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HEADACHE CURRENTS

Postural orthostatic tachycardia syndrome and migraine: A narrative review

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Abstract

Objective: In this narrative review, we summarize experimental and clinical evidence demonstrating mechanistic connections between POTS and migraine.

Background: Migraine is the most common comorbidity in patients with POTS, a heterogenous disorder of the autonomic nervous system characterized by orthostatic intolerance and positional tachycardia. POTS is a debilitating illness with few effective treatments. We aim for this narrative review to increase awareness of the mechanistic connections between POTS and migraine providing foundational information that optimizes clinical care and advances the development of pathophysiologic-based treatments.

Methods: We used the PubMed and Medline databases in November 2021 to perform a literature review and searched for the following keywords: "postural orthostatic tachycardia syndrome," "POTS," "autonomic nervous system," AND "migraine," "headache."

Results: The high prevalence of migraine in patients with POTS may be explained by common pathologic mechanisms. There is evidence that dysregulation of the sympathetic nervous system, alterations in central and peripheral hemodynamics, and central sensitization increase vulnerability to both POTS and migraine. Non-pharmacologic and pharmacologic treatments that target these shared mechanisms may provide significant benefit for the patient with POTS and migraine.

Conclusions: Identification of common affected pathways may provide important insight that advances our understanding and treatment of both migraine and POTS.

KEYWORDS
autonomic nervous system, headache, sympathetic nervous system

INTRODUCTION

Postural orthostatic tachycardia syndrome (POTS) is the most common disorder of the autonomic nervous system. Prevalence estimates vary between 0.2% and 1% of the US population.[1] POTS refers to a phenotype—positional symptomatic tachycardia—defined by an increase in heart rate of at least 30 beats per minute (bpm) on assuming an upright position in the absence of orthostatic hypotension.[2,3] POTS is a heterogenous disorder with a range of clinical presentations. To diagnose POTS, a thorough clinical history, physical exam, and a standard battery of autonomic function tests (a tilt table test and measures of cardiovagal and sudomotor nerve function) are recommended.

In addition to orthostatic intolerance and positional tachycardia, non-orthostatic symptoms including headache, fatigue, migraine, and cognitive dysfunction are common.[4,5] Migraine has an especially high prevalence in patients with POTS.[6] In a study of 24 adult patients with POTS, 23 had non-orthostatic headaches meeting

Abbreviations: AR, adrenergic receptor; IVIG, intravenous immunoglobulin; NE, norepinephrine; nVNS, non-invasive vagal nerve stimulation; POTS, Postural Orthostatic Tachycardia Syndrome.

criteria for migraine without aura or probable migraine without aura.[6] For patients presenting with pure orthostatic headache, positional tachycardia, and no history of migraine, a diagnosis of spontaneous intracranial hypotension should be considered.[7,8]

This narrative review addresses how the pathophysiology of POTS may inform treatment of patients with POTS and migraine. The first section reviews the pathophysiology and clinical characteristics of POTS subtypes. The second section discusses overlapping mechanisms common to migraine and POTS. The final section focuses on non-pharmacological and pharmacologic POTS therapies, highlighting therapies with relevance to migraine management.

Methods

We used the PubMed and Medline databases in November 2021 to perform a literature review and searched for the following keywords: "postural orthostatic tachycardia syndrome," "POTS," "autonomic nervous system," AND "migraine," "headache." Articles addressing pathophysiology, treatment, clinical trials, and observational studies were included. The search included publications in English. The reference lists of relevant and recent articles focusing on POTS and headache were also reviewed and added if considered appropriate.

POTS SUBTYPES

In this section, we discuss the pathophysiology and clinical characteristics of POTS subtypes. Although there is no official consensus regarding POTS classifications, there is evidence from autonomic and laboratory testing that three major subtypes exist: (1) neuropathic, (2) hypovolemic, and (3) hyperadrenergic.[9,10] While these subtypes illustrate that POTS has several potential etiologies, overlapping clinical features and interactions between mechanisms exist (Figure 1).

