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HEADACHE (R. B. HALKER, SECTION EDITOR)

A Practical Approach to Autonomic Dysfunction in Patients with Headache

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Abstract The presence of autonomic symptoms can make the diagnosis of headache challenging. While commonly seen with the trigeminal autonomic cephalalgias, autonomic dysfunction can also be present in patients with migraine, or with a variety of secondary headaches. The pathophysiology of cranial autonomic symptoms in headache is based between the trigeminal system and the hypothalamus. This article will review the pathophysiology and presence of autonomic dysfunction in headache and will provide techniques to help in headache diagnosis in patients with autonomic dysfunction.

Keywords Autonomic dysfunction · Trigeminal autonomic cephalalgia · Cluster headache · Migraine

Case

A 26-year-old woman presents to clinic with symptoms of episodes of severe headache. She describes the headache as a sharp, throbbing, stabbing pain behind her right eye that can last several hours. The episodes occur with associated nausea and vomiting. She notes laying down in a dark room with a compress over her eye can help the pain. She describes tearing in both of her eyes and her boyfriend has told her that her eye turns red during the episodes. These episodes occur up to four times a month and are triggered by her menses and sleep deprivation. They do not seem to occur at a particular time of day, but can be more frequent in the summer, she feels in relation to the heat.

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Introduction

Autonomic dysfunction can be associated with a variety of headache disorders. Seen most often as associated eye tearing, redness, nasal congestion, rhinorrhea, ptosis, miosis, or facial sweating, autonomic dysfunction in headache can present a challenge for appropriate diagnosis. It can be commonly seen in the trigeminal autonomic cephalalgias (TACs) such as cluster headache, or paroxysmal hemicranias, but can also be present with migraine and with secondary headache disorders such as headaches associated with pituitary dysfunction, intracranial aneurysm, and sinus headaches. Often times, unless directly asked, patients may not report associated autonomic symptoms with their headaches. Symptoms may be mild, as often in the case of autonomic symptoms associated with migraine, or may be more severe and a predominant feature of the headache, as can be seen in cluster headache.

This article will discuss autonomic dysfunction in headache disorders and how to differentiate different headache types with associated autonomic dysfunction.

Pathophysiology of Autonomic Dysfunction in Headache

In order to appreciate autonomic craniofacial phenomenon in pain, it is important to recognize where cranial

autonomic symptoms (CAS) arise from. Brain pathways that produce autonomic symptoms with headache have been well elucidated in experimental animal studies and neuroimaging studies in humans [1], and have been termed the trigeminal-autonomic reflex [2]. Cranial nociception pathways involve the trigeminal nerve. Trigeminal nerve afferents provide nociceptive innervation to cranial structures that course through the trigeminal ganglion and trigeminal sensory root. They then project to the trigeminal nucleus. Pain input from cranial structures goes through the descending tract of the trigeminal nucleus caudalis and dorsal horns of the spinal cord at the C1 and C2 level. This is called the trigeminocervical complex [3]. With activation of the trigeminocervical complex, a reflex activation of cranial parasympathetic outflow can occur [1]. Simultaneous activation in the brainstem of the trigeminal nerve and craniofacial parasympathetic nerve fibers in the superior salivary nucleus has been termed the trigeminofacial reflex [4]. Activation of this reflex occurs in patients with cluster headache and other TACs [5••]. CAS in TACs may be due to central disinhibition of the trigeminal-autonomic reflex [1].

Autonomic activation can also occur in patients with migrain-producing CAS, with reports of both hypo and hyperfunctioning of the autonomic nervous system in patients with migraine [6,7].

