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MIGRAINE AND BEYOND (R COWAN, SECTION EDITOR)

Migraine and Autonomic Dysfunction: Which Is the Horse and Which Is the Jockey?

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Abstract

Purpose of Review Symptoms of autonomic dysfunction are common in patients with migraine, both during and between migraine attacks. Studies evaluating objective autonomic testing in patients have found significant, though somewhat conflicting results. The purposes of this review are to summarize and interpret the key findings of these studies, including those evaluating heart rate variability, autonomic reflex testing, and functional imaging in patients with migraine. The neuroanatomy of the central autonomic network as it relates to migraine is also reviewed.

Recent Findings Several studies have evaluated autonomic balance in migraineurs, with conflicting results on the magnitude of sympathetic versus parasympathetic dysfunction. Most studies demonstrate sympathetic impairment, with a lesser degree of parasympathetic impairment.

Summary Three trends have emerged: (1) migraine with aura tends to produce more significant autonomic dysfunction than migraine without aura, (2) sympathetic impairment is more common than parasympathetic impairment, and (3) sympathetic impairment is common in the interictal period, with increased sympathetic responsiveness during the ictal period, suggesting adrenoreceptor hypersensitivity.

Keywords Migraine · Autonomic · HRV · Tilt table · Valsalva · Syncope · POTS dysautonomia · Sympathetic · Parasympathetic

Introduction

Migraine is one of the oldest recorded human ailments, with reports dating back to ancient Egyptian records in 1200 BCE. Symptoms of autonomic dysfunction are frequently mentioned in these early documents. Writing in 400 BCE, Hippocrates described the nausea that accompanies migraine, with symptom improvement after vomiting, which he viewed as a release of vile humors. The "sympathetic" theory of migraine gained traction during the time of Thomas Willis (1621–1675), in which migraine was thought to originate in visceral organs and propagate through the "sympathy" of the head and the viscera. Robert Whytt (1714–1766), an autonomic physician at heart and the first to describe the pupillary light reflex, describes a host of autonomic symptoms in one description of a migraine attack:

> "…an extraordinary sensation of cold and heat…syncopes and vaporous convulsions…gas in the stomach and intestines…vomiting of black matter; a sudden and abundant flow of clear pale urine…palpitations of the heart; variations in the pulse…" [1]

Since the time of these writings, we have come to understand that autonomic symptoms are quite common in migraineurs, both ictally and interictally, and may take many forms (Table 1). Cranial autonomic parasympathetic symptoms, such as lacrimation, rhinorrhea, and eyelid edema, are estimated to occur not only in the trigeminal autonomic cephalgias, but in migraine as well, affecting 27–73% of patients by different estimates [2]. The nausea and vomiting that is common in migraine is in essence an autonomic symptom, as is the need to sleep after an attack. Other autonomic symptoms such as orthostatic intolerance are thought to affect a large percentage of migraineurs, and syncope is not uncommon [3•].

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Table 1 Autonomic symptoms commonly reported with migraine headache

- Nausea/vomiting
- Hyperhidrosis
- Flushing
- Pallor
- Palpitations
- Diaphoresis
- Lightheadedness
- Constipation
- Diarrhea
- Polydipsia
- Polyuria
- Piloerection
- Pupillary dilation
- Chemosis
- Lacrimation
- Rhinorrhea
- Facial edema
- Presyncope/syncope

Not an exhaustive list

In addition, many patients with primary disorders of the autonomic nervous system (ANS) also suffer from migraine. Despite the progress the field has made since the time of the ancient Egyptians, the pathophysiology of migraine and its activation of the ANS remain incompletely understood. This article will review the neuroanatomy of the central autonomic network and its connection to the pain systems involved in migraine, as well as the current literature related to migraine and autonomic dysfunction.

