

REVIEW ARTICLE

Dysautonomia in the Ehlers–Danlos syndromes and hypermobility spectrum disorders—With a focus on the postural tachycardia syndrome

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Abstract

Dysautonomia (autonomic dysfunction) occurs in the Ehlers–Danlos syndromes (EDS) and hypermobility spectrum disorders (HSD). Symptoms include palpitations, dizziness, presyncope, and syncope, especially when standing upright. Symptoms of orthostatic intolerance are usually relieved by sitting or lying and may be exacerbated by stimuli in daily life that cause vasodilatation, such as food ingestion, exertion, and heat. Neurocardiovascular dysautonomia may result in postural tachycardia syndrome (PoTS), a major cause of orthostatic intolerance. It is defined by a rise in heart rate of >30 beats per minute (bpm) in adults and >40 bpm in teenagers while upright, without a fall in blood pressure (BP; orthostatic hypotension). In some, it can be compounded by the presence of low BP. For many, there is delay in clinicians recognizing the nature of the symptoms, and recognizing EDS or HSD, leading to delays in treatment. The onset of PoTS may be linked to an event such as infection, trauma, surgery, or stress. Gastrointestinal and urinary bladder involvement may occur, along with thermoregulatory dysfunction. In some, the mast cell activation syndrome may be contributory, especially if it causes vasodilatation. This paper reviews neurocardiovascular dysautonomia with an emphasis on PoTS, its characteristics, associations, pathophysiology, investigation, and treatment.

KEYWORDS

dysautonomia, Ehlers–Danlos, hypermobility, postural tachycardia

1 | INTRODUCTION

This review provides an outline of the autonomic nervous system (ANS) and key systems affected, with a focus on neurocardiovascular (cardiovascular autonomic) dysautonomia. Although the most common dysautonomia in the Ehlers–Danlos syndromes (EDS) and hypermobility spectrum disorders (HSD) is the postural tachycardia

syndrome (PoTS), these conditions may be associated with other autonomic disorders or related conditions, including systemic hypotension, in some due to adrenocortical insufficiency (Addison's disease). The characteristic features, investigation, pathophysiology, and management of PoTS in particular, and an update on associations with EDS and HSD will be discussed.

The ANS has two major efferent pathways, the sympathetic from the thoraco-lumbar spinal cord, and the parasympathetic from the brain stem (cranial) and sacral spinal cord. These innervate every organ in the body. In addition to influencing organ function, the ANS also controls integrative systems essential for survival, such as arterial blood pressure (BP), heart rate (HR), and body temperature. Specific

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neurotransmitters in each pathway influence activity, examples being acetylcholine in autonomic ganglia and noradrenaline in post-ganglionic neuromuscular junctions. This enables rapid and appropriate changes in specific organs and in different systems when needed, such as in maintaining BP and HR especially when changing position from lying to standing, with food ingestion and after physical exertion. Dysautonomia may result from dysfunction or lesions at different sites of the neural axis, and this may occur in the brain, spinal cord, autonomic ganglia, peripheral nerves, and in some at multiple sites. The main systems affected, with some of the key manifestations, are cardiovascular (orthostatic intolerance, postural hypotension, PoTS, and syncope), sudomotor (hyperhidrosis, hypohidrosis, temperature intolerance), alimentary tract (hypostomia, nausea, gastroparesis, constipation, and diarrhea), urinary (frequency, urgency, incontinence, and retention), reproductive (erectile and ejaculatory in male), ocular (dilated pupils and Horner's syndrome), and respiratory (inspiratory gasps, stridor, and cough).

Dysautonomia is synonymous with autonomic dysfunction. Although increasingly recognized in the new millennium, it remains undiagnosed in many. There are different forms, of importance in relation to diagnosis, understanding the pathophysiological mechanisms, and subsequent treatment. Dysautonomia may present in any age group—at birth in the rare condition familial dysautonomia (Riley-Day syndrome), in teenage years with autonomic-mediated syncope (AMS) that includes vasovagal syncope, between 15 and 40 years with the PoTS, and in those over the age of 50 with neurodegenerative disorders affecting the ANS (ANS) (Mathias, Iodice, & Ingle, 2016).

