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HEADACHE (R.B. HALKER SINGH AND J. VANDERPLUYM, SECTION EDITORS)

Headache and Autonomic Dysfunction: a Review

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Abstract

Purpose of Review We explore the anatomy of the central and peripheral autonomic pathways involved in primary headache as well as the mechanisms for secondary headache associated with disorders of the autonomic nervous system. The prevalence and clinical presentation of cranial and systemic autonomic symptoms in these conditions will be discussed, with a focus on recent studies.

Recent Findings Several small studies have utilized the relationship between headache and the autonomic nervous system to identify potential biomarkers to aid in diagnosis of migraine and cluster headache. Headache in postural orthostatic tachycardia syndrome (POTS) has also been further characterized, particularly in its association with orthostatic headache and spontaneous intracranial hypotension (SIH).

Summary This review examines the pathophysiology of primary and secondary headache disorders in the context of the autonomic nervous system. Mechanisms of headache associated with systemic autonomic disorders are also reviewed.

Keyword Headache · Migraine · Trigeminal autonomic cephalalgia · Autonomic dysfunction · POTS · Postural tachycardia · Orthostatic headache

Clinical Case

A 26-year-old woman with history of multiple concussions developed orthostatic lightheadedness and frequent syncopal events. Concurrently, she also developed a constant, low-grade headache with migrainous features and significant worsening in the upright position that improved while supine. Autonomic reflex screen demonstrated postural tachycardia along with a hypertensive response to tilt; this suggested a hyperadrenergic state which was corroborated by standing and supine catecholamine testing. She was diagnosed with hyperadrenergic POTS. Additional lab evaluation for causes of a hyperadrenergic state and POTS mimics or exacerbating conditions demonstrated two elevated urine mast cell markers in a 24-h collection. She achieved adequate control of POTS-related symptoms with a regimen of nadolol, gabapentin, midodrine, famotidine, fexofenadine, and cromolyn in addition to lifestyle measures. However, headache persisted, including the strong orthostatic phenotype despite improvement in other orthostatic symptoms. Neuroimaging did not demonstrate signs of intracranial hypotension or epidural fluid collection, but due to clinical symptoms, an empiric lumbar blood patch was performed. This resulted in significant improvement in headache. Her daily, constant headache resolved, and acute attacks were less severe.

Introduction

Autonomic dysfunction is at the forefront of the pathogenesis of multiple primary and secondary headache disorders. The central autonomic network, as well as peripheral sympathetic and parasympathetic efferents, is responsible for generating headache and cranial autonomic symptoms (CAS) in migraine and cluster headache. Additionally, more widespread systemic autonomic dysfunction may be present in those with primary headache disorders. Other disorders of systemic autonomic dysfunction that result in orthostatic intolerance are also associated with unique headache syndromes. This paper will discuss the pathophysiology involving central and peripheral autonomic pathways in primary

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and secondary headache disorders with an emphasis on recent findings and advancements in understanding the complex interconnection.

To adequately discuss these topics, a review of the baroreflex and trigeminovascular systems is necessary. The baroreflex maintains perfusion of blood to the brain when the body is upright by modulating heart rate, blood pressure, and vascular tone. The afferent arm of the baroreflex is modulated by stretch mechanoreceptors in the carotid sinus and aortic arch which are innervated by the glossopharyngeal and vagus nerves, respectively, and synapse at the nucleus tractus solitarius (NTS) in the medulla [1, 2]. The efferent portion of the baroreflex has three main components. When blood pressure is elevated, the stretch mechanoreceptors are activated which results in downstream stimulation of the NTS and activation of inhibitory interneurons that synapse at the caudal ventrolateral medulla. This ultimately modulates the rostral ventrolateral medulla, which inhibits sympathetic activity and results in vasodilation [1, 2]. Bradycardia is also induced by a connection between the NTS and preganglionic vagal cardiac ganglion cells in the nucleus ambiguus [1, 2]. A third efferent mechanism regulates the supraoptic and paraventricular hypothalamic nuclei via inhibition of noradrenergic cells in the medullary reticular formation, ultimately inhibiting vasopressin release [1, 2]. Low blood pressure results in decreased stimulation of stretch mechanoreceptors and increased sympathetic outflow causing vasoconstriction of splanchnic and skeletal muscle and tachycardia [1, 2]. Damage or dysfunction along this pathway can result in labile blood pressures and headache. The vestibular sympathetic reflex may also contribute to cardiac and vascular tone via projections to the rostral and caudal ventrolateral medulla, as seen in several animal studies [3–5], and is triggered by position change. When there is dysfunction along the vestibular sympathetic pathway, a change in posture can lead to vasovagal syncope with bradycardia and hypotension [6].

Another important pathway involving the autonomic nervous system and generation of headache is the trigeminovascular system. The trigeminovascular system is connected to the trigemino-autonomic reflex which mediates CAS in migraine and trigeminal autonomic cephalalgias (TACs). CAS include lacrimation, conjunctival injection, ptosis, eyelid swelling, nasal congestion or rhinorrhea, facial sweating, and ear fullness. During a headache attack, pain-sensing trigeminal afferent neurons innervating the meninges, meningeal blood vessels, large intracranial blood vessels, and dural venous sinuses originating from the ophthalmic branch of trigeminal nerve (V1) are activated, and together with pain-sensing afferents of the dorsal horn of C1 and C2, synapse at the trigeminocervical complex (TCC) in the brainstem [7, 8]. Neurons from the TCC project to the superior salivatory nucleus in the pons where preganglionic parasympathetic neurons are activated and travel with cranial nerve VII, particularly the greater petrosal nerve, and synapse in the sphenopalatine ganglion [7]. Postganglionic parasympathetic fibers then leave the sphenopalatine ganglion and act on the lacrimal glands, nasal, and palatal mucosa resulting in lacrimation, nasal congestion, or rhinorrhea [7]. The parasympathetic efferents also project to the meninges and intracranial arteries releasing calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), and pituitary adenylate cyclase-activating peptide-38 (PACAP-38) causing vasodilation and mast cell degranulation which further perpetuate pain [9].

