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Review

Evaluation of postural tachycardia syndrome (POTS)

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ABSTRACT

The diagnostic evaluation of a patient with suspected postural tachycardia syndrome (POTS) requires a thoughtful diagnostic approach utilizing a careful clinical history and examination, laboratory, and autonomic testing. This article outlines the importance of a thorough history in identifying mechanism of symptom onset, clinical features, associated clinical conditions or disorders, and factors that may result in symptom exacerbation. The clinical examination involves an assessment of pupillary responses, an evaluation for sudomotor and vasomotor signs, and an assessment for joint hypermobility. Laboratory testing helps to exclude mimics of autonomic dysfunction, recognize conditions that may exacerbate symptoms, and to identify conditions that may cause or be associated with autonomic nervous system disease. The purpose of autonomic testing is to confirm a POTS diagnosis, exclude other causes of orthostatic intolerance, and may provide for characterization of POTS into neuropathic and hyperadrenergic subtypes. Other diagnostic studies, such as epidermal skin punch biopsy, exercise testing, radiographic studies, sleep studies, gastrointestinal motility studies, and urodynamic studies should be considered when clinically appropriate.

1. Introduction

The evaluation of suspected postural tachycardia syndrome (POTS) requires a careful history, thorough clinical examination, and a thoughtful diagnostic evaluation. Delays in diagnosis and misdiagnoses are commonplace prior to establishing a definitive diagnosis of POTS. Data from a large survey of nearly 700 patients with POTS patients, self-reported a median time to diagnosis of just under 6 years, with 27% of the respondents reporting having been seen by > 10 physicians prior to diagnosis, and 83% of respondents reported being given a psychiatric diagnosis prior to being diagnosed with POTS (Stiles). While precise prevalence rates are not known, it has been suggested that POTS is one of the most common conditions to affect young females (Robertson et al., 2000). POTS has been estimated to affect over 500,000 individuals in the United States alone (Robertson, 1999).

The purpose of the diagnostic evaluation of a patient with suspected POTS is to confirm the presence of an excessive postural tachycardia, exclude other conditions that have the potential to mimic autonomic nervous system impairment (see Table 1), identify conditions that may be associated with or causative of autonomic dysfunction, and to exclude conditions that may exacerbate autonomic nervous system impairment. A careful history is necessary to establish the timing and mechanism of symptom onset, involves a thorough autonomic review of systems (see Table 2), and a careful medication and family history. Identification of other co-morbid conditions, particularly those commonly reported by POTS patients is another critical aspect of the evaluation. Given the heterogeneity of the clinical features associated with POTS, an individualized approach to the diagnostic evaluation is warranted.

2. History

A major focus of the clinical history is to establish the timing and mechanism of symptom onset. The majority of POTS patients report symptom onset from early teens through the 5th decade (Thieben et al., 2007). It is not uncommon for patients to report more modest symptoms of orthostatic intolerance, such as postural lightheadedness or rare episodes of vasovagal syncope in their teens, prior to developing more fulminant and severe symptoms in their late teens or twenties. POTS is more frequent in females; with a female to male ratio of at least 4.5:1 (Benarroch, 2012). Symptoms may develop acutely (< 1 month), subacutely (1–3 months), or more insidiously (> 3 month) (Thieben et al., 2007). A meticulous review of symptom onset is necessary to identify conditions that may have precipitated POTS. An antecedent history of infection is the most commonly reported (potential) precipitating event, occurring in upwards of 50% of patients (Low et al., 1995; Sandroni et al., 1999; Thieben et al., 2007). These infections are most typically upper respiratory or gastrointestinal viral illnesses (Thieben et al., 2007). Onset following a surgical procedure is sometimes reported (Thieben et al., 2007; Mathias et al., 2012) but is significantly less common than a post-infectious onset. Rarely, symptoms may begin during or following pregnancy. Symptom onset with or following

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Table 1
Conditions that mimic, cause or are associated with postural tachycardia syndrome (POTS).

Conditions that may mimic POTS
Mastocytosis
Adrenal insufficiency
Anemia
Pheochromocytoma, Paraganglioma
Carcinoid
Thyroid disease
Deconditioning
Cardiomyopathy
Panic disorder
Conditions that may be associated with POTS
Ehlers-Danlos syndrome
Concussion
Celiac disease
Hashimotos thyroiditis
Antiphospholipid antibody syndrome
Sjögren syndrome
Systemic lupus erythematosis
Mast cell activation syndrome
Mitochondrial cytopathy
Autism Spectrum Disorder
Gastroparesis
Gastrointestinal dysmotility
Chronic migraine
New daily persistent headache

Table 2
Autonomic review of systems.