Within the dysautonomia population, and often applicable to hypermobile EDS (hEDS) and HSD, a large group consist of those with intermittent autonomic malfunction, where between episodes there appear to be no obvious autonomic abnormalities, unlike in patients with autonomic failure (Mathias et al., 2011). Autonomic damage and failure may complicate common medical and neurological disorders such as diabetes mellitus, Parkinson's disease, and spinal cord injury. Damage to the ANS resulting in autonomic failure often is irreversible. Drugs that affect the ANS or cardiovascular organs can also cause dysautonomia in any age group by causing changes in fluid volume or heart rate (HR; diuretics, antihypertensive drugs, cardiac nitrates, sedatives, hypnotics, and antidepressants), or their toxic effects leading to an autonomic neuropathy. A currently relatively small but increasing proportion of cases are those with immune-mediated dysautonomia where immunotherapy is disease modifying (Gunning, Kvale, Kramer, Karabin, & Grubb, 2019), as recently demonstrated in patients with ganglionic antibodies (Koay et al., 2021) and PoTS with autoantibodies against the alpha-1 adrenergic receptor and muscarinic cholinergic receptor (Rodriguez, Hoepner, Salmen, Kamber, & Z'Graggen, 2021).

2 | THE PoTS

The PoTS has been increasingly recognized since the start of the new millennium. The term was first used by Rosen and Cryer in 1982, with

a later description by Schondorf and Low in 1993 of the “Postural Orthostatic Tachycardia Syndrome”. The acronym PoTS is ideal, but with exclusion of “orthostatic” as this is superfluous. The prevalence is estimated at 170 cases per 1,000,000 in the general population (Schondorf, Benoit, Wein, & Phaneuf, 1999). PoTS is characterized by an elevation in HR of >30 beats per minute (bpm) in adults, and >40 bpm in teenagers and adolescents (12–19 years) within 10 min of head-up tilt or standing, or when the HR is over 120 bpm while upright (Figure 1).

In PoTS orthostatic hypotension should not be present when upright, as in high spinal cord injury when HR rises because of the compensatory vagal response to the fall in BP (Figure 2). It is important that in addition to the key defining criteria (postural tachycardia and absence of orthostatic hypotension), there is no evidence of autonomic failure, or other causes and disorders that can raise HR abnormally (Mathias et al., 2011).

The history usually is of orthostatic intolerance, with palpitations, dizziness, presyncope, and in some syncope, brought on after postural change from lying down to the upright position (Table 1). Exacerbating factors include standing still, certain foods, even small amounts of alcohol, physical exertion, and hot weather (Table 2). Each of these stimuli can cause vasodilatation in different vascular beds. Some are worse during their menstrual period. Other than postural tachycardia, there usually are no abnormal cardiac findings, other than on auscultation to suggest mitral valve prolapse. Subjects often are young (below 40) and more likely to be female, although this is not exclusive, as the condition is increasingly diagnosed in specialist autonomic units, and recognition has improved in primary and secondary clinical practice. Many individuals report an onset that temporally and in retrospect may be difficult to pinpoint. This may be associated with a trigger event such as infection, trauma, stress, or surgery.

A detailed clinical examination of various systems is essential, as they may be involved, in addition to neurocardiovascular autonomic features. In our centers, PoTS is most frequently (by coincidence or otherwise) associated with hEDS (Mathias et al., 2011).

3 | PoTS, EDS, AND HSD

The relationship among joint hypermobility syndrome (JHS, i.e., pre-2017 changes in the criteria) (Castori et al., 2017; Malfait et al., 2017), hEDS, and cardiovascular autonomic dysfunction was extensively reviewed by A. Hakim, O'Callaghan, et al. (2017) and Roma, Marden, De Wandele, Francomano, and Rowe (2018). This section will consider observations since then. Though increasingly recognized, autonomic dysfunction continues to remain undiagnosed in many subjects and is the source of complex multisystemic ill-health and reduced quality of life in both EDS and HSD (Copetti et al., 2019; A. J. Hakim, 2019).

