

Trigeminal Autonomic Cephalalgias: Paroxysmal Hemicrania, SUNCT/SUNA, and Hemicrania Continua

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ABSTRACT

The trigeminal autonomic cephalalgias (TACs) are a group of primary headache disorders that include cluster headache (CH), paroxysmal hemicrania (PH), and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing/cranial autonomic features (SUNCT/SUNA). Hemicrania continua (HC) is often included with this group, although the second edition of The International Classification of Headache Disorders did not link the entities. Trigeminal autonomic cephalalgias are generally characterized by relatively short-lasting attacks of severe pain and lateralized associated features including the pain, cranial autonomic symptoms, and where present, migrainous symptoms, such as photophobia. Paroxysmal hemicrania has intermediate duration and intermediate attack frequency. Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing has the shortest attack duration and the highest attack frequency. Hemicrania continua has a continuous pain with exacerbations that can include cranial autonomic symptoms as part of the phenotype. The syndromes share much in their pathophysiology and investigation paths; however, their treatment is distinct, so that the accurate differentiation is important for optimal management.

KEYWORDS: Paroxysmal hemicrania, SUNCT, SUNA, hemicrania continua

The trigeminal autonomic cephalalgias (TACs) are a group of primary headache disorders characterized by unilateral head pain that occurs in association with prominent ipsilateral cranial autonomic features, such as lacrimation, conjunctival injection, or nasal symptoms.^{1,2} The TACs include cluster headache (CH), paroxysmal hemicrania (PH), and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing/cranial autonomic features (SUNCT/SUNA).

The TACs are grouped into Section 3 of the second edition of the International Classification of Headache Disorders (ICHD-2).³ Whether hemicrania continua (HC) should be included is a moot point, and why the ICHD-2 did not include it is open for discussion.⁴ For reasons of pathophysiology, clinical presentation, and management, HC is usefully described here with the other TACs. The TACs differ in attack duration and frequency as well as the response to therapy. CH has the

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longest attack duration and relatively low-attack frequency. Paroxysmal hemicrania has intermediate duration and intermediate attack frequency. Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing has the shortest attack duration and the highest attack frequency (Table 1). Hemicrania continua has a continuous pain with exacerbations that can include cranial autonomic symptoms as part of the phenotype. The importance of diagnosing these syndromes resides in their excellent, but highly selective response to treatment. CH is dealt with elsewhere in this issue and will not be further discussed. We will start by discussing the individual syndromes and then alert the reader to some shared issues.

PAROXYSMAL HEMICRANIA

Paroxysmal hemicrania (PH) is a rare TAC marked by relatively short attacks of very severe lateralized pain with cranial autonomic features that responds to indomethacin.⁵

Clinical Features

Attacks usually occur several times a day, with a mean of 11 in one series.⁶ The pain is usually in the ophthalmic division of the trigeminal nerve, is strictly unilateral,

although side shift may occur, and has a median length of 19 minutes.⁶ Typically described as a problem of women, this does not seem correct from a recent substantial cohort where a clear female preponderance was not evident.⁶ In one study, 27 of 31 patients noted at least one migrainous feature of photophobia, nausea, or vomiting during an attack.⁷ Photophobia and phonophobia in a large series were also seen in about two-thirds of patients,⁶ and when present, this was very often lateralized to the side of the pain.⁸ Some 80% of a large series were restless or agitated during attacks.⁶ In contrast to CH, the attacks do not have a nocturnal predilection.

Triggers

Though the majority of attacks are spontaneous, ~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 attacks in about one-fifth of patients,⁶ whereas in marked contrast to SUNCT/SUNA (see below), cutaneous triggering, such as touching the skin, chewing, or talking, is not a feature of PH. Menstruation is not an important trigger,⁶ and pregnancy does not seem to stop attacks in our experience.

Table 1 Comparison of the 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 (typical day) | 1–8 | 11 | 100 |
| Length (typical in minutes) | 30–180 | 2–30 | 1–10 |
| Triggers | | | |
| Alcohol | +++ | + | – |
| Nitroglycerin | +++ | + | – |
| Cutaneous | – | – | +++ |
| Agitation/restlessness | 90% | 80% | 65% |
| Episodic vs. chronic | 90:10 | 35:65 | 10:90 |
| Circadian/ circannual periodicity | Present | Absent | Absent |
| Treatment effects | | | |
| Oxygen | 70% | No effect | No effect |
| Sumatriptan 6 mg | 90% | 20% | <10% |
| Indomethacin | No effect | 100% | No effect |
| Migraine features with attacks | | | |
| Nausea | 50% | 40% | 25% |
| Photophobia/phonophobia | 65% | 65% | 25% |

*Based on cohorts we have studied,^{6,20,63} and patients we have seen in practice. SUNCT/SUNA, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing/short-lasting unilateral neuralgiform headache attacks with cranial autonomic features; M, male; F, female; C, cervical; V, trigeminal.