Sudomotor
Hyperhidrosis
Hypohidrosis
Anhidrosis
Heat intolerance
Secretomotor
Dry eyes
Dry mouth
Adrenergic
Postural lightheadedness
Near-syncope
Syncope
Gastrointestinal
Dysphagia
Early satiety
Abdominal bloating
Constipation
Diarrhea
Genitourinary
Nocturia
Incomplete bladder emptying
Urinary retention
Impotence

concussion has been scarcely reported (Kanjwal et al., 2010) though is an under-recognized precipitating event. Notably, autonomic testing in concussion patients has demonstrated findings typical of those seen in POTS (Goodman et al., 2013; Heyer et al., 2016). A substantial number of POTS patients will have no identifiable antecedent event or precipitant for their condition, even in those with acute-subacute symptom onset. A minority of patients will report a family history of orthostatic intolerance (Thieben et al., 2007).

2.1. Orthostatic symptoms

POTS patients by definition (see Table 3) should have symptoms of orthostatic intolerance. These symptoms typically include postural lightheadedness, near-syncope, heart racing (tachycardia), and palpitations. A history of vasovagal syncope is not uncommon. However, it is critical to recognize that any symptom present when upright, that resolves or improves with recumbency may reflect orthostatic intolerance

Table 3
POTS criteria.

1. Heart Rate increment ≥30 beats/min within 10 min of standing or head-up tilt in individuals
2. Heart Rate increment ≥40 beats/min in children/adolescents
3. Absence of orthostatic hypotension (decrease in systolic blood pressure of 20 mm Hg and diastolic blood pressure of 10 mm Hg)
4. Postural symptoms

and must be recognized as a potential symptom associated with POTS. Examples of such symptoms include nausea, chest pain, vertigo, unsteadiness, leg weakness, extremity paresthesias, dyspnea, headache, neck pain, visual symptoms, anxiety, tremor, diaphoresis, flushing, and cognitive symptoms. Failure to recognize these symptoms as a form of orthostatic intolerance is likely a major reason for delays in establishing a diagnosis of POTS. Furthermore, the aforementioned symptoms may not necessarily be solely postural. It is not uncommon, for example, for tachycardia in POTS patients to occur nocturnally and even awaken patients from sleep.

Factors other than postural change may exacerbate or even precipitate the aforementioned symptoms (Mathias et al., 2012). Many patients report that symptoms are worse in the morning, particularly upon awakening. Other common exacerbating factors include showering, dehydration, heat, food ingestion, menses, physical exertion, alcohol, and deconditioning. Insomnia may exacerbate symptoms or contribute to persistent fatigue. Exacerbation of or persistent headache or migraine may be associated with symptom worsening. Regardless of the initial mechanism of symptom onset, a surgical procedure, concussion, or infection may result in a period of transient POTS symptom exacerbation. A careful medication history is also critical, as certain medications may result in symptom exacerbation. Examples of medications (and substances) that might mimic or exacerbate POTS include stimulant medications, α and β blockers, calcium channel blockers, serotonin and norepiphrine reuptake inhibitors, monoamine oxidase inhibitors, and phenothiazines (Agarwal et al., 2007; Cheshire, 2016).

2.2. Non-orthostatic, non-autonomic symptoms

As noted above, a number of non-orthostatic, non-autonomic symptoms, may be reported by POTS patients. Fatigue is a prominent symptom in many patients, adversely impacting quality of life and activity level. It is not uncommon for POTS patients to be diagnosed with chronic fatigue syndrome at some point during their clinical course. Fatigue may be impacted by sleep complaints, which are also common in POTS patients. Indeed, 1 study of 44 POTS patients identified more severe sleep disturbances, higher fatigue, and excessive daytime somnolence relative to normal controls (Bagai et al., 2011). Cognitive complaints (often characterized by patients as “brain fog”) are present in a significant majority of POTS patients and is disabling for some. Neuropsychological testing in 28 POTS patients identified significant impairment in selective attention, executive function, and cognitive processing speed relative to healthy controls (Arnold et al., 2015). Notably, memory function, sustained attention, psychomotor speed, and verbal fluency were not significantly different in POTS patients relative to controls in this study.

2.3. Autonomic review of systems

An autonomic review of systems is necessary to establish the extent of autonomic system involvement. While delineating the presence and extent of orthostatic intolerance symptomatology is critical in establishing a diagnosis of POTS, significant impairment of other autonomic systems occurs (particularly gastrointestinal) and may be a source of significant disability for patients. Patients should be queried as to the presence of dry eyes and dry mouth, which can be seen in patients with

autonomic neuropathy and other conditions associated with autonomic failure. Gastrointestinal symptoms are commonly reported in POTS patients (Thieben et al., 2007). All patients should be questioned about dysphagia, early satiety, nausea, vomiting, abdominal pain, constipation, and diarrhea. Urinary symptoms such as increased frequency, difficulty initiating urination, nocturnal enuresis, and incomplete bladder emptying, may be reported by POTS patients. Thermoregulatory or sweating impairment may be suggested by symptoms such as heat intolerance, cold intolerance, hyperhidrosis, or hypohidrosis.