While the parasympathetic nervous system is dominant in the generation of headache and many cranial autonomic symptoms, activation of the sympathetic nervous system is also thought to be pro-nociceptive [9]. As it relates to CAS, postganglionic sympathetic fibers traveling as a plexus around the internal carotid artery may become compressed due to perivascular edema from neurogenic inflammation in the cavernous sinus during migraine or TAC attacks. This results in miosis and/or ptosis due to sympathetic hypofunction, although increased parasympathetic tone may also play a role [10, 11].

While CAS are predominantly generated by peripheral efferents of the autonomic nervous system, the TCC also sends projections to several brainstem nuclei that are part of the central autonomic network including the locus coeruleus, raphe nucleus, and periaqueductal gray, as well as the thalamus, hypothalamus, and the cortex for pain processing and perception which subsequently exert a descending modulation on the TCC [7, 8, 12]. In migraine, the periaqueductal gray, locus coeruleus, and raphe nucleus modulate cerebral blood flow, intensity of sensory phobias, pain signaling, and cortical hyperexcitability [7].

Autonomic Dysfunction in Primary Headache Disorders

Migraine

The premonitory and headache phases of migraine are innately connected to the central and peripheral autonomic network. While the connection to the autonomic nervous system during the headache phase is discussed above, Dodick describes a state of increased parasympathetic tone in the hypothalamus during the premonitory phase that is triggered by disruptions in homeostasis (altered sleep wake cycles, emotional stress, etc.) and activates pre-ganglionic parasympathetic neurons in the superior salivatory nucleus. From there, post-ganglionic parasympathetic neurons release pro-inflammatory and vasodilatory neuropeptides triggering activation of meningeal nociceptors [8, 9]. Functional MRI studies have confirmed activation of the hypothalamus and

central autonomic network during the premonitory phase of migraine as well as enhanced connections between these areas interictally [13, 14].

Cranial autonomic symptoms are known to occur in the premonitory and headache phases of migraine with a variable prevalence of 27–82% [15–21] although several recent studies examined only unilateral symptoms, likely leading to underreporting [15–17]. CAS have been associated with more severe attacks when unilateral [15–17], prolonged attacks [15, 21] and are associated with increased functional disability [20]. Some studies have also reported increased association of CAS with symptoms suggesting central sensitization, such as photophobia [15], phonophobia [21], and allodynia [15] though there is significant variability in design and data collection across these studies. Compared to cluster headache, CAS in migraine have been reported to be more likely bilateral, mild-to-moderate severity, and inconsistent from one attack to the next [19]. In a recent cross-sectional study of 373 episodic and chronic migraine patients in Japan, 42.4% reported at least one CAS and those with CAS had more severe attacks, allodynia, phonophobia and, possibly unique to this population, osmophobia [22]. Furthermore, more than half reported bilateral CAS [22]. A cross-sectional study of 904 patients in Iran reported that 56.2% of participants with episodic migraine and 70% of those with chronic migraine had CAS [23]. Similar to previous studies, unilateral headache and increased severity were more prevalent in those with CAS, but investigators also found chronic migraine, blurred vision, and increased headache frequency were more prevalent in migraine with CAS [23]. Friedman and Evans have proposed that blurred vision may be a symptom of autonomic dysfunction due to imbalance in sympathetic and parasympathetic signaling resulting in dry eye [24]. Togha et al. reported blurred vision in 17.9% of participants and the proportion was significantly higher in those with CAS [23], which may support the above proposed hypothesis.

Several studies have further investigated autonomic function in migraine by examining changes in the eyes. In a recent prospective study of 24 episodic migraine patients and 24 controls, smaller pupil size was found ictally (consistent with previous studies [25–27]) along with significantly increased accommodative response during attacks, both of which suggest sympathetic hypofunction [28]. In another study of 36 patients with migraine (chronic, episodic, and probable), those with migraine and lower photophobia threshold showed smaller dark-adapted pupils interictally suggesting sympathetic hypofunction. However, at the photophobia threshold they found larger pupil size suggesting mixed autonomic dysfunction [29]. Impairment of parasympathetic pupillary constriction latency and sympathetic pupillary re-dilation was also noted and correlated with more severe migraine disease, further supporting mixed sympathetic and parasympathetic dysfunction in those with migraine [29]. Cortez et al. studied pupillary cycle time, which assesses sympathetic and parasympathetic pathways to the eye, as a potential biomarker for migraine [30]. Pupillary cycle time is tested by shining light on the edge of the pupil with subsequent parasympathetically driven constriction outside the margin of the light. Once outside the margin of the light, the pupil dilates via sympathetic activation back within in the margin of the stimulus [30]. A fixed number of cycles are completed and the time to completion was recorded. Significantly prolonged pupil cycle time in subjects with probable, episodic, and chronic migraine was found compared to controls which again suggests mixed cranial sympathetic and parasympathetic dysfunction. A positive correlation between prolonged pupil cycle time and number of CAS in all types of migraine types was also identified [30]. Measurement of pupillary cycle time may prove to be a noninvasive way of diagnosing migraine when the clinical presentation is unclear. In the future, it would be of interest to know if pupil cycle time could also differentiate between other primary headache disorders with CAS.

Visceral symptoms, such as nausea, vomiting, constipation, diarrhea, stomach fullness, bloating, belching, frequent defecation, and frequent urination also occur in various phases of migraine [31] and are at least in part due to autonomic dysfunction. Connections between the vagus nerve and the NTS provide much of the autonomic basis for gastrointestional symptoms experienced in migraine, though the pathophysiology is likely more complex and includes alterations in serotonergic signaling and effects of inflammatory neuropeptides [32]. A prospective, cross-sectional study of 605 patients with migraine (including episodic, chronic, and with/without aura) found those with visceral symptoms had more prolonged and severe attacks and those without aura had higher prevalence of visceral symptoms during all phases of migraine [33]. Visceral symptoms were most prevalent ictally (71%), yet 52% of participants had at least one symptom during the premonitory phase and 36% after the attack [33].

Table 1 outlines the cranial and systemic autonomic symptoms and diagnostic findings in migraine as well as the other primary and secondary headache disorders described below.