Anatomy of the Autonomic System and Its Relation to the Anatomy of Migraine

The Central Autonomic Network

The autonomic nervous system is a diffuse network that regulates virtually all of the unconscious homeostatic mechanisms of the human body and is intrinsically involved in modulating physiologic pain responses, including that of migraine. The central autonomic control centers comprise the central autonomic network (CAN), a system of interconnected nuclei in the cortex and brainstem that help regulate visceromotor, neuroendocrine, respiratory, and pain responses, among other functions (Fig. 1a, b) [4•]. Important areas of the CAN that are also thought to be involved in the transmission of migraine pain include the periaqueductal gray (PAG) of the midbrain, the parabrachial nucleus of the pons, the dorsal motor nucleus of the vagus (DMV), and the nucleus tractus solitarius (NTS) of the lateral medulla [4•]. The NTS, LC, and PAG play an important role in both pain processing and cardiovascular control. The lateral PAG, which receives nociceptive inputs from the spinal and trigeminal dorsal horn, initiates sympathetic responses in fight or flight situations, resulting in norepinephrine (NE) release, hypertension, and tachycardia [5].

The Vascular Autonomic Theory of Migraine Activation

The observation that migraine is associated with symptoms of increased autonomic activity initially led investigators to consider the "autonomic theory" of migraine activation, in which an excessive release of NE triggers intracranial vasoconstriction. This vasoconstriction eventually results in a reflex release of vasodilator metabolites, triggering vasodilation and depolarization of primary nociceptive neurons within the walls of the dilated vessels [6•]. This paradigm, also known as the vascular theory, dominated the migraine literature until the early 1980s. More recently, this theory has been abandoned in favor of the neurogenic theory, in which the vasodilatory changes in migraine are thought to be the secondary to complex neuronal pathways, with genetic predisposition and central sensitization playing a prominent role [6•].

Current Concepts and Autonomic Pathways

While the pathways involved in the pain of migraine are incompletely understood, the trigeminal nucleus caudalis (TNC) of the brainstem is thought to play an important role. The majority of the brain matter lacks pain receptors; however, the dura and the proximal portions of the large intracranial vessels are highly pain-sensitive [6•]. Trigeminal sensory afferents from these meningeal and vascular structures converge on the TNC, which then ascend to synapse in the ventral posteromedial nucleus of the thalamus. Efferent projections of the TNC project to several important areas of the CAN including the PAG, LC, hypothalamus, limbic cortex, parabrachial nucleus, and the NTS [7]. Activation of the dorsal raphae nucleus and LC also leads to activation of the trigeminovascular system that may alter the monoaminergic modulation of pain [8].

In addition to these sympathetic pathways, several parasympathetic pathways are involved in the migraine response. Cranial parasympathetic pathways project to the descending tract of the TNC and the dorsal horns of the spinal cord, an area termed the trigeminocervical complex [8]. Activation of the trigeminocervical complex results in a reflex activation of cranial parasympathetic outflow. The parasympathetic fibers that innervate the cerebral vasculature exit the brainstem at the level of the pons and travel along the facial nerve, where they exert significant influence on vasomotor tone through the secretion of several neuromodulating chemicals, including