In a recent large survey, 3,276 individuals (83% of the study participants) reported being diagnosed by a physician with another medical condition in addition to PoTS (Shaw et al., 2019). Associated conditions included headache (40%), irritable bowel syndrome (30%),

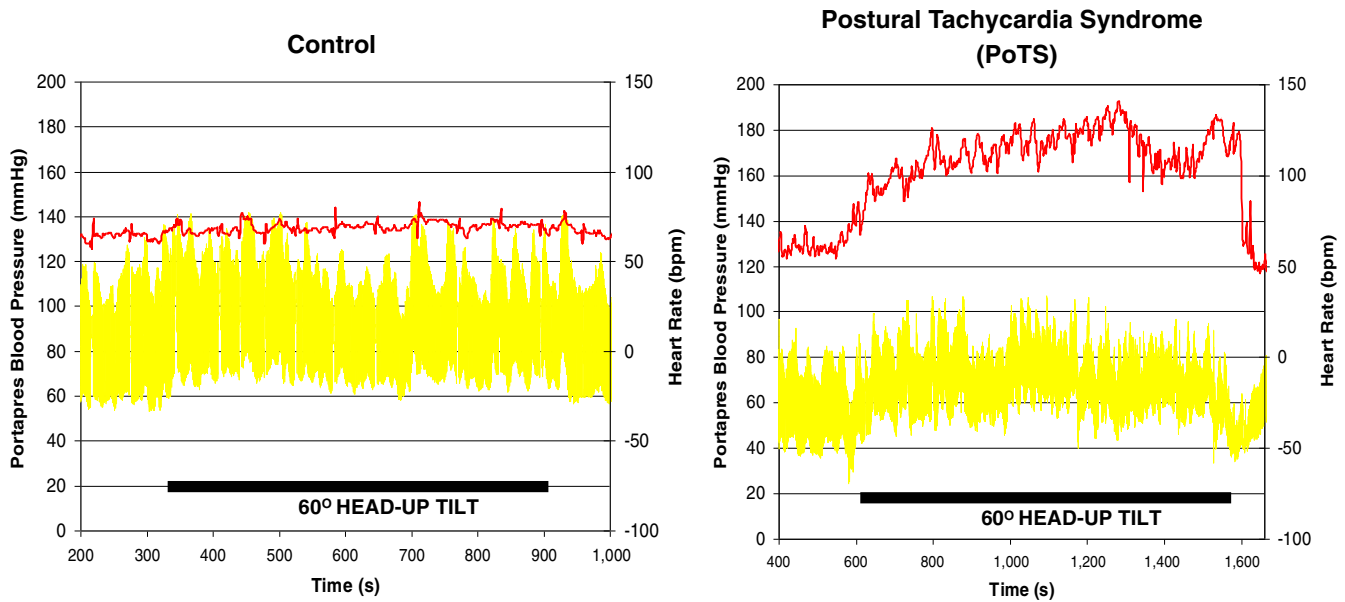


FIGURE 1 Blood pressure (BP) and heart rate (HR) measured continuously and noninvasively in a healthy subject (Control) and in a subject with postural tachycardia syndrome (PoTS) before, during, and after head-up tilt. PoTS is characterized by a rise in HR of >30 beats per minute (bpm) or greater within 10 min of head-up tilt or standing, or when HR is over 120 bpm while upright