2.4. Co-morbid conditions

The clinical history should also focus on establishing whether any associated (non-autonomic) conditions are present. In the author's experience, migraine and hypermobile Ehlers-Danlos syndrome are the most common co-morbid conditions. These conditions must be identified if present, as they may influence POTS management (Kanjwal et al., 2010; Miglis et al., 2017). Clinical features such as hypermobile joints, “double-jointedness”, joint dislocations, and clicking joints, are suggestive of EDS (Mathias). The recently revised hypermobile EDS criteria has established a 5 point questionnaire for assessing hypermobility, with affirmative responses of 2 or more of these items considered positive for hypermobility (see Table 4) (Malfait et al., 2017). This questionnaire is particularly useful in those who have physical limitations that may preclude calculation of a Beighton score.

Migraine without aura is the most common headache type associated with POTS (Khurana and Eisenberg, 2011); but other types of headache may occur, including migraine with aura, chronic migraine, tension type headache, new daily persistent headache, and an orthostatic headache that mimics a cerebrospinal fluid leak (Mokri and Low, 2003). Headache may develop prior to, concomitant with, or subsequent to the development of POTS (Khurana et al., 2010). Diffuse pain symptoms/syndromes may be reported by POTS patients, including arthralgias and myalgias, the latter of which are not uncommonly attributed to fibromyalgia (Staud, 2008). Mast cell activation syndrome (MCAS), discussed in a later chapter in this issue, is a common co-morbid condition in POTS patients (Shibao et al., 2005). Symptoms particularly suggestive of MCAS in POTS patients include flushing, hives, diarrhea, itchy skin, and urinary irritability. Chronic fatigue is a commonly reported symptom in POTS patients, and there may be similar clinical characteristics in POTS and chronic fatigue syndrome (Rowe et al., 1995; Stewart et al., 1999). Other clinical conditions present in a minority, but substantial number of POTS patients include celiac disease, Hashimotos thyroiditis, Sjögren syndrome, and irritable bowel syndrome.

3. Physical examination

The general physical examination is a critical component of the evaluation of suspected POTS, and should include a careful cardiac, dermatologic, and neurological examination (Benarroch, 2012). Supine and standing heart rate and blood pressure measurements may demonstrate an excessive increase in heart rate of > 30 beats per minute (bpm) in adults 18 years of age or older, > 40 bpm when younger than age 20, or a heart rate of > 120 bpm with standing. POTS patients by definition should not have sustained orthostatic hypotension. A careful cardiac examination is necessary to exclude structural heart disease. Pupillary responses to light should be assessed, and if abnormal (sluggish or absent responses), are typically a sign of an autonomic neuropathy. Fundoscopic examination to exclude papilledema in a patient with headache is necessary to rule out intracranial hypertension. The neurological examination may rarely show evidence of a small fiber neuropathy (diminished pinprick or temperature sensation in the extremities) but should be otherwise normal in POTS patients.

Excessive resting sweat on the palms and feet may suggest hyperhidrosis or excessive sympathetic activation. Conversely, dry skin and dry oral mucosa may indicate secretomotor impairment as can occur with medication effect (particularly anticholinergic medications) or with Sjögren syndrome. Excessive swelling in the distal lower limbs, and rarely the hands and abdomen with standing, may reflect excessive venous pooling. The presence of postural, color change in the feet and hands reflects vasomotor instability, and may manifest as blotchy, marbled, mauve or purple skin. The presence of flushing, typically present on the face and upper chest and hives, should alert the clinician to possible MCAS. Livedo reticularis may be seen in POTS patients with antiphospholipid antibody syndrome (Schofield et al., 2014).

The examination should also involve an assessment of skin and joints for hypermobile EDS. Dermatologic signs of EDS include soft or velvety skin, mild skin hyperextensibility, unexplained striae (no history of significant weight change), bilateral piezogenic papules of the heel, and atrophic scarring of at least 2 sites (Malfait). Assessment of joint hypermobility may be quantified by calculating a Beighton score, with a score ≥ 5 in those ranging from post-puberty up to age 50 suggestive of hypermobility (Malfait et al., 2017).

Table 4
Hypermobility 5-point questionnaire.

1) Can you now (or could you ever) place your hands flat on the floor without bending your knees?
2) Can you now (or could you ever) bend your thumb to touch your forearm?
3) As a child, did you amuse your friends by contorting your body into strange shapes, or could you do the splits?
4) As a child or teenager did your shoulder or kneecap dislocate on more than one occasion?
5) Do you consider yourself double-jointed?