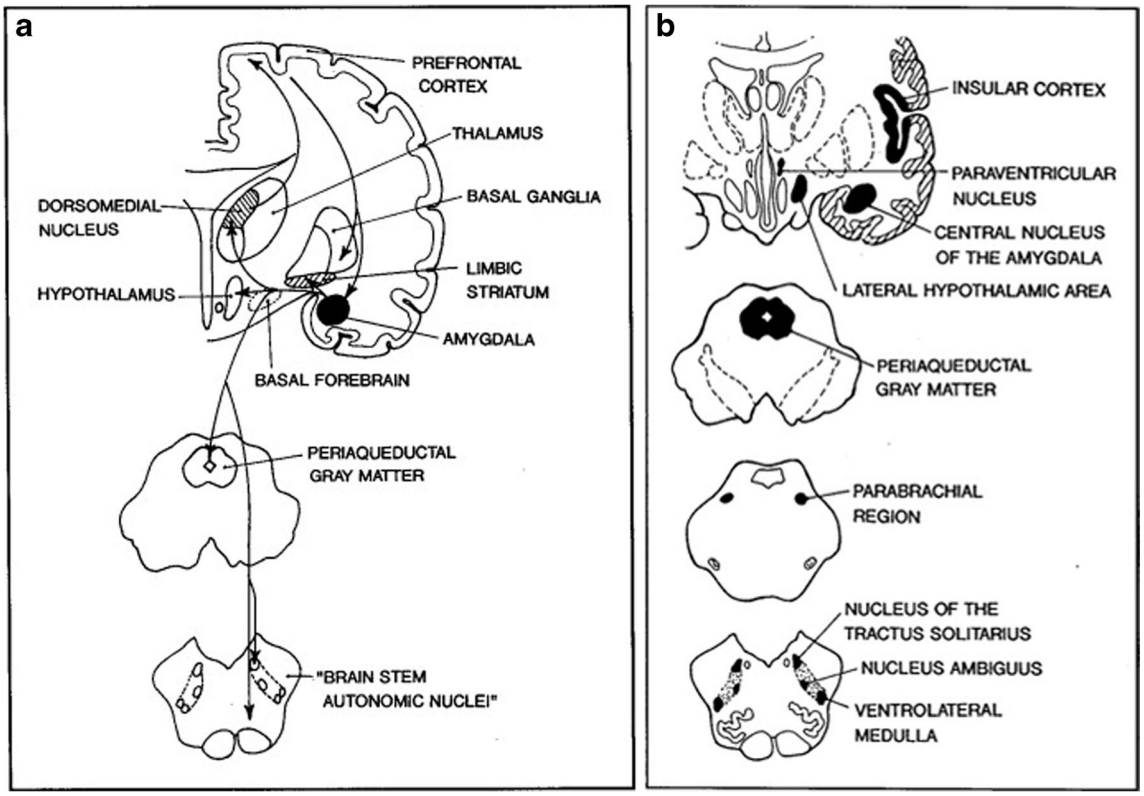

Fig. 1 **a**, **b** The Central Autonomic Network. Reprinted with permission from: Benarroch EE. The central autonomic network: functional organization, dysfunction, and perspective. Mayo Clin Proc [Internet]. 1993 Oct.

acetylcholine, calcitonin gene-related peptide (CGRP), and vasoactive intestinal peptide (VIP). These chemicals are thought to trigger the vasodilatory pain response of migraine, resulting in the "red-face migraine" referenced in older literature (as opposed to the pallor of "white-face migraine (1)"). Interestingly, researchers have demonstrated that chronic migraine patients have elevated VIP levels both ictally and interictally, suggestive of both acute and chronic parasympathetic hypersensitivity [2].

The vagus nerve is also involved in modulating migraine pain, as evidenced by the popularity of invasive and noninvasive vagal nerve stimulators now available for migraine treatment [9]. While the mechanism of these stimulators is incompletely understood, one theory involves modulations of vagal afferents that in turn downregulate efferent projections to various centers of the CAN involved in pain perception [10]. In support of this theory, stimulation of the vagus in awake rats has been shown to significantly reduce formalin-induced trigeminal nociception [11•].

Sympathetic or Parasympathetic Impairment? A Review of the Literature

There are now many studies that have evaluated the role of autonomic balance in patients with migraine, with conflicting results on the role of the sympathetic versus parasympathetic dysfunction seen in this disorder. Although most studies have reported reduced sympathetic function [12, 13, 14•, 15], some have reported increased sympathetic function [16] and some normal sympathetic function [17•]. Similarly, while most studies have reported normal parasympathetic cardiovagal function [10, 12, 13, 17•], some have reported decreased parasympathetic function [18]. This review will focus on the following types of investigations: heart rate variability studies, autonomic cardiovascular reflex testing studies, and functional imaging studies. Unless otherwise stated, all of these studies have evaluated patients in the interictal period. There are only a few studies that have evaluated patients during a migraine attack.

Heart Rate Variability Studies

Hear rate variability (HRV) is one of the most commonly utilized measures of autonomic balance, due to its ease of administration and noninvasive nature. The most common method of evaluating HRV is the time domain analysis of R-R intervals, such as the standard deviation normal to normal (SDNN) or the root-mean square of successive R-R-interval difference (RMSSD). Reduced HRV in the time domain has been correlated with generalized autonomic impairment and increased morbidity and mortality in various disease states. In

addition to the time domain, HRV can also be analyzed in frequency domains. The high-frequency (HF) RR signal (greater than 0.15 Hz) is associated with increased parasympathetic tone, and the low-frequency (LF) RR signal (0.04–0.15 Hz) is associated with increased sympathetic tone. The HF signal is most influenced by the vagally mediated respiratory sinus arrhythmia of deep breathing, while the LF signal is most likely influenced by the baroreflex-mediated heart rate (HR) response to blood pressure (BP), with some cholinergic input [18]. A greater LF/HF ratio suggests greater sympathetic drive, and a lower LF/HF ratio suggests greater parasympathetic drive. While noninvasive and easy to perform, HRV data has many confounders, such as respiratory rate, medication use, age of the subject, comorbid conditions, cardiac ectopy, pain, and time of day, many of which are relevant in migraine patients both during and between attacks and may influence results.