Cluster Headache

The posterior hypothalamus is an initiator and modulator of cluster headache, as demonstrated by PET imaging studies showing activation in the ipsilateral posterior hypothalamus in nitroglycerin-induced attacks [34]. Additional brainstem nuclei, such as the locus coeruleus, raphe nucleus, and periaqueductal gray (PAG) also play a role in the pathophysiology of cluster headache by regulating pain input and

Table 1 Cranial and systemic autonomic symptoms and corresponding diagnostic findings of select headache and autonomic disorders. N/A, information not available

Headache or autonomic disorder	Cranial autonomic symptoms	Cranial autonomic diagnostic findings	Systemic autonomic symptoms	Systemic autonomic diagnostic findings
Migraine	• Bilateral > unilateral [19] • Present in all phases of migraine [15–21] • Blurred vision may be a symptom of cranial autonomic dysfunction [23, 24]	• Smaller pupil size and increased accommodative response during attacks, as well as smaller dark-adapted pupils interictally suggest cranial sympathetic hypofunction [28, 29] • Larger pupil size at the photophobia threshold, impaired pupillary constriction and re-dilation latency, and prolonged pupil cycle time suggest mixed cranial autonomic dysfunction [29, 30]	• Present in all phases of migraine [33] • Nausea, vomiting, constipation, diarrhea, stomach fullness, bloating, belching, frequent defecation, and frequent urination [31, 33]	• Evidence is limited by heterogeneity among studies • Miglis suggests more autonomic dysfunction in migraine with aura compared to without aura, and reports that sympathetic (compared to parasympathetic) dysfunction is more prevalent in migraine [31]
Cluster headache	• Unilateral > > > bilateral • Present before and during headache [38] • Most common: nasal congestion, rhinorrhea, lacrimation, conjunctival injection [38–44]	• Local (facial) post-ganglionic sympathetic hypofunction interictally [37]	• Systemic cardiac autonomic dysfunction is thought to be subclinical [36] • "Creaky voice" and laryngeal edema [46]	• Probable increased parasympathetic tone and reduced sympathetic tone during attacks [36] • Lower second harmonic values on digital voice records, vocal cord edema on laryngoscopy [46]
Orthostatic hypotension	N/A	N/A	• Lightheadedness, presyncope, syncope, fatigue, weakness, neck pain, and headache when upright that resolve when seated or supine [48]	• Drop in blood pressure by ≥ 20 mmHg systolic and ≥ 10 mmHg diastolic within 3 min of standing [48]
Autonomic dysreflexia	• Nasal congestion and conjunctival injection [54]	N/A	• Diaphoresis, elevated temperature, and flushing above the level of the spinal cord injury. Pallor and piloerection below the level of the spinal cord injury [54]	• Systolic pressure is ≥ 30 mmHg and/or diastolic pressure is ≥ 20 mmHg from baseline [54]
Postural tachycardia syndrome (POTS)	N/A	N/A	• Dizziness, lightheadedness, presyncope, and palpitations, fatigue and "brain fog" [48] • Often associated with GI and GU dysfunction [59]	• Sustained, excessive tachycardia of ≥ 30 beats per minute (≥ 40 beats per minute in pediatric subjects) within 10 min of head-up tilt without orthostatic hypotension [48]
Spontaneous intracranial hypotension	N/A	N/A	• Some patients with SIH also have POTS (See symptoms above) [77]	• Some patients with SIH also have POTS [77]
Post-traumatic headache and post-concussive syndrome	• Post-traumatic headache with SUNA and cluster phenotypes have been reported [82, 83] • Tear disruption (dry eyes/excessive tearing) during sustained neck rotation in persistent PTH may suggest autonomic rather than vascular dysfunction [84]	• Abnormal pupillary dynamics have been demonstrated in concussed adolescents and adults, though with variable results. In the future, if consistent findings are determined, measurement of pupillary dynamics could serve as a biomarker for diagnosis of concussion [85–87]	• Orthostatic intolerance and bladder symptoms in PTH are most common on the COMPASS-31 questionnaire [81] • Other symptoms can include visual disturbances, syncope, headache, nausea, and sleep disturbances [88, 89]	• Three recent systematic reviews on autonomic dysfunction after concussion were unable to draw conclusions on the presence of autonomic dysfunction, alterations in heart rate variability, or the timing and severity of autonomic dysfunction due to variable methodology among studies (80, 90, 91)

vascular tone similar to migraine [14, 35]. Activation of the trigeminal autonomic reflex as discussed previously is the basis for CAS experienced during TAC attacks and the distribution of pain is attributed to involvement of the trigeminovascular system [11].

In addition to CAS, systemic autonomic dysfunction may be present in cluster headache, but studies thus far have demonstrated inconsistent findings likely due to variability of study designs. Additionally, various tests are unable to be performed during an acute cluster headache attack due to the debility experienced by the patient. Barloese performed a narrative review of 22 studies focusing on cardiovascular autonomic changes in cluster headache and suggested there may be increased parasympathetic tone and reduced sympathetic tone during cluster attacks along with subclinical autonomic dysfunction interictally [36]. The studies were grouped into those that evaluated cluster headache by ECG and Holter monitoring, those using specific tests of the autonomic nervous system (Valsalva, head up tilt, etc.), and those utilizing spectral analysis and measurement of baroreflex sensitivity, although there was overlap between measurements used in several of the studies. It is not noted if all studies were performed during an active cluster phase. While this review provides a much-needed summary of studies investigating systemic autonomic dysfunction in cluster headache, clear conclusions could not be made from the data gathered. Following the review by Barloese in 2016, a prospective study of 19 subjects with cluster headache demonstrated prolonged latency of skin responses on the affected side of the face interictally, suggesting local (postganglionic) sympathetic hypofunction [37]. Standardized testing and study designs are needed to further elucidate the relationship of systemic autonomic dysfunction and cluster headache.