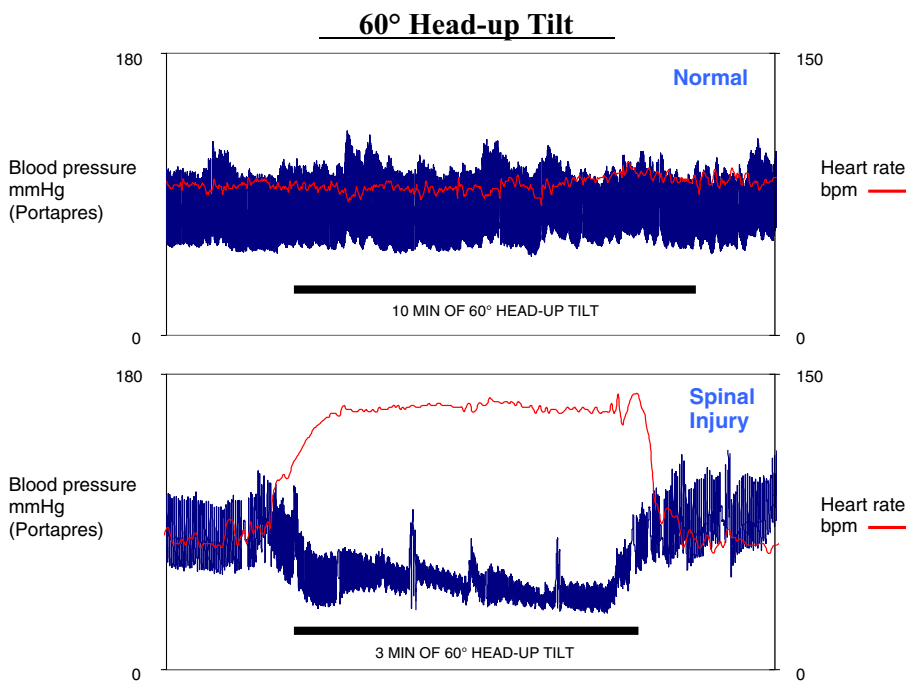


FIGURE 2 Blood pressure (BP) and heart rate (HR) measured continuously in a healthy normal subject (upper panel) and in a high spinal cord lesion (lower panel), before, during and after head-up tilt. Unlike the normal subject, there is a fall in BP (orthostatic hypotension) in the tetraplegic when upright because the sympathetic efferent outflow in the cervical spinal cord is disrupted. However, the brainstem is not affected and there is a marked rise in HR because of withdrawal of vagal nerve activity in response to the fall in BP. This differs from the HR rise in postural tachycardia syndrome (PoTS) when upright, which occurs without a BP fall when upright

EDS (25%), chronic fatigue syndrome (21%), fibromyalgia (20%), and mast cell activation syndrome (MCAS) (9%).

The mechanisms that cause or contribute to PoTS in EDS and HSD are far from discrete from each other. The interdependency among hypermobility, anxiety, autonomic dysfunction, and pain was described almost two decades ago in JHS and hEDS (A. J. Hakim & Grahame, 2004). Eccles, Owens, Mathias, Umeda, and Critchley (2015) and Eccles, Owens, Harrison, Grahame, and Critchley (2016) demonstrated relationships among joint hypermobility, anxiety, and

autonomic dysfunction (primarily tachycardia) and elucidated brain-body mechanisms including aberrant engagement of the amygdala and insula, brain centers intimately linked to each other and emotional processing (Baur, Hänggi, Langer, & Jäncke, 2013). Recent studies also indicate that psychological factors are the result, rather than the cause, of autonomic dysfunction in PoTS (Owens, Low, Critchley, & Mathias, 2018; Owens, Low, Iodice, Critchley, & Mathias, 2017). Updates on the associations between autonomic dysfunction and psychological states are discussed further in this *Special Issue of the*

TABLE 1 Symptoms of PoTS

Dizziness/light-headedness
Palpitations
Visual disturbances
Clamminess
Loss of consciousness
Nausea
Headache
Pain (abdomen or chest)
Shortness of breath
Nonspecific—fatigue, attentional deficits, brain fog

Note: These usually occur when upright and are relieved by lying flat.
Abbreviation: PoTS, postural tachycardia syndrome.

TABLE 2 Factors that induce or worsen orthostatic intolerance and PoTS

Time of day (usually worse in the morning, especially on waking)
Speed of positional change
Prolonged, especially stationary standing
Raised temperature (hot weather, hot bath/shower)
Dehydration
Food ingestion (in some refined carbohydrates or large meals)
Alcohol
Physical exertion
Menstrual period
Deconditioning or prolonged recumbency
Drugs that cause vasodilatation

Abbreviation: PoTS, postural tachycardia syndrome.

American Journal of Medical Genetics, Part C (A. J. Hakim, Tinkle, Francomano, 2021).

In addition, PoTS is increasingly recognized as being associated with gastroparesis and functional gastrointestinal disorders (FGID) (Alomari et al., 2020; Mehr, Barbul, & Shibao, 2018; Tu, Abell, Raj, & Mar, 2020). Autonomic intervention through vagal neuromodulation is a treatment modality gaining attention in the management of gastroparesis and abdominal pain (Kovacic, Kolacz, Lewis, & Porges, 2020; Nightingale et al., 2020). In a study of 616 subjects, Tai et al. (2020) found that PoTS-positive individuals were more likely to fulfill criteria for Rome IV FGID across various organ domains and experience both upper and lower gastrointestinal symptoms more frequently. An association among FGID, PoTS, and HSD/hEDS subjects was found even after adjustments for age, presence of chronic fatigue syndrome and/or fibromyalgia, and depression scores.