Several studies have demonstrated impaired HRV in migraineurs, in both time and frequency domains. In a study of 27 patients with migraine, migraine with aura (MA) patients ($n = 10$) had reduced SDNN, as well as an increased LF/HF ratio, suggesting sympathetic hyperactivity [16]. The migraine without aura (MO) patients ($n = 17$) had similar impairment, though not as severe as in the MA group. Other studies have failed to replicate these findings. Thomsen and colleagues compared cardiovascular responses in 50 participants (27 MO and 23 MA). All patients underwent head-up tilt (HUT) testing, Valsalva maneuver, and cold-pressor testing, in which the subject's hand is submerged in an ice water bath at 5 °C for 1 min, a test designed to produce a sympathetic stress response. The authors reported no significant difference in HRV between migraine patients and controls either during baseline or during these tests [19].

In a study of 8 MO patients during sleep, the authors found a significant reduction in the LF/HF ratio during stage 2 and stage 3 of non-REM sleep when compared to controls [20], suggestive of reduced sympathetic tone. A meta-analysis that evaluated 7 HRV studies concluded that vagally mediated HRV (both RMMD and HF) was reduced in migraineurs when compared to controls [18]. In summary, the results from HRV studies are inconsistent; however, taken together seem to suggest an impairment in both sympathetic and parasympathetic function in the interictal period, during both wake and sleep.

Autonomic Cardiovascular Reflex Testing

Autonomic cardiovascular reflex testing can include many specialized autonomic tests, but at a minimum should include measures of HRV with deep breathing (cardiovagal parasympathetic), Valsalva maneuver (sympathetic adrenergic), and 70-degree head up tilt (HUT [sympathetic adrenergic]) for a minimum of 10 min, all performed with continuous BP and HR monitoring. Testing is performed in the autonomic laboratory under controlled conditions, and patients should refrain from large meals, alcohol, nicotine, caffeine, or any medications that might alter the test results.

One early study by Havanka-Kanniainen et al. evaluated 10 patients (6 MA and 4 MO), during a migraine attack, and demonstrated no clinically significant difference in tests of either sympathetic or parasympathetic function in patients compared to controls [17•]. This is one of the few studies that have evaluated autonomic function in patients during the ictal period. While the sample size was small, the results indicate that even while patients are demonstrating clear symptoms of autonomic impairment (several patients were unable to complete the Valsalva maneuver due to vomiting), their autonomic reflexes during an attack may be normal.

Another early study by Pogacnik et al. found a reduced response to handgrip testing in 62 migraineurs (21 MA and 31 MO) [12], a test in which the patient is asked to grip a dynamometer at 30% of maximal strength for several minutes; this test produces a rise in BP and HR that is thought to be sympathetically mediated. The authors concluded that migraine patients have reduced sympathetic activity. It should be noted, however, that the degree of sympathetic impairment observed was mild, and not necessarily clinically significant. The results were similar in MA and MO patients, and there was no gender difference (48 females and 14 males). Measures of parasympathetic cardiovagal function were normal in both groups.

Gotoh et al. demonstrated several more robust findings suggestive of sympathetic impairment in patients with MA ($n = 10$) and MO ($n = 11$), including reduced phase IV overshoot of the Valsalva maneuver, a more significant reduction in systolic BP on HUT (-13.4 ± 6.5 mmHg in the MA group and -14.8 ± 12.7 mmHg in the MO group, though mean BP change in both groups was within the range of normal), and low NE levels at baseline and during HUT [14•]. The authors added an interesting aspect to their study by administering a NE infusion to patients (bolus injection of 0.1 mg/kg of norepinephrine bitartrate), then measured steady-state levels. They found that the recovery times for migraine patients were significantly longer than controls (101.3 ± 29.8 s in MA and 90.9 ± 33.6 s in MO patients, compared to 21.2 ± 14.9 s in controls), suggestive of adrenoreceptor hypersensitivity, presumably due to sympathetic deficiency.