Neuropathic POTS

Approximately 50% of patients with POTS have neuropathic POTS.[2] While there are no universally accepted criteria for diagnosing neuropathic POTS, studies have typically used thermoregulatory sweat testing or quantitative sudomotor axon reflex testing to measure sweat production from post-ganglionic sympathetic efferents. Skin biopsies are also used to assess intraepidermal nerve fiber density.[11]

Pathophysiology

In patients with neuropathic POTS, patchy anhidrosis in the lower extremities and reduced intraepidermal nerve fiber density

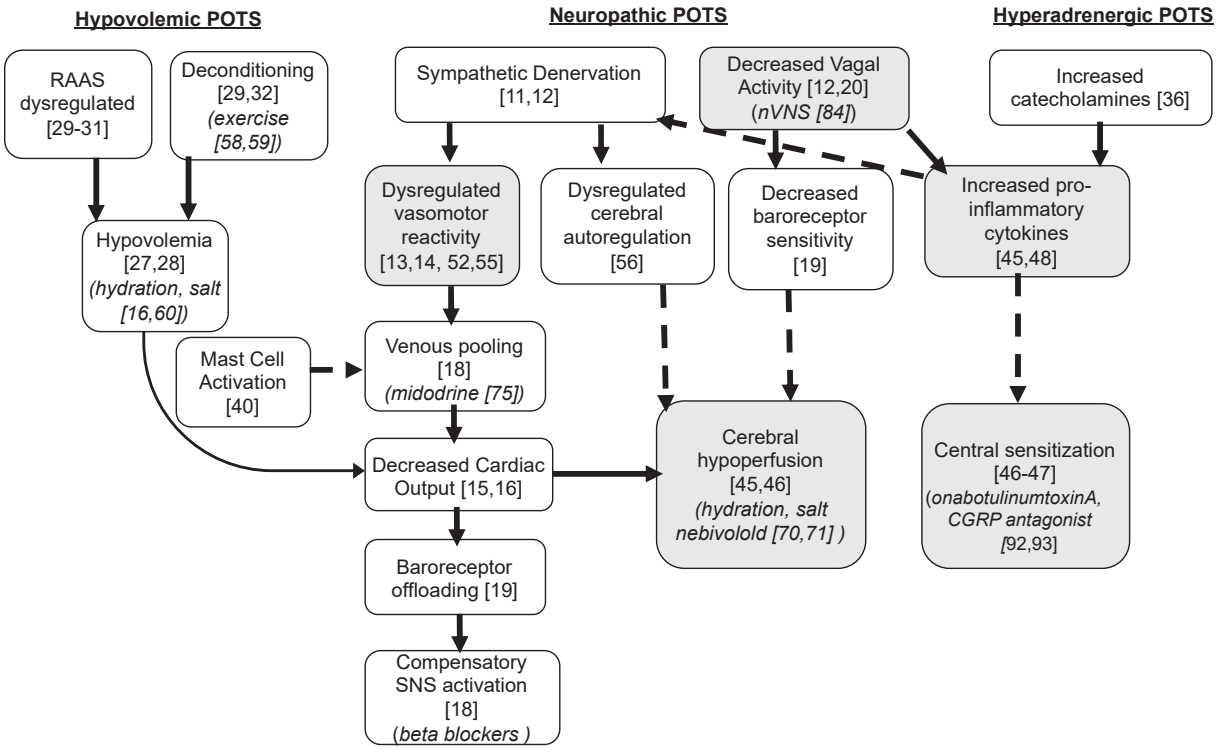

FIGURE 1 Overlapping pathophysiology in postural orthostatic tachycardia syndrome (POTS) and migraine. Dotted lines indicate connections requiring further study. Shading denotes pathophysiology present in patients with migraine and POTS. Therapies targeting pathophysiology are listed in parentheses. CGRP, calcitonin gene-related peptide; nVNS, non-invasive vagal nerve stimulation; RAAS, renin–angiotensin–aldosterone system; SNS, sympathetic nervous system.