More recent studies have attempted to increase knowledge about the associated symptoms in cluster headache in a standardized manner. Wei and Goadsby conducted a single-blind, placebo-controlled, cross-over study of nitroglycerin-induced attacks in 24 patients with episodic and chronic cluster headache [38]. In the blinded arm, CAS were induced in 84% of participants and the most common CAS were nasal congestion, lacrimation and conjunctival injection [38]. CAS were experienced by 58% prior to the headache and 16% during the headache [38]. Findings were similar to previous studies with the most common CAS being nasal congestion/rhinorrhea in 41–89%, lacrimation in 59–91%, and conjunctival injection in 41–72% [39–44]. Snoer et al. also conducted a prospective diary study comparing retrospective attack descriptions of 57 episodic and chronic cluster subjects [45]. In this study, the most common reported CAS in prospective descriptions included lacrimation and conjunctival injection [45]. They also reported a high prevalence of migrainous symptoms similar between retrospective and prospective reports, although these symptoms were reported more by women than men [45]. Women also reported longer and more severe intensity which is important to highlight as women may be misdiagnosed with migraine based on these symptom descriptions [45].

Given frequently overlapping symptoms with migraine and other TACs, identifying physiological tests to assist in diagnosis is also needed. A recent study examined digital voice records and video laryngostroboscopy of male subjects with cluster headache ($n = 20$) and hemicrania continua ($n = 13$) [46]. They found significantly lower second harmonic values in cluster headache subjects during an attack manifested by a "creaky voice" along with significantly higher mild-to-moderate vocal cord edema and laryngopharyngeal reflux [46]. The findings were proposed as extracranial manifestations of autonomic dysfunction in cluster headache with disrupted vagal tone allowing relaxation of the esophageal sphincter and laryngeal edema [46].

Secondary Headache due to Systemic Autonomic Dysfunction

Orthostatic intolerance is a broad term to describe conditions associated with an inability to tolerate upright posture due to symptoms of lightheadedness, near fainting, cognitive impairment, headache, fatigue, nausea, palpitations, weakness, tremulousness, and others [6, 47]. Orthostatic hypotension, reflex syncope, and postural orthostatic tachycardia syndrome (POTS) are included under the umbrella of orthostatic intolerance.

Orthostatic Hypotension

Orthostatic hypotension is defined as persistently decreased systolic blood pressure of at least 20 mm Hg and diastolic blood pressure of 10 mm Hg from baseline within 3 min after standing with resultant lightheadedness, weakness, headache, neck pain, or cognitive symptoms [48]. Potential etiologies include hypovolemia, medications, cardiac disorders, and autonomic dysfunction [6]. Headache associated with orthostatic hypotension has been described as a dull ache with variable intensity in a coat-hanger distribution involving the cranium, occiput, neck, and shoulders that is provoked shortly after sitting or standing and improves after lying down [6, 49–51]. In a study comparing orthostatic hypotension in pure autonomic failure (PAF) and multiple system atrophy (MSA), the greater degree of orthostatic hypotension correlated positively with frequency of neck pain [50]. Ischemia of the neck muscles has been the main hypothesis for headache in orthostatic hypotension [50]. However, others have suggested a more complex interplay of activation of nociceptive pathways in the posterior fossa,

epidural hypotension, and decreased headache threshold as a result of vagal dysfunction [6, 51].

Orthostatic hypotension is also seen in baroreflex failure, a condition that occurs due to damage or dysfunction anywhere along the afferent pathway from the stretch mechanoreceptors to the level of the medulla resulting in labile blood pressures. Additional symptoms include palpitations, flushing, diaphoresis, and findings of episodic tachycardia or bradycardia [1]. It is most often secondary to damage of carotid baroreceptors in the neck by radiation, surgery, or trauma but can also occur due to brainstem lesions, sensory neuropathies, or may be idiopathic [1]. Headache in baroreflex failure can occur during hypo- or hypertensive episodes though specific headache characteristics and frequency are not well defined.

Reflex Syncope

Reflex syncope, described as spontaneous cerebral hypoperfusion with resultant transient loss of consciousness and postural tone followed by recovery [6], is also associated with headache. It is caused by transient baroreceptor dysfunction that triggers abrupt sympathetic hypofunction brought on by strong emotion or prolonged orthostasis [6]. However, the underlying mechanism for this sudden change in an otherwise normal functioning baroreflex is not fully understood. A case–control study of 16 adolescents with history of headache and syncope were evaluated during tilt-table testing and those who experienced syncope and postictal headache were found to have a larger pulsatile cerebral blood flow velocity during and after the tilt-table test [52]. Authors hypothesized that postsyncopal headache may be due to the wide fluctuation of blood flow which triggers nitric oxide release with downstream release of CGRP and activation of trigeminal nociceptors [52].

Autonomic Dysreflexia

Headache secondary to autonomic dysreflexia is characterized as sudden-onset severe headache in patients with spinal cord injuries (SCI) at or above T6 when systolic pressure is ≥ 30 mm Hg and/or diastolic pressure is ≥ 20 mm Hg from baseline [53]. The headache is often described as throbbing with radiation to the neck and may be unilateral or bilateral [54]. Headache as the presenting symptom ranges from 56 to 89% [55, 56]. Autonomic dysreflexia is a result of impaired communication between the sympathetic and parasympathetic systems above and below the level of the SCI [57]. The pathophysiology of headache in autonomic dysreflexia has not been determined but may be due to dilation of cerebral vessels secondary to increased prostaglandin E_2 [54, 58], which activates the trigeminovascular pathway [58, 59].

Postural Orthostatic Tachycardia Syndrome

Postural orthostatic tachycardia syndrome (POTS) in adults is defined as sustained, excessive tachycardia of ≥ 30 beats per minutes (≥ 40 beats per minute in pediatric subjects) within 10 min on head-up tilt table test (HUTT) without orthostatic hypotension [48]. POTS is a heterogenous disorder associated with other conditions including but not limited to connective tissue and autoimmune disease [59]. Similarly, other conditions may mimic POTS such as anemia, thyroid dysfunction, mastocytosis, and adrenal dysfunction [59]. Symptoms include but are not limited to dizziness, lightheadedness, presyncope, and palpitations; many patients also experience fatigue and "brain fog" [59]. Headache in patients with POTS has a reported prevalence of 41–96% including primary headache disorders such as migraine and secondary headache disorders such as spontaneous intracranial hypotension (SIH) [60–64]. Consistent with previous findings [61, 64], headache was the most commonly reported neurological co-morbidity in a recent pediatric retrospective study of 134 patients with POTS. Migraine was reported in 43% of patients followed by 22% with nonspecific headache, 14% with chronic daily headache, and 4% with new daily persistent headache. Interestingly, orthostatic headache was only reported by 2% [65]. In another pediatric study of 112 predominantly female participants with orthostatic intolerance and abnormal HUTT, headache was the second most common presenting symptom (46%) [66]. While the relationship between primary headache disorders and POTS is not fully understood, Ojha et al. hypothesized that the high prevalence of pain syndrome comorbidities like migraine may be due to dysregulation at the level of the brainstem including the raphe nuclei or the locus coeruleus [61]. Although there is still a lot of work to be done to understand POTS and its associated co-morbidities, we tend to agree that at least part of the answer may be in the brainstem where there is overlap of key structures involved in both migraine and autonomic regulation.