In addition to the trigeminal system, the hypothalamus likely plays a role in CAS. The hypothalamus is involved in regulating autonomic functions and maintaining homeostasis. Hypothalamic dysfunction is linked to both TACs and migraine [5••,8]. Neuroimaging studies in TACs have shown ipsilateral posterior hypothalamic activation [9–12]. The hypothalamus modulates nociceptive and autonomic pathways. In TACs, an abnormality in the hypothalamus may activate cranial autonomic and trigeminovascular nociceptive pathway [13]. Newer studies looking at autonomic response to the head-up tilt table test have shown that patients with cluster headache have a decreased autonomic response [14••]. This adds further evidence to dysregulation in the posterior hypothalamus possibly contributing to autonomic responses in patients with cluster headache.

Hypothalamic activation occurs in migraine as it does in cluster headache and other pain disorders [15]. In 2014, neuroimaging studies of patients with migraine reported enhanced functional connectivity between the hypothalamus and brain areas that regulate autonomic functions [16]. What is not well understood is if hypothalamic activation leads to CAS in both migraine and TACs, and if so, why are CAS often unilateral in TACs and more often bilateral in migraine? The trigeminal autonomic reflex does have a minor contralateral component due to crossover in the brainstem [17]. It has been theorized that in TACs, such as cluster headache, the contralateral trigeminal autonomic reflex may be suppressed due to some unknown mechanism [18]. Why this would occur in a small portion of patients with migraine, and not occur in a small portion of patients with cluster headache who have bilateral CAS is unknown at this time.

Primary Headache Disorders with Cranial Autonomic Symptoms

The TACs are a group of headache disorders that are characterized by severe pain in the trigeminal distribution with associated autonomic features (Table 1). Pain is unilateral, often in V1-V2, though the pain can travel into V3. Pain is often severe and disabling. Patients with cluster headache may consider suicide due to the nature of attacks. Headache episodes in the TACs are usually of short duration, lasting seconds and up to 3 hours. Attacks often repeat numerous times through the day, sometimes at regular and predictable intervals (such as soon after falling asleep in cluster headache). Autonomic symptoms can vary but are a prominent part of TACs. An example of this is seen in the syndrome LASH, long-lasting autonomic symptoms with hemicranias (LASH) [19, 20, 21••]. In this syndrome, patients with hemicrania can have CAS occurring hours prior to unilateral head pain. CAS can appear for days and may continue for hours after headache resolves. LASH syndrome is an interesting phenomenon that may imply a greater activation of the trigeminal-autonomic reflex vs. indicate greater dysfunction in the autonomic pathways in these patients.

Migraine is a moderate to severe headache disorder with associated symptoms of nausea, vomiting, photophobia, and phonophobia, made worse by physical activity [22]. CAS are an often underreported and little known occurrence in migraine. In 2008, Lai and colleagues reported on CAS in migraine [18]. They found that 56 % of patients with migraine have a least one CAS. In migraine, bilateral CAS symptoms are more common than unilateral symptoms (occurring in around 32 % of patients). CAS appears inconsistently with headaches, is unrestricted to headache side, and can occur in mild to moderate headache intensity, though is often seen in more severe headaches and may represent a more severe migraine attack. Forehead and facial sweating is more common than lacrimation. Less than one third of migraine patients had CAS with every headache.

Gelfand and colleagues in 2013 reported on CAS in pediatric patients with migraine [23••]. They found that 70 % of pediatric patients with migraine had at least one CAS with their headaches, though most had more than