Another study of 32 MO patients supported this theory [21]. These researchers administered phenylephrine, an alpha-1 adrenergic receptor agonist, and demonstrated that migraine patients had an exaggerated pressor response, suggestive of adrenoreceptor hypersensitivity. A larger study of episodic ($n = 51$) and chronic ($n = 22$) patients, most of whom had MO, found a BP increase during phase II of the Valsalva Maneuver, possibly due to an enhanced baroreflex response, also suggestive of increased sympathetic reactivity [22]. This

was supported by increased vasoconstrictive reactivity in the cold pressor test, another sign of sympathetic reactivity. There was no clinical or statistical difference in the Valsalva HR ratio or HR variability with deep breathing, tests which are thought to reflect parasympathetic cardiovagal function. HUT testing was normal in both groups.

A study utilizing standardized autonomic testing at the Mayo Clinic demonstrated findings in MA ($n = 8$) and MO ($n = 9$) consistent with decreased sympathetic drive, with reduced phase IV of the Valsalva maneuver and a lower BP increment during handgrip test [13]. The authors performed the cold pressor testing and the results were not different from controls. On HUT, the BP response was normal in both groups. LF/HF frequency variations in BP were significantly increased in both MA and MO groups, which suggests either increased sympathetic tone or decreased parasympathetic tone. Given the other findings suggestive of sympathetic impairment, the authors conclude that decreased parasympathetic tone is the likely culprit. However, HRV to deep breathing was not significantly different between groups, indicating intact parasympathetic function, as in other studies.

One unique feature of this study was the evaluation of sweat function, a sympathetic cholinergic function, with the quantitative sudomotor axon reflex test (QSART), in which acetylcholine is iontophoresed into a vacuum-sealed capsule on the subject's extremities, resulting in an axon reflex-mediated sweat response that is quantified with a sudorometer. The composite sweat production from the four sites tested tended to be lower in the MA group, compared to MO and controls, suggestive of sympathetic cholinergic dysfunction. Taken together, the data from this study do suggest reduced sympathetic tone, likely central in origin.

Finally, one study utilizing microneurography in migraineurs is worth mentioning. Microneurography is a highly specialized technique whereby a microneurographic tungsten needle electrode is inserted directly into the sympathetic nerves, most commonly the superficial branches of the peroneal nerve, in order to measure sympathetic nerve activity (SNA). This technique was performed in eight MO patients, in both the ictal and interictal periods [8]. SNA did not change in either period as compared to baseline recordings. While there were no control patients, this study provides evidence against peripheral sympathetic vasomotor dysfunction; however, these results cannot be extrapolated to dysfunction of the central sympathetic outflow.

In summary, the results from autonomic cardiovascular reflex testing studies are mixed, with some studies demonstrating decreased sympathetic drive, some demonstrating decreased parasympathetic drive, and others demonstrating no difference when compared to healthy controls. The trend that has emerged, however, is a relative sympathetic impairment in the interictal period, with paradoxical sympathetic hypersensitivity during the period of migraine attack.

Imaging Studies

The development of functional imaging has allowed researchers to study the physiological changes of migraine in more dynamic fashion, and there have been several imaging studies that have focused on functional autonomic activity in patients with migraine. One study utilizing positive emission tomography (PET) imaging during an attack in episodic MO patients ($n = 7$) demonstrated increased activity of the hypothalamus [23•]. Symptoms of hypothalamic autonomic impairment are common in migraineurs before and after an attack, including changes in alertness, appetite, and thirst. Another study utilizing functional MRI performed during the interictal period in a group of episodic MO patients ($n = 12$) demonstrated enhanced functional connectivity (FC) between the hypothalamus and several autonomic regions including the LC, caudate, and pontine nuclei [24]. These data are intriguing and suggest that these autonomic pathways may become sensitized and thus more easily activated in migraine patients. One limitation of these types of studies is that they cannot determine whether such changes in regional cerebral blood flow represent excitation or inhibition and do not provide information about the nociceptive pathways that modulate the pain response and influence the imaging findings. Another limitation is that MA patients were not included in these studies, and it would be interesting to see if these patients exhibited even greater enhancement of FC between brain regions.