POTS and SIH can both present with orthostatic or postural headache without findings of arterial hypotension. The similar presentations can be difficult to differentiate, and to complicate the matter further, POTS and SIH can co-occur. The connection between SIH and POTS is unclear, but theories include deconditioning and reduction in venous return to the inferior vena cava leading to epidural venous hypotension [67, 68]. If examined within the context of hypovolemia, a known mechanism of POTS, the epidural venous hypotension theory may offer a connection between the disorders [69, 70]. If there is low pressure in the inferior vena cava, due to a hypovolemic state, the pressure gradient will drive the flow of spinal fluid to the epidural space and veins resulting in reduced CSF volume [68]. Franzini et al. suggested that SIH may be due to aspiration of spinal fluid

at arachnoid diverticula in those with predisposed weakness of the dura rather than an actual tear in the dura. This may explain normal imaging results frequently encountered in patients with orthostatic headache, as described in the clinical case above [68]. This theory for orthostatic headache is further supported by the increased prevalence of connective tissue disorders in POTS, such as joint hypermobility and Ehlers-Danlos syndrome (12–39%) [71–73], which increases the risk of SIH [74]. Another study of 113 pediatric patients with POTS and orthostatic hypotension hypothesized that cerebral hypoperfusion may be a potential cause of orthostatic headache based on findings of decreased cerebral oxygenated hemoglobin level on infrared spectroscopy oximetry more prominently in those with orthostatic headache on active stand testing [75].

While postural headache is common to POTS and SIH, other headache characteristics are more variable among the disorders. In a prospective study of 24 patients with POTS, 14 patients (58%) described orthostatic headache as frontal or holocranial with pressure-like or throbbing quality and moderate-to-severe intensity. [62]. Twenty-three subjects (96%) reported non-orthostatic headache, 20 of which met migraine criteria and 3 for probable migraine [62]. In a systematic review of 33 studies with 1694 subjects with SIH, headache was the most frequent reported symptom (97%) of which 92% were orthostatic [76]. Compared to orthostatic headache in POTS, headache in SIH was occipital, holocranial, and frontal with associated symptoms of nausea/vomiting, neck pain/stiffness, dizziness, hearing disturbances, tinnitus, hyperacusis, and aural fullness [76]. In a retrospective study comparing 9 patients with SIH and 48 patients with POTS, orthostatic headache was present in all with SIH and in 27% of those with POTS. Additionally, all patients with SIH had excessive tachycardia on HUTT meeting criteria for POTS [77]. Overall, orthostatic headache seems to be more prominent in SIH. One small study utilized transorbital ultrasound to help differentiate the two disorders and compared differences in optic nerve sheath diameter in upright and supine position in those with POTS with ($n=7$) or without orthostatic headache ($n=7$) and those with SIH ($n=8$). They found a decrease in optic nerve sheath diameter during orthostatic stress in SIH, but not in POTS [78]. While no significant conclusions can be made, it highlights the need for additional non-invasive tests to differentiate these disorders.

Posttraumatic Headache

Autonomic dysfunction is a known complication of traumatic brain injury (TBI) but understanding the extent of dysautonomia is limited due to variability of autonomic testing, patient populations, and severity of TBI. Autonomic dysfunction in these patients is likely due to microscopic axonal shearing and subsequent uncoupling of the sympathetic and parasympathetic nervous systems as well as dysregulation of cerebral blood flow [79, 80]. In a cross-sectional cohort study examining subjects with persistent posttraumatic headache (PPTH) and migraine compared to controls, autonomic symptom burden was assessed using the COMPASS-31 questionnaire (a survey of gastrointestinal, vasomotor, secretomotor, orthostatic intolerance, bladder, and pupillomotor symptoms) [81]. Those with PPTH had significantly higher scores in all domains, particularly in orthostatic intolerance and bladder domains, compared to those with migraine and controls. In post hoc analyses, there was a positive relationship between total COMPASS-31 scores and number of lifetime TBIs [81]. The patients in this study did not undergo autonomic reflex testing [81]. Table 1 further outlines cranial and systemic autonomic findings in PTH and post-concussive syndrome though findings are limited by variable methodology across studies.

Conclusion

Migraine and cluster headache are innately connected with the autonomic nervous system. This connectivity is demonstrated by the presence of cranial autonomic symptoms as well as extracranial manifestations that involve the vocal cords, cardiovascular system, and GI tract. While there may be reduced systemic sympathetic tone in migraine and cluster headache, results of autonomic testing have been variable, and mixed systemic sympathetic and parasympathetic dysfunction are likely at play. With more time and understanding, standardized measurements of the clinical manifestations of autonomic dysfunction in primary headache disorders may improve diagnostic accuracy. Secondary headache in orthostatic hypotension, autonomic dysreflexia, POTS, and SIH is incredibly common, but the headache phenotype is variable. The mechanism of headache in these disorders is continuing to be characterized, but hypovolemia and weakened connective tissue may play a role in headache associated with POTS and SIH. Future research will benefit from standardized autonomic testing to further characterize systemic autonomic dysfunction and identify additional biomarkers that may assist in diagnosis overlapping headache and autonomic disorders.

Declarations

Human and Animal Rights and Informed Consent The clinical case was shared with permission from the patient.

Conflict of Interest The authors declare no competing interests.