Table 1 Trigeminal autonomic cephalalgias classification

Cluster headache	Paroxysmal hemicrania	Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)	Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA)	Hemicrania continua
A. At least five attacks fulfilling criteria B–D	A. At least 20 attacks fulfilling criteria B–E	A. At least 20 attacks fulfilling criteria B–D	A. At least 20 attacks fulfilling criteria B–D	A. Unilateral headache fulfilling criteria B–D
B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 min (when untreated)	B. Severe unilateral orbital, supraorbital, and/or temporal pain lasting 2–30 min	B. Moderate or severe unilateral head pain, with orbital, supraorbital, temporal, and/or other trigeminal distribution, lasting for 1–600 s and occurring as single stabs, series of stabs, or in a saw tooth pattern	B. Moderate or severe unilateral head pain, with orbital, supraorbital, temporal, and/or other trigeminal distribution, lasting for 1–600 s and occurring as single stabs, series of stabs, or in a saw tooth pattern	B. Present for >3 months, with exacerbations of moderate or greater intensity
C. Either or both of the following:	C. At least one of the following symptoms or signs, ipsilateral to the pain:	C. At least one of the following cranial autonomic symptoms or signs, ipsilateral to the pain:	C. At least one of the following cranial autonomic symptoms or signs, ipsilateral to the pain:	C. Either or both of the following:
1. At least one of the following symptoms or signs, ipsilateral to the headache:	1. Conjunctival injection and/or lacrimation	1. Conjunctival injection and/or lacrimation	1. Conjunctival injection and/or lacrimation	1. At least one of the following cranial autonomic symptoms or signs, ipsilateral to the pain:
(a) Conjunctival injection and/or lacrimation	2. Nasal congestion and/or rhinorrhea	2. Nasal congestion and/or rhinorrhea	2. Nasal congestion and/or rhinorrhea	(a). Conjunctival injection and/or lacrimation
(b) Nasal congestion and/or rhinorrhea	3. Eyelid edema	3. Eyelid edema	3. Eyelid edema	(b). Nasal congestion and/or rhinorrhea
(c) Eyelid edema	4. Forehead and facial sweating	4. Forehead and facial sweating	4. Forehead and facial sweating	(c). Eyelid edema
(d) Forehead and facial sweating	5. Forehead and facial flushing	5. Forehead and facial flushing	5. Forehead and facial flushing	(d). Forehead and facial sweating
(e) Forehead and facial flushing	6. Sensation of fullness in the ear	6. Sensation of fullness in the ear	6. Sensation of fullness in the ear	(e). Forehead and facial flushing
(f) Sensation of fullness in the ear	7. Miosis and/or ptosis	7. Miosis and/or ptosis	7. Miosis and/or ptosis	(f). Sensation of fullness in the ear
(g) Miosis and/or ptosis	D. Attacks have a frequency above 5 per day for more than half the time	D. Attacks have a frequency of at least once a day for more than half of the time when the disorder is active.	D. Attacks have a frequency of at least once a day for more than half of the time when the disorder is active.	(g). Miosis and/or ptosis
2. A sense of restlessness or agitation	E. Attacks are prevented absolutely by therapeutic doses of indomethacin	E. Have conjunctival injection and lacrimation	E. Only one or neither of conjunctival injection and lacrimation	2. A sense of restlessness or agitation or aggravation of the pain by movement
D. Attacks have a frequency between one every other day and eight per day for more than half of the time when the disorder is active	F. Not better accounted for by another ICHD-3 diagnosis	F. Not better accounted for by another ICHD-3 diagnosis	F. Not better accounted for by another ICHD-3 diagnosis.	D. Responds absolutely to therapeutic doses of indomethacin
E. Not better accounted for by another ICHD-3 diagnosis.				E. Not better accounted for by another ICHD-3 diagnosis.

Headache Classification Committee of the International Headache Society (HS). The International Classification of Headache Disorders 3rd edition. Cephalalgia 2013;33:629–808

one. Like Lai et al., Gelfand et al. found that most CAS in migraine is bilateral. In the pediatric population, aural fullness, facial sweating/flushing, and lacrimation were the most common CAS seen.

Secondary Headaches and Autonomic Dysfunction

In the presence of autonomic symptoms with headache, one should always consider secondary headaches on the differential. There are many secondary headaches that present with TAC-like headaches and can be difficult to distinguish from primary TACs without neuroimaging. Secondary causes of headache with autonomic dysfunction include cerebellopontine angle tumors [24], internal carotid artery dissection [25], sphenoiditis [26], sinus disease [27,28], parasagittal hemangiopericytoma [29], moyamoya [30], pituitary lesions [31], and post schwannoma excision [32]. Consider imaging of the brain with magnetic resonance imaging (MRI) and/or magnetic resonance angiography (MRA) in patients with autonomic symptoms and headache, especially in SUNCT or SUNA, or with headache with CAS with headache features that are changed from baseline.