An answer of yes, to 2 or more of these questions suggests joint hypermobility with 80–85% sensitivity and 80–90% specificity. Malfait et al., 2017.

3.1. POTS subtypes

It has been suggested that POTS is a “final common pathway” resulting from a number of different pathophysiologic mechanisms (Raj, 2006). It is notable that symptoms attributed to POTS resulting from concussion, and presumably impairment of central autonomic control, are often indistinguishable from those resulting from an (peripheral) autonomic neuropathy. Identification of different subtypes of POTS may be useful, though it must be recognized that these classification schemes are descriptive, and different POTS subtypes may be concomitantly present. Primary POTS subtypes include: Hyperadrenergic POTS, Neuropathic POTS, and POTS with Volume dysregulation (Benarroch, 2012).

Hyperadrenergic POTS may be identified by observing orthostatic hypertension, excessive phase IV overshoot on the Valsalva maneuver, and a standing norepinephrine level that exceeds 600 pg/mL (Thieben et al., 2007; Raj, 2013). There are currently no consensus criteria for what constitutes neuropathic POTS, though abnormal results on quantitative sudomotor axon reflex testing, distal impairment on thermoregulatory sweat testing, and abnormal epidermal skin punch biopsy may provide evidence in favor of a peripheral process affecting autonomic and small fiber nerves (Thieben et al., 2007; Gibbon et al., 2013). Many POTS patients have been demonstrated to have low plasma, red cell, and total blood volumes (Streeten et al., 2000; Raj and Robertson, 2007; Stewart et al., 2009). Some POTS patients with hypovolemia have been demonstrated to have reduced standing renin and aldosterone levels relative to normal controls with normovolemia. Furthermore, some patients have had inappropriately high angiotensin II levels without an increase in the metabolite angiotensin, suggesting abnormal angiotensin II metabolism (Stewart et al., 2009). Additionally, POTS patients have been demonstrated to have an impaired vasopressor response to angiotensin II (Mustafa et al., 2012); a finding that may contribute to blood pressure instability and postural tachycardia in POTS patients.

Table 5
Laboratory evaluation of POTS.

Consider in all suspected POTS patients
Complete blood count
Thyroid cascade
Vitamin B12
Am cortisol
Serum and urine metanephrines
Antinuclear antibody
ssa, ssb
Consider in POTS patients with chronic, refractory symptoms; particularly those with autonomic neuropathy or GI dysmotility
Dysautonomia autoantibodies: voltage gated potassium channel complex, N-type calcium channel antibodies, P/Q-type calcium channel antibodies, ganglionic AChR antibodies
Antiphospholipid antibodies: lupus anticoagulant, anticardiolipin antibodies, beta-2-glycoprotein antibodies
Complement: total, C3, C4
Supine and standing catecholamines
Serum tryptase
24 h urine studies: *n*-methylhistamine, 11-beta prostaglandin F2, leukotriene E4

4. Diagnostic evaluation

Given that there is not a single test that is sufficiently or exclusively diagnostic of POTS, much of the diagnostic evaluation is focused on excluding conditions that may mimic or exacerbate POTS and identifying co-morbid conditions that impact management. Ideally, formal autonomic testing may suggest potential mechanisms of symptom manifestation, which better inform treatment decisions. The following discussion is not intended to suggest that all diagnostic studies be done on all POTS patients, but rather to serve as a guide for test selection in particular clinical circumstances, and is also intended to serve as a review of the current state of diagnostic testing in POTS patients.

4.1. Laboratory studies

Basic laboratory studies should be considered in all POTS patients, including a complete blood count, thyroid cascade, am cortisol, plasma and urinary metanephrines, vitamin B12, celiac testing, antinuclear antibody testing, and Sjögren antibody testing (ssa, ssb), (see Table 5) (Benarroch, 2012). Assessment of plasma supine and standing catecholamines may be helpful in elucidating baroreflex sympathoexcitation and in providing evidence of hyperadrenergic POTS (Benarroch, 2012). The extent of laboratory testing should be influenced by the duration, severity, and treatment responsiveness of the patient's condition. In patients with chronic, severe, and refractory symptoms, more extensive laboratory testing may be indicated, and particularly in individuals with significant systemic symptoms, the author recommends aggressive pursuit of autoimmune causes. Additional autoantibody testing can be considered, including voltage-gated potassium channel complex antibodies, N-type calcium channel antibodies, ganglionic acetylcholine receptor antibodies, and P/Q-type calcium channel antibodies. The prevalence of these autoantibodies in POTS patients may not be increased relative to the general population (this is the author's experience); however, these autoantibodies have been associated with autonomic neuropathy and autoimmune gastrointestinal dysmotility (Flanagan et al., 2014), both conditions that may share some clinical resemblance to POTS. Whether these autoantibodies have clinical significance in POTS, in the absence of autonomic neuropathy or gastrointestinal dysmotility is not clear at this time.