References

1. Benarroch EE. The arterial baroreflex: functional organization and involvement in neurologic disease. Neurology. 2008;71(21):1733–8.
2. Kaufmann H, Norcliffe-Kaufmann L, Palma JA. Baroreflex dysfunction. N Engl J Med. 2020;382(2):163–78.
3. Holstein GR, Friedrich VL Jr, Martinelli GP. Projection neurons of the vestibulo-sympathetic reflex pathway. J Comparative Neurol. 2014;522(9):2053–74.
4. Holstein GR, Friedrich VL, Martinelli GP, Ogorodnikov D, Yakushin SB, Cohen B. Fos expression in neurons of the rat vestibulo-autonomic pathway activated by sinusoidal galvanic vestibular stimulation. Front Neurol. 2012;3:4.
5. McBride DW, Reis C, Frank E, Klebe DW, Zhang JH, Applegate R, et al. An experimental model of vasovagal syncope induces cerebral hypoperfusion and fainting-like behavior in awake rats. PLoS One. 2016;11(9):e0163280.
6. Khurana RK. Syncope and headache. Curr Pain Headache Rep. 2018;22(8):54.
7. Dodick DW. Migraine Lancet. 2018;391(10127):1315–30.
8. Akerman S, Holland PR, Summ O, Lasalandra MP, Goadsby PJ. A translational in vivo model of trigeminal autonomic cephalalgias: therapeutic characterization. Brain. 2012;135(Pt 12):3664–75.
9. Dodick DW. A phase-by-phase review of migraine pathophysiology. Headache. 2018;58(Suppl 1):4–16.
10. Drummond PD. Mechanisms of autonomic disturbance in the face during and between attacks of cluster headache. Cephalalgia. 2006;26(6):633–41.
11. Wei DY, Goadsby PJ. Cluster headache pathophysiology - insights from current and emerging treatments. Nat Rev Neurol. 2021;17(5):308–24.
12. Goadsby PJ, Holland PR. Pathophysiology of migraine. Neurol Clin. 2019;37(4):651–71.
13. Maniyar FH, Sprenger T, Monteith T, Schankin C, Goadsby PJ. Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. Brain. 2014;137(Pt 1):232–41.
14. Moulton EA, Becerra L, Johnson A, Burstein R, Borsook D. Altered hypothalamic functional connectivity with autonomic circuits and the locus coeruleus in migraine. PLoS One. 2014;9(4):e95508.
15. Barbanti P, Aurilia C, Dall'Armi V, Egeo G, Fofi L, Bonassi S. The phenotype of migraine with unilateral cranial autonomic symptoms documents increased peripheral and central trigeminal sensitization A case series of 757 patients. Cephalalgia. 2016;36(14):1334–40.
16. Obermann M, Yoon MS, Dommes P, Kuznetsova J, Maschke M, Weimar C, et al. Prevalence of trigeminal autonomic symptoms in migraine: a population-based study. Cephalalgia. 2007;27(6):504–9.
17. Barbanti P, Fabbrini G, Pesare M, Vanacore N, Cerbo R. Unilateral cranial autonomic symptoms in migraine. Cephalalgia. 2002;22(4):256–9.
18. Riesco N, Pérez-Alvarez AI, Verano L, García-Cabo C, Martínez-Ramos J, Sánchez-Lozano P, et al. Prevalence of cranial autonomic parasympathetic symptoms in chronic migraine: usefulness of a new scale. Cephalalgia. 2016;36(4):346–50.
19. Lai TH, Fuh JL, Wang SJ. Cranial autonomic symptoms in migraine: characteristics and comparison with cluster headache. J Neurol Neurosurg Psychiatry. 2009;80(10):1116–9.
20. Shin YW, Park HJ, Shim JY, Oh MJ, Kim M. Seasonal variation, cranial autonomic symptoms, and functional disability in migraine: a questionnaire-based study in tertiary care. Headache. 2015;55(8):1112–23.
21. Gupta R, Bhatia M. A report of cranial autonomic symptoms in migraineurs. Cephalalgia. 2007;27(1):22–8.
22. Danno D, Wolf J, Ishizaki K, Kikui S, Yoshikawa H, Takeshima T. Cranial autonomic symptoms of migraine in Japan: prospective study of 373 migraine patients at a tertiary headache center. Headache. 2020;60(8):1592–600.
23. Togha M, Jafari E, Moosavian A, Farbod A, Ariyanfar S, Farham F. Cranial autonomic symptoms in episodic and chronic migraine: a cross sectional study in Iran. BMC Neurol. 2021;21(1):493.
24. Friedman DI, Evans RW. Are blurred vision and short-duration visual phenomena migraine aura symptoms? Headache. 2017;57(4):643–7.
25. Mylius V, Braune HJ, Schepelmann K. Dysfunction of the pupillary light reflex following migraine headache. Clin Auton Res. 2003;13(1):16–21.
26. Drummond PD. Pupil diameter in migraine and tension headache. J Neurol Neurosurg Psychiatry. 1987;50(2):228–30.
27. Drummond PD. Disturbances in ocular sympathetic function and facial blood flow in unilateral migraine headache. J Neurol Neurosurg Psychiatry. 1990;53(2):121–5.
28. Yildiz MB, Yildiz E, Balci S, Hasirci Bayir BR, Çetinkaya Y. Effect of migraine attack on pupil size, accommodation and ocular aberrations. Eur J Ophthalmol. 2021;31(6):3450–5.
29. Cortez MM, Rea NA, Hunter LA, Digre KB, Brennan KC. Altered pupillary light response scales with disease severity in migrainous photophobia. Cephalalgia. 2017;37(8):801–11.
30. Cortez MM, Rae N, Millsap L, McKean N, Brennan KC. Pupil cycle time distinguishes migraineurs from subjects without headache. Front Neurol. 2019;10:478.
31. Miglis MG. Migraine and autonomic dysfunction: which is the horse and which is the jockey? Curr Pain Headache Rep. 2018;22(3):19.
32. Aurora SK, Shrewsbury SB, Ray S, Hindiyeh N, Nguyen L. A link between gastrointestinal disorders and migraine: insights into the gut-brain connection. Headache. 2021;61(4):576–89.
33. Togha M, Martami F, Jafari E, Ariyanfar S, Hashemi SM. The prevalence and characteristics of visceral autonomic symptoms among migraineurs: a population-based study. Cephalalgia 2021 3331024211056849.
34. May A, Bahra A, Büchel C, Frackowiak RS, Goadsby PJ. Hypothalamic activation in cluster headache attacks. Lancet. 1998;352(9124):275–8.
35. May A, Schwedt TJ, Magis D, Pozo-Rosich P, Evers S, Wang SJ. Cluster headache. Nat Rev Dis Primers. 2018;4:18006.
36. Barloese MCJ. A review of cardiovascular autonomic control in cluster headache. Headache. 2016;56(2):225–39.
37. Altiokka O, Mutluay B, Koksal A, Ciftci-Kavaklioglu B, Ozturk M, Altunkaynak Y, et al. Evaluation of interictal autonomic function during attack and remission periods in cluster headaches. Cephalalgia. 2016;36(1):37–43.
38. Wei DY, Goadsby PJ. Comprehensive clinical phenotyping of nitroglycerin infusion induced cluster headache attacks. Cephalalgia. 2021;41(8):913–33.
39. Taga A, Russo M, Manzoni GC, Torelli P. Cluster headache with accompanying migraine-like features: a possible clinical phenotype. Headache. 2017;57(2):290–7.
40. Uluduz D, Ayta S, Özge A, Yalin OÖ, Turkish Headache Database Study Group, Temel GÖ, et al. Cranial autonomic features in migraine and migrainous features in cluster headache. Noro Psikiyatr Ars. 2018;55(3):220–4.
41. Bahra A, May A, Goadsby PJ. Cluster headache: a prospective clinical study with diagnostic implications. Neurology. 2002;58(3):354–61.
42. Rozen TD, Fishman RS. Cluster headache in the United States of America: demographics, clinical characteristics, triggers,