Differentiating Headaches with Autonomic Features

In 2013, Viana and colleagues published a study reviewing the management of TACs [33••]. In their study, they reported continued misdiagnosis of TACs. Primary TACs are often diagnosed as either migraine, trigeminal neuralgia, sinus infections, dental pain, or temporal mandibular disorder. The delay to diagnosis for cluster headache is up to 3 years [34]. Often up to three physicians are consulted prior to the diagnosis of cluster [33••]. Migraine with CAS and cluster headache with migraine features, such as aura, photophobia, phonophobia, make distinguishing cluster headache more difficult. Viana et al. reported after a review of studies on TACs that up to 61.2 % of cluster attacks can be associated with photophobia and phonophobia. Twenty-seven percent of cluster attacks can be associated with nausea and vomiting. One fourth of cluster headache patients had migraine aura prior to attacks. Fourteen percent of cluster headache can side shift during a cluster period, again making differentiation based on diagnostic criteria somewhat difficult.

In order to differentiate cluster headache and TACs from other primary headache disorders, one should consider the following items (Table 2); duration of headache, severity of headache, associated agitation or pacing, timing of headache/headache recurrence, prominence and laterality of CAS

Table 2 How to differentiate between TAC, migraine, and other headache disorders

Features of Headache	TAC	Migraine	Other
Duration	Seconds up to 90 min	4 h to 3 days +	Trigeminal neuralgia will be seconds to minutes
			Sinus headaches will be continuous
Severity	Severe	Moderate to severe	Mild to severe in sinus disease, moderate in TMD, severe in trigeminal neuralgia
Associated agitation	Present	Infrequent, often improves laying down	Infrequent in sinus headaches, can be worse laying down
Timing/recurrence	More than one attack per day, often recur in predictable pattern (time of day, time of year) for cluster headache	Can be daily in chronic migraine, sometimes more noticeable in am or late in day, worse at a certain time of year, but rare occurring ONLY at a certain time of day or certain time of year	Medication overuse headache may have predictable timing based on wear off of medication being used daily
CAS	Severe Unilateral	About ½ patients with have, not with every headache. Bilateral symptoms	None in trigeminal neuralgia
Number of attacks/day	Numerous	1–2	Can be numerous for trigeminal neuralgia
Photophobia/phonophobia	Can be seen in small portion of cluster headache	Frequent in migraine	Can be seen with subarachnoid hemorrhage, headache with meningitis
	Symptoms are ipsilateral to headache	Occur bilateral	
Rhinorrhea	Clear	Clear	Purulent in sinus infection

Duration of attacks, associated agitation/pacing, severity and laterality of CAS are the most helpful in differentiating TAC from other primary headache disorders

symptoms, number of attacks in one day, laterality of photophobia and phonophobia (in cluster headache, these symptoms are often seen unilateral to the headache attack [35]), and nature of rhinorrhea (clear vs. purulent). Taken in consideration together, diagnosis of TAC vs. other primary headache disorder becomes clearer.

Return to Our Case

Features That Can Help Differentiate Our Patient's Headache

Length of headache: Untreated the headache lasts for several hours.

Features of headache: Severe, unilateral, has a component of throbbing, with nausea, vomiting and photophobia that is bilateral. Laying down is helpful.

Autonomic features: Bilateral eye tearing and eye redness, though is not clear if redness is unilateral or bilateral. Symptoms are not always associated with every headache and are often seen in more severe attacks.

Time pattern of headache: Headaches have triggering factors, do not occur a particular time of day or year, though they are more frequent in the summer.

Our patient was diagnosed with migraine without aura.