A number of novel autoantibodies have been reported in association with POTS patients, though additional research is necessary to determine the role and clinical significance of these antibodies in clinical practice. A study of 14 POTS patients demonstrated the presence of α1 adrenergic receptor and β1 adrenergic receptor autoantibodies in all patients, presence of β2 adrenergic autoantibodies in half of the POTS patients, and absence of these antibodies in normal controls (Li et al., 2014). The authors suggest that antagonistic antibodies to α1 AR receptors may result in failure of peripheral vasoconstriction to orthostatic demands, and that activating, agonistic antibodies to β1 and β2 adrenergic receptors may accentuate the compensatory tachycardia in these patients. More recently the presence of these antibodies in a cohort of 17 European patients with POTS was reported, with 8 patients demonstrating α1 adrenergic autoantibodies, 11 with β1 adrenergic antibodies, and 12 with β2 adrenergic antibodies (Fedorowski et al., 2016). Additional research is necessary to validate these findings in larger POTS cohorts.

POTS has been associated with antiphospholipid antibody syndrome (Schofield et al., 2014), as well as Sjögren syndrome (Goodman, 2017; Goodman et al., 2017). Further research is necessary to determine whether these conditions are causative of autonomic (and systemic) signs and symptoms in POTS, and most importantly whether there is a role for immunotherapy in these conditions. Sjögren syndrome is a common autoimmune disorder characterized by keratoconjunctivitis sicca and xerostomia (dry eyes and dry mouth), and the development of systemic, extraglandular involvement occurs in at least 1/3 of patients. Establishing a diagnosis of Sjögren syndrome can be problematic given that sicca symptoms not infrequently develop after neurological or autonomic signs develop (Goodman, 2017), and the significantly suboptimal sensitivity of standard Sjögren syndrome (ss-a, ss-b) antibodies (Birnbaum, 2010). A novel Sjögren syndrome antibody panel includes antibodies to salivary gland protein-1, parotid secretory protein, and carbonic anhydrase VI; may have a role in establishing a diagnosis in patients with suggestive signs and symptoms (Suresh et al., 2015). While more research is necessary to validate and determine the significance and role of these antibodies in clinical practice, minor salivary gland biopsy is an accepted diagnostic tool used to confirm a diagnosis of Sjögren syndrome (Shiboski et al., 2017). Further studies are necessary to determine the role of minor salivary gland biopsy in POTS patients.

A history of multiple, repeated infections should prompt consideration of immunoglobulin quantification and possibly, immunology referral for evaluation of possible immunodeficiency. Patients with a strong family history of autonomic dysfunction and a POTS phenotype, particularly those with significant gastrointestinal dysmotility, might benefit from genetics consultation and consideration of genetic testing for mitochondrial disorders. Genetic testing is not at this point recommended for hypermobile EDS.

4.2. Cardiac testing

Cardiac testing should be considered in all patients, including electrocardiogram, echocardiogram, and 24-h Holter monitoring. The purpose of this testing is to exclude significant, structural cardiac disease and inappropriate sinus tachycardia (IST) or other forms of cardiac dysrhythmia. IST may be difficult to distinguish from POTS, as this condition is also characterized by high heart rates and symptoms of orthostatic intolerance, predominantly in young women. Tachycardia in IST is typically not posturally-mediated and resting heart rate commonly exceeds 100 bpm (Nwazue et al., 2014). Most patients with POTS become deconditioned at some point during their symptom course, and formal exercise testing can be considered to assess exercise capacity. A comprehensive study involving formal exercise testing in 184 patients with orthostatic intolerance, identified deconditioning (defined as $VO_{2max} < 85\%$) in 90% of the patients in this cohort (Parsaik et al., 2012).

4.3. Neurologic testing

A brain MRI with and without contrast should be considered in patients with chronic migraine, orthostatic headache, and new daily persistent headache. While many POTS patients have at least a modest postural component to their headaches (Khurana and Eisenberg, 2011),

a headache that is primarily orthostatic should prompt an investigation for spontaneous intracranial hypotension, resulting from a cerebrospinal fluid (CSF) leak. Individuals with hypermobile EDS may be at increased risk for spontaneous CSF leaks (Reinstein et al., 2013; Schievink, 2006). Brain MRI findings in patients with spontaneous intracranial hypotension may demonstrate sagging of the brain, subdural fluid collections, pachymeningeal enhancement, pituitary hyperemia, subdural fluid collections, and engorgement of venous structures (Schievink, 2006). Treatment options for spontaneous intracranial hypotension range from bed rest and caffeine, to injection of autologous blood into the spinal epidural space (epidural blood patch), application of fibrin sealant, and ultimately surgical repair, if more conservative approaches are unsuccessful.