suicidality, and personal burden*. Headache: J Head Face Pain. 2012;52(1):99–113.
43. Zidverc-Trajkovic J, Podgorac A, Radojicic A, Sternic N. Migraine-like accompanying features in patients with cluster headache. How Important Are They? Headache: J Head Face Pain. 2013;53(9):1464–9.
44. van Vliet JA, Eekers P, Haan J, Ferrari M. Features involved in the diagnostic delay of cluster headache. J Neurol Neurosurg Psychiatry. 2003;74(8):1123–5.
45. Snoer AH, Lund N, Jensen RH, Kristoffersen ES, Barloese M, Hansen JM. More precise phenotyping of cluster headache using prospective attack reports. Eur J Neurol. 2019;26(10):1303-e85.
46. Silvestro M, Dovetto FM, Corvino V, Apisa P, Malesci R, Tessitore A, et al. Enlarging the spectrum of cluster headache: extracranial autonomic involvement revealed by voice analysis. Headache. 2021;61(9):1452–9.
47. Stewart JM, Boris JR, Chelimsky G, Fischer PR, Fortunato JE, Grubb BP, et al. Pediatric disorders of orthostatic intolerance. Pediatrics. 2018;141(1):e20171673.
48. Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Auton Neurosci. 2011;161(1–2):46–8.
49. Robertson D, Kincaid DW, Haile V, Robertson RM. The head and neck discomfort of autonomic failure: an unrecognized aetiology of headache. Clin Auton Res. 1994;4(3):99–103.
50. Bleasdale-Barr KM, Mathias CJ. Neck and other muscle pains in autonomic failure: their association with orthostatic hypotension. J R Soc Med. 1998;91(7):355–9.
51. Khurana RK. Coat-hanger ache in orthostatic hypotension. Cephalalgia. 2012;32(10):731–7.
52. Ocon AJ, Messer Z, Medow MS, Stewart JM. Increased pulsatile cerebral blood flow, cerebral vasodilation, and postsyncopal headache in adolescents. J Pediatr. 2011;159(4):656-662.e1.
53. Gobel H. 10.3.5 Headache attributed to autonomic dysreflexia [Internet]. ICHD-3. [cited 2022 Apr 1]. Available from: https://ichd-3.org/10-headache-attributed-to-disorder-of-homoeostasis/10-3-headache-attributed-to-arterial-hypertension/10-3-5-headache-attributed-to-autonomic-dysreflexia/.
54. Furlan JC. Headache attributed to autonomic dysreflexia: an underrecognized clinical entity. Neurology. 2011;77(8):792–8.
55. Kewalramani LS. Autonomic dysreflexia in traumatic myelopathy. Am J Phys Med. 1980;59(1):1–21.
56. Lindan R, Joiner E, Freehafer AA, Hazel C. Incidence and clinical features of autonomic dysreflexia in patients with spinal cord injury. Paraplegia. 1980;18(5):285–92.
57. Duvall JR, Mathew PG, Robertson CE. Headache attributed to autonomic dysreflexia: clinical presentation, pathophysiology, and treatment. Curr Pain Headache Rep. 2019;23(11):80.
58. Arca KN, Halker Singh RB. The hypertensive headache: a review. Curr Pain Headache Rep. 2019;23(5):30.
59. Goodman BP. Evaluation of postural tachycardia syndrome (POTS). Auton Neurosci. 2018;215:12–9.
60. Cook GA, Sandroni P. Management of headache and chronic pain in POTS. Auton Neurosci. 2018;215:37–45.
61. Ojha A, Chelimsky TC, Chelimsky G. Comorbidities in pediatric patients with postural orthostatic tachycardia syndrome. J Pediatr. 2011;158(1):20–3.
62. Khurana RK, Eisenberg L. Orthostatic and non-orthostatic headache in postural tachycardia syndrome. Cephalalgia. 2011;31(4):409–15.
63. Shaw BH, Stiles LE, Bourne K, Green EA, Shibao CA, Okamoto LE, et al. The face of postural tachycardia syndrome - insights from a large cross-sectional online community-based survey. J Intern Med. 2019;286(4):438–48.
64. Chelimsky G, Kovacic K, Nugent M, Mueller A, Simpson P, Chelimsky TC. Comorbid conditions do not differ in children and young adults with functional disorders with or without postural tachycardia syndrome. J Pediatr. 2015;167(1):120–4.
65. Staples A, Thompson NR, Moodley M. Pediatric-onset postural orthostatic tachycardia syndrome in a single tertiary care center. J Child Neurol. 2020;35(8):526–35.
66. Gourishankar A, Belton MD, Hashmi SS, Butler IJ, Lankford JE, Numan MT. Demographic and clinical features of pediatric patients with orthostatic intolerance and an abnormal head-up tilt table test; a retrospective descriptive study. Pediatr Neonatol. 2020;61(1):68–74.
67. Kato Y, Hayashi T, Arai N, Tanahashi N, Takahashi K, Takao M. Spontaneous intracranial hypotension associated with postural tachycardia syndrome. Intern Med. 2019;58(17):2569–71.
68. Franzini A, Messina G, Nazzi V, Mea E, Leone M, Chiapparini L, et al. Spontaneous intracranial hypotension syndrome: a novel speculative physiopathological hypothesis and a novel patch method in a series of 28 consecutive patients. J Neurosurg. 2010;112(2):300–6.
69. Benarroch EE. Postural tachycardia syndrome: a heterogeneous and multifactorial disorder. Mayo Clin Proc. 2012;87(12):1214–25.
70. Mar PL, Raj SR. Postural orthostatic tachycardia syndrome: mechanisms and new therapies. Annu Rev Med. 2020;71:235–48.
71. Boris JR, Bernadzikowski T. Prevalence of joint hypermobility syndromes in pediatric postural orthostatic tachycardia syndrome. Auton Neurosci. 2021;231:102770.
72. Miller AJ, Stiles LE, Sheehan T, Bascom R, Levy HP, Francomano CA, et al. Prevalence of hypermobile Ehlers-Danlos syndrome in postural orthostatic tachycardia syndrome. Auton Neurosci. 2020;224:102637.
73. Wallman D, Weinberg J, Hohler AD. Ehlers-Danlos syndrome and postural tachycardia syndrome: a relationship study. J Neurol Sci. 2014;340(1–2):99–102.
74. Dobrocky T, Nicholson P, Häni L, Mordasini P, Krings T, Brinjikji W, et al. Spontaneous intracranial hypotension: searching for the CSF leak. The Lancet Neurology. 2022;21(4):369–80.
75. Go S, Yamanaka G, Kasuga A, Kanou K, Takamatsu T, Takeshita M, et al. Orthostatic headache in children including postural tachycardia syndrome and orthostatic hypotension: a near-infrared spectroscopy study. J Clin Med. 2020;9(12):E4125.
76. D'Antona L, Jaime Merchan MA, Vassiliou A, Watkins LD, Davagnanam I, Toma AK, et al. Clinical presentation, investigation findings, and treatment outcomes of spontaneous intracranial hypotension syndrome: a systematic review and meta-analysis. JAMA Neurol. 2021;78(3):329–37.
77. Graf N, Fernandes Santos AM, Ulrich CT, Fung C, Raabe A, Beck J, et al. Clinical symptoms and results of autonomic function testing overlap in spontaneous intracranial hypotension and postural tachycardia syndrome: a retrospective study. Cephalalgia Reports. 2018;1:2515816318773774.
78. Cipriani D, Rodriguez B, Häni L, Zimmermann R, Fichtner J, Ulrich CT, et al. Postural changes in optic nerve and optic nerve sheath diameters in postural orthostatic tachycardia syndrome and spontaneous intracranial hypotension: a cohort study. PLoS One. 2019;14(10):e0223484.
79. Dobson JL, Yarbrough MB, Perez J, Evans K, Buckley T. Sport-related concussion induces transient cardiovascular autonomic dysfunction. Am J Physiol Regul Integr Comp Physiol. 2017;312(4):R575-84.
80. Mercier LJ, Batycky J, Campbell C, Schneider K, Smirl J, Debert CT. Autonomic dysfunction in adults following mild traumatic brain injury: a systematic review. NRE. 2022;50(1):3–32.