Subtypes

Paroxysmal hemicrania is classified as either episodic or chronic. About 20% of patients have *episodic paroxysmal hemicrania*, diagnosed when remissions last one month or longer; the remaining patients have *chronic paroxysmal hemicrania*, in which no remission occurs within one year.⁶ It is remarkable in contrast to CH, and almost in the same proportion in reverse, that the chronic form of PH dominates. This difference is not understood.

Treatment

Although the response to indomethacin is characteristic and long-lasting,⁹ patients who develop gastrointestinal problems present an important clinical challenge. Some of these patients have responded to COX-II selective inhibitors,^{10–12} although their long-term issues¹³ makes this option problematic. There are no controlled trial data for PH management when indomethacin cannot be used. Topiramate has been reported to be useful^{14,15}; it is our first choice after indomethacin. Interestingly, most attacks of PH are short and thus not suited to acute therapy; nevertheless, some are longer. Both response¹⁶ and lack of response^{17,18} to sumatriptan have been reported in PH. This is consistent with a large cohort in which 20% of patients responded.⁶ Greater occipital nerve injection with lidocaine and methylprednisolone is helpful in some patients with PH.¹⁹ Some patients with PH have been treated off-label with neuromodulation devices, and these may hold an important key for the future management of this cohort of patients.

SUNCT/SUNA

Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing/cranial autonomic symptoms (SUNCT/SUNA) is a relatively rare TAC that is marked by very short-lasting attacks of lateralized severe head pain associated with prominent cranial autonomic features and often triggered by cutaneous stimuli.²⁰

Clinical Features

Although the International Headache Society describes the site of pain in SUNCT as unilateral orbital, supra-orbital, or temporal pain,³ it is clear from a large series that the pain may be experienced anywhere in the head.²⁰ The attacks may have three broad forms: single stabs, which are usually short-lived; groups of stabs; or a longer attack comprised of many stabs between which the pain does not resolve to normal, thus giving a “saw-tooth” phenomenon with attacks lasting many minutes (Fig. 1).²⁰ The term SUNA is applied when both conjunctival injection and tearing are not present, and in practice the two conditions are likely a one spectrum disorder.

Differential Diagnosis and Triggers

When typical, which is to say very short-lasting, SUNCT/SUNA is clinically very characteristic. The major differential diagnosis is with trigeminal neuralgia.²¹ Characteristics of SUNCT/SUNA that distinguish it from trigeminal neuralgia include the prominent distribution of pain in the ophthalmic division of the trigeminal nerve, triggering of attacks from cutaneous stimuli, and a lack of a refractory period to these triggers.²⁰ In contrast to PH, there is no reproducible indomethacin effect in SUNCT/SUNA, and in contrast to CH no important effect of oxygen, sumatriptan, or verapamil.²⁰ Pituitary pathology (see below) is an important generic issue in TACs; in general terms, it is good practice where possible to image the posterior fossa with magnetic resonance imaging (MRI) in all cases of suspected SUNCT/SUNA.

Treatment

For many years it was said that SUNCT was untreatable.²² The literature suggests that lamotrigine is the most likely medicine to be effective in SUNCT/SUNA,^{23–29} with approximately two-thirds of patients responding.³⁰ Similarly, topiramate is helpful,^{30–32} as is

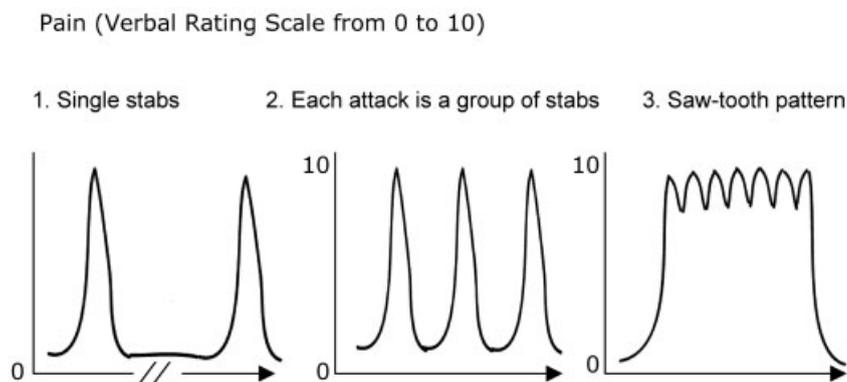


Figure 1 The three types of clinical picture of attacks of SUNCT/SUNA.²⁰

gabapentin.^{30,33–35} Five male patients with SUNCT were randomized into a placebo-controlled, double-blind crossover trial of topiramate 50 mg twice daily with the primary endpoint of a reduction in attack frequency by 50% for 10 days at maximum dose compared with baseline. Two patients responded very well, one responded to placebo, and two had no response at all.³⁶ Given limitations on studying rare headaches, these data certainly suggest that topiramate is worthwhile using for this condition.