Nerve conduction studies and needle electromyography should be considered in patients with both symptoms and signs of a large-fiber peripheral neuropathy. Significant large-fiber peripheral neuropathy is uncommon in POTS patients, and if identified should prompt an aggressive diagnostic evaluation for an underlying condition responsible for both, particularly Sjögren syndrome. POTS patients may more commonly demonstrate signs and symptoms suggestive of small-fiber peripheral neuropathy (SFN). Such symptoms may include numbness, tingling, and burning extremity symptoms, along with abnormal sensory testing to pinprick and temperature. In cases of suspected SFN, epidermal skin punch biopsy should be considered. This technique involves 3 mm skin punch biopsies from proximal and distal sites in the lower limb, with application of protein gene product 9.5 that stains intraepidermal nerve fibers, and allows for calculation of intraepidermal nerve fiber density (IENFD). Decreased IENFD may be seen in patients with SFN, and abnormal findings on skin biopsy were reported in 9 of 24 POTS patients in one study (Gibbon et al., 2013). Abnormal IENFD may indicate a neuropathic form of POTS as previously discussed.

4.4. Autonomic testing

Autonomic testing should be considered in cases of suspected POTS in order to confirm the diagnosis and to provide for more precise categorization into different pathophysiologic POTS subtypes (Benarroch, 2012). Tilt-table testing (TTT) at 60° for at least 10 min, ideally with noninvasive plethysmographic blood pressure and heart rate monitoring, allows for continuous beat-to-beat assessment during head-up tilt (HUT). A sustained heart rate increment ≥ 30 bpm with HUT or heart rate ≥ 120 bpm in the absence of orthostatic hypotension suggests a diagnosis of POTS in the appropriate clinical context (see Fig. 1). A careful medication review is necessary to ensure that medication effects have not influenced HUT. Stimulant medications (or substances), calcium channel blockers, beta blockers, beta adrenergic agonists (such as isoproterenol), and nitroglycerin can affect blood pressure and heart rate during HUT, and may potentially result in a misdiagnosis of POTS or OH (Cheshire, 2016). Orthostatic hypertension, as defined by an increase in systolic blood pressure > 10 mm Hg on HUT may suggest a hyperadrenergic form of POTS (Grubb, 2008) (see Fig. 1). Beat-to-beat heart rate and blood pressure measurements often demonstrate considerable variability.

Assessment of cardiovagal reflexes involves an analysis of heart rate variability with deep breathing and the Valsalva ratio (Low et al., 1997). Cardiovagal function is only rarely abnormal in POTS patients; with only 9.9% of 152 POTS patients demonstrating abnormal cardiovagal function in 1 study (Thieben et al., 2007). Analysis of blood pressure response to the Valsalva maneuver, provides an assessment of adrenergic function (Low et al., 1997), and in POTS patients may demonstrate excessive early phase II, attenuation of late phase II, and an exaggerated phase IV overshoot. An excessive phase IV overshoot may be seen in patients with hyperadrenergic POTS (Raj, 2006; Raj, 2013).

Sudmotor function is most commonly assessed through analysis of quantitative sudomotor axon reflex testing (QSART) and much less commonly, thermoregulatory testing (TST). The QSART involves the iontophoresis of acetylcholine at 4 sites, which includes the forearm, proximal-lateral leg, medial-distal leg, and proximal foot, and provides an assessment of postganglionic sympathetic sudomotor function (Low et al., 1997). Abnormal QSART testing was reported in 42.8% of 152 POTS patients in 1 series (Thieben et al., 2007), and other smaller series reported abnormalities ranging from 33%–63% of patients (Al-Shekhlee et al., 2005; Peltier et al., 2010; Gibbon et al., 2013). Abnormal postganglionic sympathetic sudomotor function is generally considered to reflect a neuropathic form of POTS. TST involves the application of an indicator powder, followed by placement of the patient in a humidity-controlled cabinet used raise body temperature and demonstrate sweating. Abnormal findings on TST were seen in 53.8% of POTS patients in a large cohort, with most in this group demonstrating a distal pattern of sweat loss (Thieben et al., 2007).