Conclusion

CAS in association with headache can be seen in TACs, migraine, and a number of secondary causes of headache. The pathophysiology of CAS in headache disorders likely is related to the trigeminal autonomic reflex and activation of the posterior hypothalamus. CAS is more common in migraine that has been recognized in the past, with occurrence in 56 % of adults and 70 % of pediatric migraine sufferers. There are subtle distinguishing features between TACs and migraine. The most helpful features of headache to help differentiate TACs from other primary headache disorders are duration of attacks, associated agitation or pacing, and prominence and laterality of CAS. It is difficult to rule out secondary causes of headache with CAS without neuroimaging, so if clinical suspicion is high based on new onset symptoms, patients age, associated risk factors (history of cancer, pituitary issues in past), or other systemic symptoms, consider pursuing further work-up.

Compliance with Ethical Standards

Conflict of Interest Jessica Ailani reports personal fees from Allergan and Teva outside the submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Goadsby PJ. Trigeminal autonomic cephalalgias: fancy term or constructive change to the IHS classification? J Neurol Neurosurg Psychiatry. 2005;76:301–5.
2. May A, Goadsby PJ. The trigeminovascular system in humans: pathophysiological implications for primary headache syndromes of the neural influences on the cerebral circulation. J Cereb Blood Flow Metab. 1999;19:115–27.
3. Goadsby PJ, Hoskin KL. The distribution of trigeminovascular afferents in the nonhuman primate brain Macaca nemestrina: a c-fos immunocytochemical study. J Anat. 1997;190:367–75.
4. Goadsby PJ, Lipton RB. A review of paroxysmal hemicranias, SUNCT syndrome and other short lasting headaches with autonomic feature, including new cases. Brain. 1997;120:193–209.
5. •• Leone M, Cecchini AP, Franzini A, et al. From neuroimaging to patients' bench: what we have learnt from trigemino-autonomic pain syndromes. Neurol Sci. 2012;33(S1):S99–102. **Good review of pathophysiology of autonomic symptoms in TAC**.
6. Shechter A, Stewart WF, Silberstein SD, Lipton RB. Migraine and autonomic nervous system function: a population-based, case–control study. Neurology. 2002;58:422–7.
7. Yerdelen D, Acil T, Goksel B, et al. Heart rate recover in migraine and tension-type headache. Headache. 2008;48:221–5.
8. Gass JJ, Glaros AG. Autonomic dysregulation in headache patients. Appl Psycholphysiol Biofeedback. 2013;38:257–63.
9. May A, Bahra A, Buchel C, et al. Hypothalamic activation in cluster headache attacks. Lancet. 1998;352:275–8.
10. May A, Bahra A, Buchel C, et al. Functional MRI in spontaneous attacks of SUNCT: short-lasting neuralgiform headache with conjunctival injection and tearing. Ann Neurol. 1999;46:791–3.
11. May A, Bahra A, Buchel C, et al. PET and MRA findings in cluster headache and MRA in experimental pain. Neurology. 2000;55:1328–35.
12. Sprenger T, Boeker H, Tolle TR, et al. Specific hypothalamic activation during a spontaneous cluster headache attack. Neurology. 2004;62:516–7.
13. Bartsch T, Levy MJ, Knight YE, et al. Differential modulation of nociceptive dural input to [hypcretin] Orexin A and B receptor activation in the posterior hypothalamic area. Pain. 2004;109:367–78.
14. •• Barloese M, Brinth L, Mehlsen J, et al. Blunted autonomic response in cluster headache patients. Cephalalgia. 2015;35:1269–77. **Interesting study about cluster headache and autonomic symptoms**.
15. Denuelle M, Fabre N, Payoux P, et al. Hypothalamic activation in spontaneous migraine attacks. Headache. 2007;47:1418–26.
16. Moulton EA, Becerra L, Johnson A, et al. Altered hypothalamic functional connectivity with autonomic circuits and the locus coeruleus in migraine. PLoS One. 2014;9, e95508. doi:10.1371/journal.pone.0095508.