suggest the presence of a small fiber neuropathy impacting sympathetic efferents.[11,12] Several studies have shown that local infusions of norepinephrine (NE) in the legs produce exaggerated vasoconstriction indicative of partial sympathetic denervation and compensatory hypersensitivity of α-adrenergic receptors.[13,14] In many patients with neuropathic POTS, inadequate blood vessel constriction is believed to produce venous pooling in the lower extremities, pelvic, and splanchnic vascular beds, decreasing venous return.[13,15–18] A decrease in venous return leads to a reduction in cardiac output that is sensed by baroreceptors in the carotid arch and transmitted by vagal nerve afferents producing a compensatory increase in heart rate and blood vessel constriction to maintain blood pressure.[18–20]

A vagal neuropathy may also contribute to the development of POTS.[12,21] The vagus nerve is the main component of the parasympathetic nervous system and its actions are associated with a lower heart rate, cardiac flexibility, and anti-inflammatory actions.[22] Intact vagal function is also needed for normal function of the baroreceptor reflex.[19] Patients with neuropathic POTS were more likely to have reduced cardiovagal function as measured by cardiovascular reflex tests (e.g., tilt-table testing and Valsalva maneuver) and resting heart rate variability compared to both healthy controls and POTS patients without evidence of neuropathy.[12,21]

The etiology of small fiber neuropathy in patients with POTS remains unclear. Several studies have proposed that immune system dysregulation may contribute. Antibodies to α1-AR (adrenergic receptor) have been found in a small number of patients with POTS and could produce a partial functional autonomic neuropathy.[23] A vagal neuropathy may also contribute as the loss of vagus nerve activity is associated with an increase in pro-inflammatory cytokines.[24,25] A study examining cytokine levels in skin biopsies found patients with small fiber neuropathy had increased expression of proinflammatory cytokines, interleukins 2, 6, and 8, compared to healthy controls.[25] Further, patients with a length-dependent neuropathy had higher pro-inflammatory gene expression in the affected distal skin than in nonaffected skin.[25] However, the association between small fiber neuropathy and pro-inflammatory cytokines has not been consistently reported.[26]

Clinical presentation

There is significant variability in the clinical presentation of patients with neuropathic POTS that likely stems from differences in the severity of autonomic neuropathy, length of illness, and the extent of sympathetic nervous system compensation. Generally, neuropathic POTS patients have an increased prevalence of gastrointestinal symptoms and headache, which may reflect the greater prevalence of vagus nerve pathology.[12,27] An important physical exam finding common in patients with neuropathic POTS is acrocyanosis, a term denoting red-blue discoloration of the lower extremities that occurs when assuming an upright posture.[28] The underlying mechanism is thought to involve a deficit in nitric oxide production that leads to impairments in cutaneous vasodilation of the microvasculature.[28]

Hypovolemic POTS

Approximately 30% of patients with POTS are hypovolemic.[29] Studies using iodinated human serum albumin demonstrate an average decrease in plasma volume of 11% to 13%.[30]

Pathophysiology

In primary hypovolemic POTS, there is evidence that the renin–angiotensin–aldosterone system is dysregulated.[31] The renin–angiotensin–aldosterone system plays an important role in maintaining blood volume via increasing renal sodium and water reabsorption. Studies have repeatedly demonstrated a disparity between blood volume and expected renin–angiotensin–aldosterone system function in patients with POTS.[32] Dysfunction of the angiotensin II receptor may play a role.[30] In a small study, autoantibodies to the angiotensin II receptor were present in 12/17 patients with hypovolemic POTS.[33] In addition, patients with hypovolemic POTS showed a mitigated blood pressure increase to infused angiotensin II, which could be explained by autoantibodies acting as a functional antagonist to the angiotensin II receptor.[32]

Deconditioning may also be an important contributor to hypovolemic POTS. After just 16 days of spaceflight, astronauts had an almost 6% decrease in blood volume.[31] In previously healthy individuals, 2 weeks of bed rest resulted in a 17% reduction in plasma volume and a 10% reduction in stroke volume.[34] A reduction in intravascular volume leads to a reduction in blood pressure, which is sensed by baroreceptors and leads to an increase in heart rate and blood vessel constriction to maintain blood pressure.