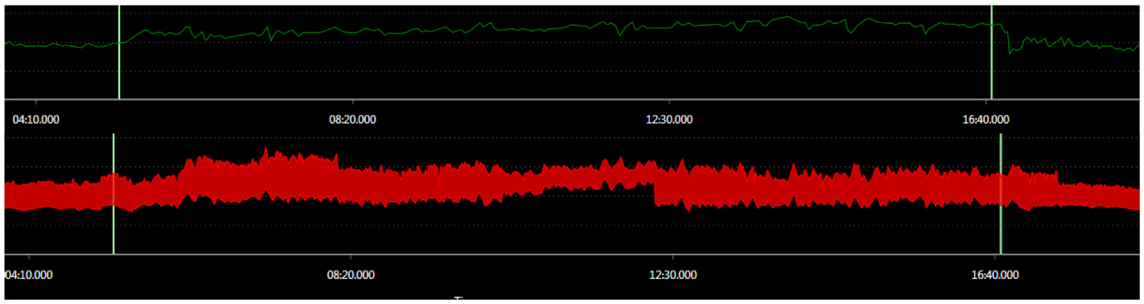
4.5. Gastrointestinal evaluation

As noted above, gastrointestinal symptoms are common in POTS patients, with nearly 70% of patients in 1 series reporting gastrointestinal symptoms (Al-Shekhlee et al., 2005). While these symptoms may reflect a visceral motility disorder, primary gastrointestinal disorders such as celiac disease, gastroesophageal reflux, esophagitis, gastritis, eosinophilic disorders, and inflammatory bowel disease must be considered and excluded through diagnostic testing, when appropriate. Lactose intolerance, fructose intolerance, cyclic vomiting, and MCAS may also contribute to significant gastrointestinal symptomatology.

Gastrointestinal symptoms in POTS patients are commonly underrecognized and suboptimally investigated, resulting in frustratingly few treatment options for patients. It is not yet known precisely how or to what extent hypermobile EDS impacts gastrointestinal function in POTS patients, though gastrointestinal involvement in EDS has been well described (Beckers et al., 2017; Fikree et al., 2017). It is not known whether the presence or severity of gastrointestinal dysmotility in POTS patients is predictive of an underlying autoimmune condition, though given the recent description of immunoresponsive autoimmune gastrointestinal dysmotility (Flanagan et al., 2014), the author recommends an aggressive autoantibody assessment in POTS patients with dysmotility. Esophageal, gastric, and intestinal motility testing should be considered in POTS patients, as indicated by the nature of symptoms. Esophageal dysmotility may be demonstrated in POTS patients with dysphagia, and gastroparesis may be seen in patients with early satiety, abdominal pain, nausea, and post-prandial abdominal bloating. Gastric emptying studies in 163 POTS patients identified rapid gastric emptying in 48% and a delay in gastric emptying in 18% of patients (Loavenbruck et al., 2015). In this cohort, vomiting was significantly associated with delayed gastric emptying, and delayed colonic transit was noted in 27% of 121 patients tested (Loavenbruck et al., 2015).

A number of different modalities may be utilized to establish the presence of an esophageal, gastric, or intestinal motility disorder (see Table 6). While plain radiograph, computerized tomography, and MR enterography may demonstrate dilated intestinal loops and are helpful to exclude mechanical obstruction, they lack adequate sensitivity in identifying a motility disorder. Gastric emptying scintigraphy involves the ingestion of a radiolabeled meal, and ideally, an assessment of retention at 0, 1, 2, and 4 h (Rao et al., 2010). Likewise, small intestine motility can be assessed through scintigraphic studies, typically as a component of whole gut transit study (Rao et al., 2010). Colonic transit using radiopaque markers allows for calculation of transit times through the colon, and has been widely adopted to assess constipation and unexplained diarrhea in patients with a suspected motility disorder (Hinton et al., 1969). Colonic transit scintigraphy is an alternative method for assessing motility in patients with regional colonic or whole gut motility disorders (Camilleri, 2010; Rao et al., 2010). Wireless

Top tracing depicts excessive heart rate increment with head-up tilt, while the lower tracing depicts collapse in pulse pressure with marked blood pressure instability in POTS patient.



Top tracing depicts excessive heart rate increment with head-up tilt; while lower tracing showing increase in blood pressure in hyperadrenergic form of POTS with associated Sjögren syndrome.

Fig. 1. Tilt-table testing in POTS.
Top tracing depicts excessive heart rate increment with head-up tilt, while the lower tracing depicts collapse in pulse pressure with marked blood pressure instability in POTS patient.
Top tracing depicts excessive heart rate increment head-up tilt; while lower tracing showing increase in blood pressure in hyperadrenergic form of POTS with associated Sjögren syndrome.

Table 6
Indications & testing modalities for motility assessment in POTS patients.