81. Howard L, Dumkrieger G, Chong CD, Ross K, Berisha V, Schwedt TJ. Symptoms of autonomic dysfunction among those with persistent posttraumatic headache attributed to mild traumatic brain injury: a comparison to migraine and healthy controls. Headache. 2018;58(9):1397–407.
82. Jacob S, Saha A, Rajabally Y. Post-traumatic short-lasting unilateral headache with cranial autonomic symptoms (SUNA). Cephalalgia. 2008;28(9):991–3.
83. Grangeon L, O'Connor E, Chan CK, Akijian L, Pham Ngoc TM, Matharu MS. New insights in post-traumatic headache with cluster headache phenotype: a cohort study. J Neurol Neurosurg Psychiatry. 2020;91(6):572–9.
84. Hammerle MH, Lu LH, Thomas LC, Swan AA, Hoppes CW, Nelson JT, et al. Possible autonomic or cranial nerve symptoms triggered during sustained neck rotation in persistent headache post-concussion: a retrospective observational cross-sectional study. J Man Manip Ther. 2022 1–11.
85. Master CL, Podolak OE, Ciuffreda KJ, Metzger KB, Joshi NR, McDonald CC, et al. Utility of pupillary light reflex metrics as a physiologic biomarker for adolescent sport-related concussion. JAMA Ophthalmol. 2020;138(11):1135–41.
86. Truong JQ, Ciuffreda KJ. Comparison of pupillary dynamics to light in the mild traumatic brain injury (mTBI) and normal populations. Brain Inj. 2016;30(11):1378–89.
87. Thiagarajan P, Ciuffreda KJ. Pupillary responses to light in chronic non-blast-induced mTBI. Brain Inj. 2015;29(12):1420–5.
88. Purkayastha S, Stokes M, Bell KR. Autonomic nervous system dysfunction in mild traumatic brain injury: a review of related pathophysiology and symptoms. Brain Inj. 2019;33(9):1129–36.
89. Heyer GL, Fischer A, Wilson J, MacDonald J, Cribbs S, Ravindran R, et al. Orthostatic intolerance and autonomic dysfunction in youth with persistent postconcussion symptoms: a head-upright tilt table study. Clin J Sport Med. 2016;26(1):40–5.
90. Pertab JL, Merkley TL, Cramond AJ, Cramond K, Paxton H, Wu T. Concussion and the autonomic nervous system: an introduction to the field and the results of a systematic review. NeuroRehabilitation. 2018;42(4):397–427.
91. Charron J, Soto-Catalan C, Marcotte L'Heureux V, Comtois AS. Unclear outcomes of heart rate variability following a concussion: a systematic review. Brain Inj. 2021;35(9):987–1000.