Clinical presentation

Patients with hypovolemic POTS are more likely to be young and report significant weakness and exercise intolerance. Decreased lower extremity muscle mass is noted on physical exam.[35] Although the exact prevalence of migraine has not been reported in hypovolemic POTS, it appears lower than those with neuropathic and hyperadrenergic POTS.[36,37]

Hyperadrenergic POTS

It is estimated that 25% to 50% of patients with POTS have a hyperadrenergic state.[38] Hyperadrenergic POTS is characterized by an exaggerated sympathetic response to standing, defined as an increase in systolic blood pressure more than 10 mmHg or an orthostatic NE level greater than 600 pg/ml.[38]

Pathophysiology

For the majority of patients, a secondary hyperadrenergic state develops to maintain blood pressure in patients with primary neurogenic or hypovolemic POTS (Figure 1).[18] However, in a minority of patients, alterations to the NE transporter or autoantibodies to ARs may cause primary hyperadrenergic POTS. At the synaptic junction, 80% to 90% of released NE is recycled through the NE transporter and 20% spills over into the circulation.[39] Genetic missense mutations, autoantibodies, and epigenetic modifications that decrease NE transporter function increase NE spillover into the circulation.[40,41] Finally, in a subset of patients, it has been hypothesized that mast cells, located in close proximity to blood vessels and peripheral nerves cells, may be activated by catecholamines and release vasodilators that lead to venous pooling.[20] However, this mechanism requires further study.

Clinical presentation

In a case series of 27 patients with hyperadrenergic POTS, the most common symptoms included anxiety (67%), tremulousness (67%), excessive sweating (52%), and fatigue (51.9%). The most common comorbidities were hypertension (28.9%) and migraine (29.6%).[36]

MIGRAINE AND POTS PATHOPHYSIOLOGY

The etiology underlying the comorbidity of POTS and migraine is not understood. Activation of brain regions involved in both regulation of the autonomic nervous system and pain generation are thought to underlie prominent autonomic symptoms experienced by many migraineurs (e.g., nausea, vomiting, fatigue).[42] There is also accumulating evidence that local and systemic actions of the sympathetic nervous system play an important role. In this section, we first briefly review sympathetic nervous system physiology focusing on its main effector molecule, NE. We then discuss findings that suggest systemic NE may act to increase vulnerability to POTS and migraine through actions at α-AR.

Sympathetic nervous system physiology

There are two sources of NE: (1) post-ganglionic sympathetic efferents, which release NE at high concentrations into the synaptic junction where it acts on local α- and β-ARs, and (2) the sympathoadrenal medullary system, which is activated by the hypothalamus in response to stress and releases NE into the circulation.[43] Norepinephrine has a higher binding affinity to α-ARs compared to β-ARs.[44] As NE plasma concentrations are lower than those found at the synaptic junction, circulating NE acts predominantly at α-ARs, while NE released into the synaptic junction acts at local α- and β-ARs.[45] Arterioles and venules are constricted by activation of α1-ARs and dilated by activation of β2-ARs.[26] Norepinephrine also impacts immune system signaling. On the surface of B-cells and T-cells, NE binding to α-ARs increases pro-inflammatory cytokines, tumor necrosis factor alpha, and interleukin-6.[46]

Pathophysiology in POTS and migraine

Central sensitization, an important feature of migraine,[47] has recently been demonstrated in patients with POTS (both with and without migraine) and may be a significant shared pathophysiology.[48] Central sensitization in POTS and migraine may involve elevations in pro-inflammatory cytokines[47,49] as well as interactions between pain and autonomic circuitry.[50]