It is possible that multisystemic involvement in PoTS contributes to sleep impairment and fatigue. Cognitive features in PoTS include fatigue (V. Raj, Opie, & Arnold, 2018), often present on waking in the morning while feeling unrefreshed. This is not necessarily related to, but often is associated with, sleep disturbances that include either getting to sleep

or being interrupted, for reasons that could include nocturnal palpitations. Fatigue may occur even in those who sleep normally, or for prolonged periods of time (Bagai et al., 2011, 2016). Cognitive impairment, including those affecting short-term memory (attention and recall abilities), has been reported in PoTS (Anderson et al., 2014; V. Raj et al., 2009). In PoTS with comorbid chronic fatigue syndrome, working memory, accuracy, and information processing are impaired when upright, yet the cause of common “brain fog” reported by many remains elusive, despite investigations into cerebral blood velocity, sleep quality, and neurotransmitter function (Ocon, 2013; Ross, Medow, Rowe, & Stewart, 2013). Chronic fatigue is a significant concern in EDS and HSD (A. Hakim, De Wandele, O’Callaghan, Pocinki, & Rowe, 2017).

The relationship of autonomic and neuropsychological symptoms to sleep impairment in PoTS remains unclear. Children and adolescents who sleep less than 8 hr daily are six times more likely to develop PoTS (Lin et al., 2014). Around half (55%) of adults with PoTS have a nondipping nocturnal BP profile (Figuroa et al., 2014) and prolonged rapid eye movement (REM) stage latency (Mallien, Iseemann, Mrazek, & Haensch, 2014; Miglis et al., 2016; Pengo et al., 2015). However, the prevalence of anecdotal fatigue and poor sleep quality reported is not reflected in polysomnography studies (Bagai et al., 2016; Mallien et al., 2014). Mild obstructive sleep apnea as reported in a third with PoTS (Miglis et al., 2016) maybe due to a predisposition in EDS to upper airway collapse (Guilleminault et al., 2013), and apnea seen in EDS (Gaisl et al., 2017).

Finally, MCAS may play a role in PoTS in individuals with EDS or HSD (Seneviratne, Maitland, & Afrin, 2017). The associations and the pathological mechanism that link PoTS, EDS, and MCAS are not clear (Kohn & Chang, 2020). However, this is a new area of clinical research, and clinicians internationally are identifying patients with this complex triad; MCAS discussed further in this *Special Issue of the American Journal of Medical Genetics, Part C* (A. J. Hakim et al., 2021).

4 | AUTONOMIC AND ALLIED EVALUATION

Autonomic evaluation should include a complete history, consideration of associated disorders that influence autonomic function, and a detailed clinical examination. Investigations often are needed, to objectively determine the autonomic deficit and plan treatment, and in some for allied diagnostic purposes.

The initial clinical examination may provide important clinical pointers toward dysautonomia and underlying disease. These include dryness of skin, hyperhidrosis, and pupillary changes. Measurement of BP and HR, lying, and standing (or sitting) will determine if orthostatic hypotension is present, and whether there is postural tachycardia. The extent and distribution of neurological and other system abnormalities may provide important signs of an underlying central or peripheral disorder contributing to or causing dysautonomia. Examination of other systems, as in diabetes mellitus, renal and hepatic disease is necessary along with urine testing for glucose and protein.

The combination of a detailed history and physical examination is crucial in determining if autonomic disease is present, in ascertaining the probable underlying diagnosis, and for interpreting the results of autonomic tests in the context of the associated disorder.

4.1 | Autonomic investigations

As well as diagnosis, the key aims of investigation are to determine the pathophysiological basis of disturbed autonomic function (as this often aids treatment strategies) and to ascertain the degree of impairment to guide management. Autonomic investigations (Table 3) ideally should be undertaken in a dedicated autonomic laboratory with continuous noninvasive techniques to record BP and HR while lying and standing, and with different homeostatic challenges, as described in Mathias, Iodice, Low, and Bannister (2013).