Migraine and Primary Disorders of Autonomic Dysfunction

Not only do many patients with migraine suffer from symptoms of autonomic impairment, many patients with primary autonomic disorders also suffer from migraine. One study demonstrated a 1.48x greater incidence of syncope in migraineurs without prior autonomic disease than in control subjects [25]. A more recent study evaluating autonomic cardiovascular reflex testing in migraineurs with syncope found that 1/3 of their syncope patients met criteria for syncopal migraine [3•]. The syncopal migraine group reported a longer duration of syncope and a longer recovery time to normal, with 62% of patients reporting loss of consciousness > 1 min, which is rare in most types of syncope. Interestingly, migraine medications reduced syncope in 50% of the syncopal migraine subjects.

Migraine is quite common in postural tachycardia syndrome (POTS), affecting at least 25% of patients [26]. It can be postulated that migraine induces central somatic and visceral sensitization in POTS patients [27]. Migraine is also common in other conditions associated with deconditioning such as chronic fatigue syndrome, fibromyalgia, and

hereditary connective tissue disorders such as Ehlers-Danlos syndrome. The reasons for this association are unknown. Many of these conditions affect younger women, in which migraine is more common. Other plausible theories include intracranial hypersensitivity, heightened interoception, and increased sympathetic tone. Deconditioning, insufficient sleep time, circadian rhythm disorders, and chronic pain are also likely contributing factors.

Conclusions

It is still unclear which is the horse and which is the jockey in the painful race of autonomic dysfunction in migraine. What is clear is that patients with migraine suffer myriad autonomic symptoms, both ictally and interictally. The results of controlled studies evaluating autonomic function in migraineurs are conflicting, perhaps due to discrepancies in the many factors that influence the results of autonomic testing. These include—but are not limited to—age, weight, sex, patient selection (episodic vs chronic migraine, with or without aura, headache frequency, comorbid headache disorders, etc.), method of testing, food ingestion, medication effects, hydration status, time of day, and comorbid medical disorders. Migraine is a dynamic state, and measurements in the same patient may yield different results on different days. The conflicting results in the autonomic migraine literature may speak to the heterogeneity of migraine, as not all migraine patients manifest with the same set of symptoms, and not all patients may manifest the same type or degree of autonomic imbalance. Nonetheless, the trends that have emerged in this review include the following:

- Migraine with aura tends to produce more significant autonomic impairment than migraine without aura.
- Those with migraine tend to have reduced sympathetic activity in the interictal period, with increased sympathetic responsiveness during the ictal period. The reason for this is unclear. One explanation is a state of sympathetic "exhaustion," in which repeated stimulation of the central sympathetic autonomic network during migraine attacks eventually results in downregulation of sympathetic outflow and plasma NE release. This might explain why plasma NE is lower in migraineurs. Over time, this relative NE deficiency may result in upregulation of post-synaptic adrenergic receptors, resulting in hypersensitivity and an exaggerated sympathetic response during the attack, as demonstrated in several studies mentioned.
- Parasympathetic activity remains less affected than sympathetic activity in the interictal period. HRV studies have demonstrated more robust parasympathetic impairment than autonomic cardiovascular reflex testing studies. Possible explanations for this include greater artifact in HRV analysis, including respiratory rate, which is often higher in migraineurs [13], medications (many migraine preventatives affect HRV), and sensitivity of analysis (autonomic reflex testing may be more specific but lack sensitivity, especially in younger women who are otherwise healthy).

Of course, more controlled studies with larger sample sizes are necessary. Although we have an understanding of the potential mechanisms involved in migraine and a wide array of treatment strategies, migraine remains a disabling condition for a large portion of society, and new treatments targeting the central pain generators of migraine, including those involved in autonomic activation, are crucial for more efficacious treatment of this disease.

Compliance with Ethical Standards

Conflict of Interest Mitchell G. Miglis declares no conflict of interest.

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.

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