HEMICRANIA CONTINUA

Hemicrania continua is characterized by a continuous, unilateral headache that varies in intensity, waxing and waning without disappearing completely. Exacerbations may be accompanied by ipsilateral cranial autonomic symptoms, and there is an absolute and robust response to indomethacin.

Clinical Diagnosis

The International Headache Society defines HC as having no side-shift; the pain is associated with lacrimation, conjunctival injection, nasal symptoms, and ptosis/miosis as the only cranial autonomic symptoms, and mandates a response to indomethacin.³ A unilateral continuous indomethacin-sensitive headache was first described by Medina and Diamond,³⁷ and the term “hemicrania continua” coined a few years later.³⁸ There are no more than a few hundred cases in the literature. Hemicrania continua is likely underdiagnosed,^{39,40} but the absolute requirement for an indomethacin effect and no clear biologic marker has been a problem. Cases with bilateral pain have been reported,^{41–43} and patients with unilateral, side-alternating attacks^{44–48} has been described. Nausea, photophobia, phonophobia, and cranial autonomic symptoms are infrequent during the background pain, though more common with exacerbations.^{39,49,50} Although unusual, four cases have been described in whom a typical migrainous visual aura occurred in association with the exacerbation of HC.⁵¹ In general terms, the background pain of HC is more severe than the interparoxysmal pain of the other TACs, and the worsening in HC are longer than the paroxysms of the other TACs. This is particularly important in differentiating HC from PH.

Treatment

As with PH, the essential management problem arises when indomethacin produces peptic ulcer disease. Again the COX-II inhibitors offer a way forward,⁵² but are not now recommended. Topiramate has been reported to be useful in HC,^{14,46,53} and this is borne out in practice. Similarly, greater occipital nerve injection

with lidocaine and methylprednisolone has been reported to be helpful.¹⁹ The most promising approach has been occipital nerve stimulation,⁵⁴ which is likely to have a role at some point.

SOME GENERAL ISSUES AROUND TACS

Lateralization Is a Key to the Phenotypes

A feature of attacks that is emerging in importance is of lateralization of symptoms and signs in the TACs.⁵⁵ In a cohort of consecutive patients, less than 5% with unilateral migraine referred their photophobia or phonophobia to the side of the pain; for TACs, up to 10 times that proportion will say their photophobia or phonophobia, or both, are located ipsilateral to the pain.⁸ Similarly, comparing cranial autonomic symptoms between patients with migraine and CH, CH patients were more likely to have lateralized, prominent symptoms stereotypically linked to attacks of pain, whereas when present in migraine sufferers, cranial autonomic symptoms were more likely bilateral, less prominent, and variable in manifestation.⁵⁶ The simple rule of lateralization is a useful one in practice to differentiate TACs from migraine.

Investigating TACS

THE PITUITARY GLAND

A remarkable range of pathology has been identified as presenting with TAC-like headaches. An important theme that has emerged has been the propensity for pituitary and peripituitary gland pathology to present as a phenotypic TAC. In a cohort of 84 patients with pituitary tumors and headache problems, 10% had a TAC-like headache.⁵⁷ This is about 100-fold the distribution of the conditions; although migraine was the most common headache form, the excess of TACs was prominent. The involvement of the region of the hypothalamus on brain imaging in TACs⁵⁸ perhaps reinforces this link to the pituitary, as does the neuroendocrine disturbance that is well recognized in CH.⁵⁹ Taken together with other clinical contributions,⁶⁰ it seems reasonable to recommend a brain MRI scan with pituitary views and pituitary function tests as a reasonable part of the work-up in all TAC patients when the tests are available. Given the conditions are rare and lifelong,⁹ and the treatment of the pituitary pathology resolves the headache problem,^{61,62} investigation seems appropriate.

CONCLUSIONS

The TACs are a group of primary headache disorders characterized by unilateral head pain that occurs in association with prominent ipsilateral cranial autonomic

features, such as lacrimation, conjunctival injection, or nasal symptoms. The TACs include CH, PH, and SUNCT/SUNA. Hemicrania continua should probably be included in this grouping. CH has the longest attack duration and relatively low-attack frequency. Paroxysmal hemicrania has intermediate duration and intermediate attack frequency. Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing/short-lasting unilateral neuralgiform headache attacks with cranial autonomic features have the shortest attack duration and the highest attack frequency. Hemicrania continua is a continuous pain with exacerbations that can include cranial autonomic symptoms as part of the phenotype. The importance of diagnosing these syndromes resides in their excellent, but highly selective response to treatment.

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