As discussed in section 2.0, post-ganglionic sympathetic denervation and augmented activity of the sympatho-adrenal medullary axis contribute to the development of neurogenic and hyperadrenergic POTS, respectively. There is emerging evidence that similar pathology exists in people with migraine.[42] A recent study at the Cleveland Clinic reported that close to 50% of people with migraine had evidence of small fiber neuropathy on skin biopsy.[51] The clinical significance of small fiber neuropathy in those with migraine is not known. However, this finding aligns with previous studies performed in people with migraine that report hypersensitivity of vascular α1-ARs,[22,52,53] decreased inter-ictal plasma levels of NE,[54] and enhanced cold-induced vasoconstriction.[52,55] It has been posited that sympathetic denervation may also impact cerebral hemodynamics.[56] Reduced cerebral perfusion has been demonstrated during migraine[46] and in patients with POTS during an orthostatic challenge.[47] Similar to patients with POTS, the release of NE via the stress activated sympatho–adrenal–medullary axis pathway appears to be intact in patients with migraine. Compared to inter-ictal levels, plasma concentration of NE, free fatty acids, cyclic adenosine monophosphate, and dopamine beta hydroxylase are elevated during migraine.[57] Thus, it can be hypothesized that people with migraine with sympathetic denervation and an elevation in catecholamines during migraine are similar to patients with neuropathic POTS and hyperadrenergic compensation.

TREATMENT

In this section, we review non-pharmacologic and pharmacologic treatment options targeting pathophysiologic mechanisms that lead to POTS. Treatments relevant to migraine management are highlighted. In the final subsection, migraine treatments that may influence POTS symptoms are discussed.

Treatments that increase blood volume

Non-pharmacologic

Cardiovascular exercise increases plasma volume and is a critical component of POTS treatment. Compared to propranolol, 3 months

of exercise training was superior at improving orthostatic hemodynamics, increasing plasma volume, and improving quality of life.[58] In a meta-analysis, approximately 70% of patients with POTS who completed a 3-month exercise regimen reported improved symptoms and no longer had hemodynamic changes that met criteria for POTS. To improve compliance with an exercise regimen, it is recommended that patients begin with recumbent or semi-recumbent forms of exercise and gradually increase intensity and frequency.[59]

Hydration with 2–3 L of water per day is an important therapy for all patients with POTS. Rapid ingestion of approximately 500 ml of water reduced orthostatic heart rate increase by 15 bpm.[60] Augmentation of dietary salt and electrolytes should accompany hydration to increase effectiveness of volume expansion and prevent hyponatremia. One small prospective study demonstrated that six consecutive days of a high-sodium diet (300 mEq/day) had a beneficial effect on orthostatic hemodynamics compared to a low-sodium diet (10 mEq/day).[16] A gradual increase in dietary salt is preferable to salt tablets, as tablets may acutely increase the osmotic load and cause gastrointestinal symptoms. There is inconsistent evidence for intravenous infusions of normal saline.[61] Given complications associated with central catheters and repeated infusions, intravenous normal saline infusions are not recommended as a long-term treatment for patients with POTS.[62]

For the patient with migraine and POTS, studies have demonstrated hydration, increased dietary sodium, and cardiovascular exercise may also improve migraine control. Several studies have demonstrated that increased water intake may be associated with a reduction in migraine frequency, severity, and duration for some patients.[63–65] Findings from the National Health and Nutrition Examination Survey indicate an inverse relationship between dietary sodium intake and migraine for females with a body mass index < 50%.[66] Finally, regular cardiovascular exercise is recommended to decrease migraine frequency.[67,68] Compared to people with migraine who completed moderate continuous exercise, those who completed a 12-week regimen of high-intensity exercise training had fewer migraine days and superior retinal vascular adaptations, a marker of cerebrovascular health.[69] However, the optimal frequency and intensity needed to improve migraine for patients with POTS is not known and patients should be encouraged to gradually increase exercise intensity and frequency. The mechanism linking these non-pharmacologic interventions and improved migraine control is not well understood. It has been hypothesized that increased intravascular volume (through hydration and dietary sodium)[70,71] and augmented cardiac output (through high-intensity cardiovascular exercise) both increase cerebral perfusion and modulate neuronal excitability; this in turn may be beneficial in patients with migraine given the literature suggesting a role for cortical hyperexcitability in migraine pathophysiology.[72,73]