17. Goadsby PJ. Lacrimation, conjunctival injection, nasal symptoms…cluster headache, migraine and cranial autonomic symptoms in primary headache disorders—what's new? J Neurol Neurosurg Psychiatry. 2009;80:1057–8.
18. Lai TH, Fuh JL, Wang SJ. Cranial autonomic symptoms in migraine: characteristics and comparison with cluster headache. J Neurol Neurosurg Psychiatry. 2009;80:1116–9.
19. Rozen TD. LASH: a syndrome of long-lasting autonomic symptoms with hemicrania (a new indomethacin-responsive headache). Headache. 2000;40:483–6.
20. Rozen TD. LASH syndrome: a third reported case twelve years after the first. Headache. 2012;52:1433–8.
21.•• Rozen TD, Beams JL. A case of post-traumatic LASH syndrome responsive to indomethacin and melatonin (a man with a triad of indomethacin-responsive trigeminal autonomic cephalalgias). Cephalalgia 2014. **Rozen presents three interesting case reports about a new TAC syndrome**.
22. Headache Classification Committee of the International Headache Society (HS). The international classification of headache disorders 3rd edition. Cephalalgia. 2013;33:629–808.
23.•• Gelfand AA, Reider AC, Goadsby PJ. Cranial autonomic symptoms in pediatric migraine are the rule, not the exception. Neurology. 2013;81:431–43. **Insightful study showing prevalence of autonomic symptoms in pediatric migraine**.
24. Rodgers SD, Marascalchi BJ, Strom RG, et al. Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing syndrome secondary to an epidermoid tumor in the cerebellopontine angle. Neurosurg Focus. 2013;34, E1.
25. Candeloro E, Canacero I, Maurelli M, et al. Carotid dissection mimicking a new attack of cluster headache. J Headache Pain. 2013;14:84.
26. Pong DL, Marom T, Pine HS. Short-lasting unilateral neuralgiform headache attacks with conjunctiva injection and tearing presenting as sphenoiditis. Am J Otolaryngol. 2013;34:166–8.
27. Bichuetti DB, Yamoaka WY, Bastos JR, et al. Bilateral SUNCT syndrome associated to chronic maxillary sinus disease. Arq Neuropsiquiatr. 2006;64:504–6.
28. Choi JY, Seo WK, Kim JH, et al. Symptomatic SUNCT syndrome associated with ipsilateral paranasal sinusitis. Headache. 2008;48:1527–30.
29. Fontaine D, Almairac F, Mondot L, et al. Cluster-like headache secondary to parasagittal hemangiopericytoma. Headache. 2013;53:1496–8.
30. Sewell R, Johnson D, Fellows D. Cluster headache associated with moyamoya. J Headache Pain. 2009;10:65–7.
31. Cittadini E, Matharu MS. Symptomatic trigeminal autonomic cephalalgias. Neurologist. 2009;15:305–12.
32. Royce JS, Goadsby PJ. Migraine with cranial autonomic features following surgically induced post-ganglionic sympathetic lesion. Acta Neurol Scand. 2014;129:e6–8. doi:10.1111/ane.12170.
33.•• Viana M, Tasorelli C, Allena M, et al. Diagnostic and therapeutic errors in trigeminal autonomic cephalalgia and hemicranias continua: a systemic review. J Headache Pain. 2013;14:14. **Excellent article discussing TACS vs. other headache syndromes and misdiagnosis**.
34. Van Alboom E, Louis P, Van Zandijcke M, et al. Diagnostic and therapeutic trajectory of cluster headache patients in Flanders. Acta Neurol Belg. 2009;109:10–7.
35. Irimia P, Cittadinie E, Paemeleire K, et al. Unilateral photophobia or phonophobia in migraine compared with trigeminal autonomic cephalalgias. Cephalalgia. 2008;28:626–30.