Region	Indications for testing	Testing modalities
Esophagus	Dysphagia, vomiting, chest pain, Regurgitation, reflux, nausea, Globus	Esophageal manometry Esophageal scintigraphy
Gastric	Early satiety, Nausea, vomiting, Bloating, post-prandial fullness, Upper abdominal pain	Gastric emptying scintigraphy Wireless motility capsule Breath test
Small bowel	Nausea, vomiting, bloating, Diarrhea, abdominal pain	Breath test Scintigraphy Wireless motility capsule
Large bowel	Constipation, diarrhea, Abdominal pain, bloating	Wireless motility capsule Radioopaque markers Colonic scintigraphy

motility capsule is an alternative technique that involves a single-use, ingested but non-digestible capsule that measures pH, pressure, and temperature throughout the GI tract (Rao et al., 2010). Whole gut transit time, gastric emptying, small bowel transit time, and colonic transit time can be calculated using the wireless motility capsule (Rao et al., 2010; Paine et al., 2013). Wireless motility capsule may be suboptimal in assessing gastric function relative to scintigraphic studies and is contraindicated in cases of severe dysmotility or pseudo-obstruction given a risk of capsule retention (Paine et al., 2013). Manometry studies may distinguish myopathic from neuropathic conditions in the small intestine (Stanghellini et al., 2000; Smout, 2001), may demonstrate esophageal dysmotility, and anorectal manometry may provide evidence of pelvic floor dysfunction. Breath testing involves ingestion of a non-digestible carbohydrate such as lactulose, which upon contact with enteric mucosa generates gases that transverse the mucosa, are transported to the lungs, and are exhaled, providing an assessment of small bowel tansit time (Rao et al., 2010).

Patients with gastrointestinal dysmotility are at risk for small intestinal bacterial overgrowth (SIBO), which is defined as a bacterial population in the small intestine exceeding 10^5–10^6 organisms/mL (Corrazza et al., 1990). While diminished gastric acid secretion and small intestine dysmotility are most commonly associated with SIBO, other risk factors include anatomical problems or anomalies, celiac disease, diabetes mellitus, cirrhosis, renal failure, inflammatory bowel disease, immunodeficiency states, malnutrition, and recurrent antibiotic use (Dukowicz et al., 2007). Clinicians must have a high index of suspicion for SIBO given that symptoms are nonspecific and may include bloating, abdominal distension, abdominal pain, diarrhea, and fatigue (Dukowicz et al., 2007). Breath testing as discussed above is the primary study used to identify SIBO. Treatment of SIBO involves correction of the underlying cause (if possible), nutritional support, and treatment of the overgrowth (Dukowicz et al., 2007). SIBO treatment often requires broad spectrum antimicrobial therapy, which in some patients may require repeat or cyclical therapy, along with dietary modifications (Rezaie et al., 2016).

4.6. Genitourinary evaluation

A recent study of 19 POTS patients reported findings from a quantitative overactive bladder (OAB) screening questionnaire, and found that 13 of 19 patients met clinical criteria for a diagnosis of probable clinically significant OAB, with nocturia, increased daytime frequency, and urgency most problematic for patients (Kaufman et al., 2017). Urodynamic studies might be considered in POTS patients with significant lower urinary tract symptoms that suggest urinary retention. The components of urodynamic testing include uroflowmetry, postvoid residual measurements, cystometry, leak point pressure measurements, pressure flow studies, and in some centers, electromyography and video urodynamic studies. A video urodynamic study of 16 POTS patients referred for evaluation of lower urinary tract symptoms, identified a pattern of impaired sensation of bladder fullness, inefficient emptying with straining pattern of voiding, and no loss of bladder compliance (Fuare, Walker).

4.7. Sleep evaluation

As previously noted, fatigue, daytime sleepiness, and sleep disturbances are common in POTS patients. Other complaints often reported by POTS patients that may reflect a sleep disorder include headache upon awakening, repeated nocturnal awakening, nocturnal sweating, nocturnal palpitations and tachycardia. Polysomnography in 25 POTS patients was compared to that performed in 31 control subjects, demonstrating similar sleeping times between the groups, but a higher percentage of stage 2 sleep was noted in POTS patients, and no statistically significant difference in REM sleep and percentage of slow wave sleep was seen in the POTS group relative to controls (Mallien et al., 2014). It was noted by the authors, however, that 4 POTS patients in this cohort did not achieve REM sleep during polysomnography.

5. Conclusions

POTS is a common, though under-recognized, heterogeneous disorder that requires a thorough clinical history and examination, and a thoughtful diagnostic approach, in order to identify relevant clinical features and associated conditions. An individualized diagnostic approach is necessary given the multi-system heterogeneity of the condition, which can better inform treatment decisions in POTS patients. In the author's opinion, present and future clinical research aimed at understanding the pathogenesis of POTS, should ideally involve much larger case series than those previously reported with more optimal identification of comorbid conditions, and a focus on the interplay between autoimmunity and genetics.

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