Pharmacologic

Fludrocortisone is a synthetic mineralocorticoid that is functionally similar to aldosterone and structurally related to cortisol. It is used to increase plasma volume through retention of sodium.[74] There are no randomized controlled clinical trials evaluating the use of fludrocortisone in patients with POTS. However, several small observation studies indicate it may be helpful, particularly for pediatric POTS[75] or for patients with low aldosterone.[62] Fludrocortisone is associated with hypokalemia, and electrolytes must be regularly monitored. In patients with migraine and POTS, fludrocortisone should be used with caution, as it may exacerbate migraine.[76]

Treatments that increase venous return

Non-pharmacologic

Application of external compression (e.g., compression stockings and abdominal binders) aids vasoconstriction of vascular beds and may be useful for all subtypes of POTS. Physical maneuvers (e.g., leg crossing, lower extremity muscle squeezing) that increase venous return could be useful; however, randomized clinical trials are needed to evaluate efficacy.[77]

Pharmacologic

Midodrine, a peripheral α1-AR agonist, is a vasoconstrictor used to decrease venous pooling. In a crossover study, midodrine reduced postural tachycardia and increased vascular constriction in the calf of patients with neuropathic POTS.[78] However, a similar benefit was not seen for patients with hyperadrenergic POTS.[78] The recommended starting dose of midodrine is 2.5 mg three times a day and can be increased to a maximum of 10 mg three times a day. This medication should not be prescribed to patients with POTS with evidence of enhanced vasomotor activity (e.g., Raynaud's syndrome, acrocyanosis, hypertension) as it may increase the risk of reversible cerebral vasoconstriction syndrome.[79] Increasing actions of NE through its precursor, droxidopa[80] or atomoxetine, a NE transporter inhibitor,[81] have been trialed in patients with POTS. However, clinical improvement is minimal and the effect on migraine has not been studied.

Treatments that decrease sympathetic activity

Non-pharmacologic

Application of external compression, hydration, and dietary salt is important to maintain cardiac output, preventing baroreceptor offloading and compensatory activation of the sympathetic nervous system (see section 4.1).

Pharmacologic

β-blockade has been a pharmacologic foundation for the treatment of orthostatic intolerance in POTS patients.[82] Numerous β-blockers

exist and vary in their affinity and specificity for β-receptor subtypes. A recent clinical trial compared 3 months of propranolol to bisoprolol in treating symptoms of orthostatic intolerance and quality of life in patients with POTS.[83] Both treatments resulted in significant improvement in patient-reported orthostatic tolerance, quality of life, and depression scores. Symptoms reported by patients taking 10–20 mg of propranolol twice a day were modestly improved compared to patients taking 2.5 or 5 mg of bisoprolol once a day. However, authors report that this was not a statistically significant difference.[83]

For individuals with migraine with comorbid POTS, β-blockers may improve the symptoms of both conditions. There is level A evidence for the use of propranolol, metoprolol, and timolol for migraine prevention. However, for those with migraine and POTS, these medications may cause worsening fatigue and hypotensive episodes at doses needed to prevent migraine.[84] Propranolol has been shown to decrease cerebral blood flow velocity and frontal lobe oxygenation.[85] Nebivolol, although not as extensively studied for migraine prophylaxis, may be a better choice. It is a highly selective β1-AR that increases endothelial nitric oxide production and does not negatively impact cerebral hemodynamics.[85,86] In a randomized, double-blind study, nebivolol 5 mg was found to be equally as effective as 142.5 mg of metoprolol in preventing migraine attacks. However, a lower percentage of patients taking nebivolol (44%) reported fatigue compared to metoprolol (79%).[87] This is a significant benefit for patients with POTS, as fatigue can be a debilitating component of the disease.

