	Quality	Sharp/stab/throb	Sharp/stab/throb	Sharp/stab/throb
	Severity	Very severe	Very severe	Severe
	Distribution	V1>C2>V2>V3	V1>C2>V2>V3	V1>C2>V2>V3
Attacks				
	Frequency (per day)	1–8	20	100
	Length (minutes)	30–180	2–30	1–5
Triggers				
	Alcohol	+++	+	–
	Nitroglycerin	+++	+	–
	Cutaneous	–	–	+++
Agitation/restlessness (%)		90	80	65
Episodic versus chronic		90:10	35:65	10:90
Circadian/circannual periodicity		Present	Absent	Absent
Treatment effects (%)				
	Oxygen	70	No effect	No effect
	Sumatriptan 6mg	90	20	<10
	Indomethacin	No effect	100	No effect
Migraine features with attacks (%)				
	Nausea	50	40	25
	Photophobia/phonophobia	65	65	25

Comparison is based on cohorts we have studied[5,7,8,70] and patients we have reviewed.[71]
C = cervical; F = female; M = males; SUNCT = short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; SUNA = short-lasting unilateral neuralgiform headache attacks with cranial autonomic features; V = trigeminal; + = level of response; – = no response.

and allodynia in TACs represent the co-existence of the TAC and migrainousness biology. The clinical importance is that one needs to be aware of these overlaps so as to identify the major presenting problem that requires treatment.

Periodicity of Trigeminal Autonomic Cephalalgias

Periodicity is less obvious with PH and SUNCT/SUNA than with CH, although this is partly based on the belief that PH and SUNCT/SUNA are dominated by the so-called 'chronic' varieties, when an untreated break of less than one month is compared with CH. If one looks at chronic CH, PH and SUNCT/SUNA, there are so-called micro-periods where seasonal variation can be seen, e.g. SUNCT,[14] and we have certainly seen this in our practice in all the TACs. As chronic CH is more common than the other two conditions, this phenomenon of seasonal variation may be characterised as otherwise stable patients apparently destabilising. Unaware of this, clinicians and patients may feel prophylactics have 'stopped working' although, in fact, the disorder has changed. Over years, this can lead to an upwards creep of medicine doses and eventual accrual of side effects. If one is aware of the phenomenon of periodicity even in chronic CH, the physician can, after a period of increased dosing, revert to the previous dose, or use other strategies for short-term care to avoid changing the baseline preventative dose.

Investigating Trigeminal Autonomic Cephalalgias – The Pituitary Gland

A remarkable range of pathology has been identified as presenting with TAC-like headaches. An important theme that has emerged in recent times has been the propensity for pituitary and peri-pituitary gland pathology to present as a phenotypic TAC. In a cohort of 84 patients with pituitary tumours and headache problems, 10% had a TAC-like headache.[15] This increased the distribution of the conditions about 100-fold compared with presentations in populations and, while migraine was the most common headache form, the excess of TACs was prominent. The involvement of the region of the diencephalon on brain imaging in TACs[16] perhaps reinforces this link to the pituitary, as does the neuroendocrine disturbance, which is well recognised in CH.[17]

Taken with other clinical contributions,[18] it seems reasonable to recommend brain magnetic resonance imaging (MRI) with pituitary views and pituitary function tests as a reasonable part of the work-up in all TAC patients, if the tests are available. Given that the conditions are rare and lifelong[19] and the treatment of the pituitary pathology resolves the headache problem,[20,21] it seems that the time and money are well spent.

Medication Overuse and the Trigeminal Autonomic Cephalalgias

Medication overuse has not typically been recognised as a problem for patients with CH or indeed TACs in general. A study of regular oral sumatriptan 100mg three times daily as a preventative treatment did not record headache induction as relevant,[22] although ergotamine-induced headache has been recognised in CH.[23] Daily headache has been recognised with subcutaneous sumatriptan in CH,[24] as has increased attack frequency.[25–28] From a cohort of 430 patients with CH, 17 (4%) were reported to have medication overuse problems.[29] There were two patterns of overuse: a dull, generalised, featureless headache and a more obviously migrainous headache. Most remarkably, 15 of the 17 had a personal or family history, or both, of migraine and the other two a family history of otherwise unspecified headache. Overall, it is clear that medication overuse occurs in CH and, indeed, we have seen it in other TACs and HC. The principle seems to be that patients who have a TAC and also have migrainous biology are susceptible to medication overuse problems.[30] Given that not all migraineurs exposed to frequent acute attack medicines develop medication overuse problems,[31,32] there must be a biological predisposition that is co-morbid with migraine. In practice, medication overuse occurs in TACs and needs careful management.

Cluster Headache

CH is a strictly unilateral headache that occurs in association with cranial autonomic features.[4] It is an excruciating syndrome and is probably one of the most painful conditions known to humans, with female patients describing each attack as being worse than childbirth. In most patients, it has a striking circannual and circadian periodicity. By neurological standards it is not uncommon, with about one patient per 1,000 of the population[33,34] suffering, which is about as common as multiple sclerosis in the UK.[35] Both clinical trials and experience are providing insights into the management of the disorder.