Treatments that increase vagal activity

Non-pharmacologic

Several small observational studies suggest non-invasive vagal nerve stimulation (nVNS) may decrease orthostatic tachycardia in POTS patients.[88] Currently, five clinical trials registered on ClinicalTrials.gov act are evaluating nVNS for the treatment of POTS. As nVNS is a US Food and Drug Administration–approved treatment for migraine and cluster headache,[89] nVNS may provide dual benefit for those with migaine and POTS.

Pharmacologic

Acetylcholine is the main neurotransmitter used by the vagus nerve. Pyridostigmine bromide is an acetylcholinesterase inhibitor that augments the effect of acetylcholine, by inhibiting its breakdown in the synaptic cleft and increasing its interaction with both nicotinic and muscarinic receptors. In a randomized crossover design, a single dose of 30 mg pyridostigmine significantly decreased both tachycardia and symptom burden in patients with POTS.[90] No studies have examined the impact of pyridostigmine on migraine.

Treatments that reduce immune activation

Several case series and retrospective analyses suggest immunomodulatory treatment may be beneficial for patients with refractory POTS. In a study of six patients with POTS, 6 months of intravenous immunoglobulin (IVIG) at a dose of 1 g/kg was associated with a 40% decrease in symptom severity and an improvement in cardiovascular function.[91] In a retrospective study of 38 patients with refractory dysautonomia, the presence of anti-phospholipid antibodies or Sjogren's antibodies predicted a successful response to IVIG.[92] A randomized, placebo-controlled trial is now underway to study the safety and efficacy of IVIG in POTS patients. The most common side effect of IVIG is headache, and an exacerbation of migraine may occur for patients with migraine and POTS.[93]

Migraine treatments that may influence symptoms of POTS

Several migraine prophylactic treatments should be avoided in patients with both migraine and POTS. The anticholinergic actions of amitriptyline, a tricyclic antidepressant (TCA), may exacerbate tachycardia and fatigue.[94] Protriptyline is an activating TCA and may be preferable for those with migraine and POTS.[84] Venlafaxine, a mixed serotonin and NE reuptake inhibitor, may worsen symptoms related to excessive catecholamines.[84] Finally, the word-finding difficulties and cognitive slowing reported by patients taking topiramate may be particularly problematic for patients with POTS. It is not known how numerous medications commonly used to treat migraine, including steroids, triptans, onabotulinumtoxinA, and calcitonin gene-related peptide antagonists, impact POTS. Migraine treatments that decrease peripheral and central sensitization, including onabotulinumtoxinA[95] and calcitonin-gene-related peptide antagonists,[96] may improve POTS symptoms, but this has not been studied.

CONCLUSIONS

The high prevalence of migraine in patients with POTS may be explained by common pathologic mechanisms. There is accumulating evidence that local and systemic actions of NE may increase vulnerability to both POTS and migraine. In addition, central sensitization, peripheral neuropathy, as well as alterations in peripheral and cerebral hemodynamics are common to both diseases. Treatment options for POTS are limited and many questions remain regarding management of migraine in the setting of POTS. Therefore, an understanding of shared pathophysiology may provide critical insight into the development of individualized treatment strategies for patients with POTS and migraine and inform future studies aimed at identifying novel therapeutic targets.

AUTHOR CONTRIBUTIONS

Study concept and design: Bridget R. Mueller, Jessica Robinson-Papp. *Drafting of the manuscript*: Bridget R. Mueller. *Revising it for intellectual content*: Jessica Robinson-Papp. *Final approval of the completed manuscript*: Bridget R. Mueller, Jessica Robinson-Papp.

CONFLICTS OF INTEREST

There are no conflicts for any author.

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