Management

Triptans

It is clear that sumatriptan 6mg subcutaneous is the most efficacious form of acute therapy in CH.[36,37] However, limitation of its use to two doses in 24 hours is an important concern in some patients. It must be said that the limit is artificial and makes no particular sense in most patients, and one may argue for smaller doses, such as the 4mg dose,[38] being made available for more frequent use. It is likely that a patient with CH who has no cardiovascular risk factors and no personal or family history of migraine (see above) could tolerate more dosing in 24 hours. More data are needed on this matter. There are placebo-controlled data for the use of sumatriptan 20mg nasally[39] and two randomised placebo-controlled studies for the use of zolmitriptan 5mg nasal spray[40,41] in acute cluster headache. A proportion of patients will find nasal sprays useful, and one hopes these formulations will be licensed at some point.

Greater Occipital Nerve Injections

Greater occipital nerve (GON) injections are useful in the short-term preventative treatment of a range of primary headaches.[42] In a randomised, controlled, parallel-group study comparing saline with a mixture of a long- and rapid-acting betamethasone, 80% of the active arm and none of the placebo arm were attack-free after a week.[43] Interestingly, changes in the nociception-specific blink reflex do not predict a clinical effect,[44] suggesting that the mechanism is rostral in the central nervous system (CNS). GON injection is a safe and useful procedure to reduce CH burden in the short term.

Oxygen

It is generally accepted that patients with acute CH respond well to treatment with oxygen inhalation,[45,46] although the evidence base for this is rather poor. Recently, 80 patients (66 male) with episodic CH (ECH) and 28 patients (23 male) with chronic CH (CCH) who were naïve to high-flow oxygen were randomised into a placebo-controlled, double-blind, cross-over study. Patients treated four CH attacks using two treatments each of air placebo or 100% oxygen at 12l/min for 15 minutes. Fifty-seven patients with ECH and 19 with CCH were available for the intention-to-treat analysis. For the primary end-point of pain-free at 15 minutes, the difference between oxygen – 78% (n=150) – and air – 20% (n=148) – was significant (p<0.001). There were no important adverse events.[47] The data suggest that oxygen should be widely and easily available to patients with CH.

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Verapamil

CH is a devastating illness when not controlled and so adequate preventative therapy can be helpful. Verapamil is the treatment of choice for the preventative management of CH when bouts are long enough to stabilise the medicine. Verapamil has been recognised as a useful option for some time.[48] It is superior to placebo[49] and compares favourably with lithium.[50] What has clearly emerged from clinical practice is the need to use higher doses than had initially been considered, and certainly higher than those used in cardiological indications. Although most patients will start on doses as low as 40mg twice daily, doses up to 960mg daily are now employed.[51] Side effects, such as constipation and leg swelling, can be a problem,[52] but more difficult is the matter of cardiovascular safety. Verapamil can cause heart block by slowing conduction in the atrioventricular node,[53] as demonstrated by prolongation of the A–H interval.[54] Given that the PR interval on the electrocardiogram (ECG) is made up of atrial conduction, A–H and His bundle conduction, it may be difficult to monitor subtle early effects as verapamil dose is increased.

> Early reports suggest that most patients with previously medically intractable cluster headache will have improvement after occipital nerve stimulation sufficient to recommend it to other patients.

In an audit of verapamil use, a 20% incidence of ECG abnormalities was noted.[55] We recommend performing a baseline ECG and starting patients on 80mg three times daily; thereafter the total daily dose is increased in increments of 80mg every 10–14 days. An ECG is performed prior to each increment. The dose is increased until the cluster attacks are suppressed, side effects intervene or the maximum dose of 960mg daily is achieved.[55] Patients need to be warned of the side effect of gingival hyperplasia[56] so that dental hygiene is monitored closely. Given these caveats, verapamil is useful in CH management.

Neurostimulation

Even with advances in medical therapies, there remains a cohort of patients who are medically intractable.[57] Historically, these patients have been treated with destructive procedures such as radiofrequency trigeminal ganglion ablation[58] or trigeminal rhizotomy.[59,60] These procedures have considerable morbidity and, while minimal, also mortality and failure rates. The identification using functional imaging methods of an important role for the region of the posterior hypothalamic grey matter in CH[61] led to the use of deep brain

stimulation in that region to treat medically intractable chronic CH.[62] While this has been an effective strategy, it is not without concerns.[63] Integrating basic science data on the interaction between trigeminal and cervical nociceptive inputs in the trigeminocervical complex[64] and functional imaging findings in chronic migraine patients treated with occipital nerve stimulation (ONS),[65] we reasoned that ONS would be helpful in other primary headaches. Early reports in reasonably sized cohorts[66–68] suggest that most patients with previously medically intractable CH will have improvement after ONS sufficient to recommend it to other patients. While there is much still to be achieved in this area, ONS offers a way forward to patients otherwise devastated by the disorder and thus considerable promise for these patients.[69] ■

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