In those with intermittent autonomic dysfunction, such as PoTS, syncope, and presyncope, BP and HR responses to head-up tilt will also determine if the cause is autonomic in nature, thus confirming the mechanisms causing autonomic-mediated presyncope or AMS (Mathias, Owens, & Iodice, 2020). This is of relevance as the cardioinhibitory form of AMS, although rare, can necessitate intervention with a cardiac pacemaker. Asystole on head-up tilt has been reported in PoTS (Alsheklee, Guerch, Ridha, Mcneeley, & Chelimsky, 2008) and has been attributed to a surge in parasympathetic outflow preceding syncope. Autonomic testing additionally

TABLE 3 Autonomic investigations for PoTS

Initial tests
Head-up tilt (at an angle of 60° for 10 min)
Pressor stimuli (to determine sympathetic vasoconstrictor function): with isometric exercise, cutaneous cold, Valsalva maneuver and mental arithmetic
Heart rate responses (to determine cardiac parasympathetic responsiveness): during deep breathing, Valsalva maneuver, hyperventilation, standing, and head-up tilt
Plasma noradrenaline and adrenaline levels: supine, and upright (during head-up tilt or standing)
Ambulatory blood pressure/heart rate autonomic monitoring using the Mathias et al. protocol
Additional tests
Prolonged head-up tilt (60° for up to 45 min)
Liquid meal challenge—to determine preprandial and postprandial neurocardiovascular autonomic responses to the transition from supine to head-up tilt or standing
Graded supine exercise—to determine neurocardiovascular autonomic responses to exercise while flat, and to compare the responses before/after exercise and while standing

Note: These measure the neurocardiovascular autonomic responses (BP/HR) to postural change (such as standing/head-up tilt) and determine the responsiveness of the autonomic nervous system to stimuli in daily life. They exclude other autonomic conditions, such as those that result in autonomic failure.

Abbreviations: BP, blood pressure; HR, heart rate; PoTS, postural tachycardia syndrome.

should include the response to stimuli in activities of daily living (other than postural change) that may worsen PoTS through vasodilatation in splanchnic and muscle vascular beds, such as food and exercise. A thermoregulatory sweat test may provide further information on sudomotor function in those susceptible to body temperature dysregulation. Laboratory testing ideally should include measurement of plasma catecholamines (plasma noradrenaline and adrenaline) which may be elevated in the hyperadrenergic PoTS phenotype, although our experience indicates this is not common. Elevated plasma catecholamine levels may result from venepuncture, especially in those with blood-injection-injury phobia (that is common in AMS), and in the “whitecoat syndrome.” If raised, 24-hr urinary measurements of catecholamines and their metabolites should be performed to confirm or exclude excessive secretion.

In addition to laboratory studies, remote measurements should include domiciliary BP/HR autonomic profiles using an autonomic protocol (Mathias et al., 2013), time-stamping symptoms recorded during different activities of daily living with BP/HR changes. This aids diagnosis and has additional value in management advice (Figure 3). The autonomic profile also helps to determine the effect of non-pharmacological and pharmacological interventions by linking subjective measures and events with objective recordings.

4.2 | Nonautonomic investigations

The need for nonautonomic investigation is dependent upon the organ and system needing evaluation, and considerations of associations and conditions contributing to vasodilatation, especially when upright (Table 2). Examples include echocardiography (for valvular prolapse), continuous 24-hr or longer periods of HR/ECG recordings, structural neuroimaging especially of the craniocervical junction to exclude a Chiari malformation (ideally with upright neuroimaging) as can occur in some with EDS, and neurophysiological studies to exclude a small fiber neuropathy (Cazzato et al., 2016). Specific testing of urinary bladder, gastrointestinal and pelvic function, and anatomy also may be needed.

4.3 | Differential diagnosis

Several factors may mimic orthostatic intolerance and PoTS, and in addition to the autonomic investigations described above more may be needed in some to definitively exclude, for example, a pheochromocytoma, adrenocortical deficiency/Addison's disease, and other endocrine conditions such as inappropriate antidiuretic hormone (ADH) secretion (Mathias, Iodice, Low, & Galizia, 2015).

5 | TREATMENT OF CARDIOVASCULAR AUTONOMIC DYSFUNCTION

Treatment of cardiovascular autonomic dysfunction usually needs to be multipronged, with a holistic approach to addressing multiple

24-hr ambulatory BP & HR profile

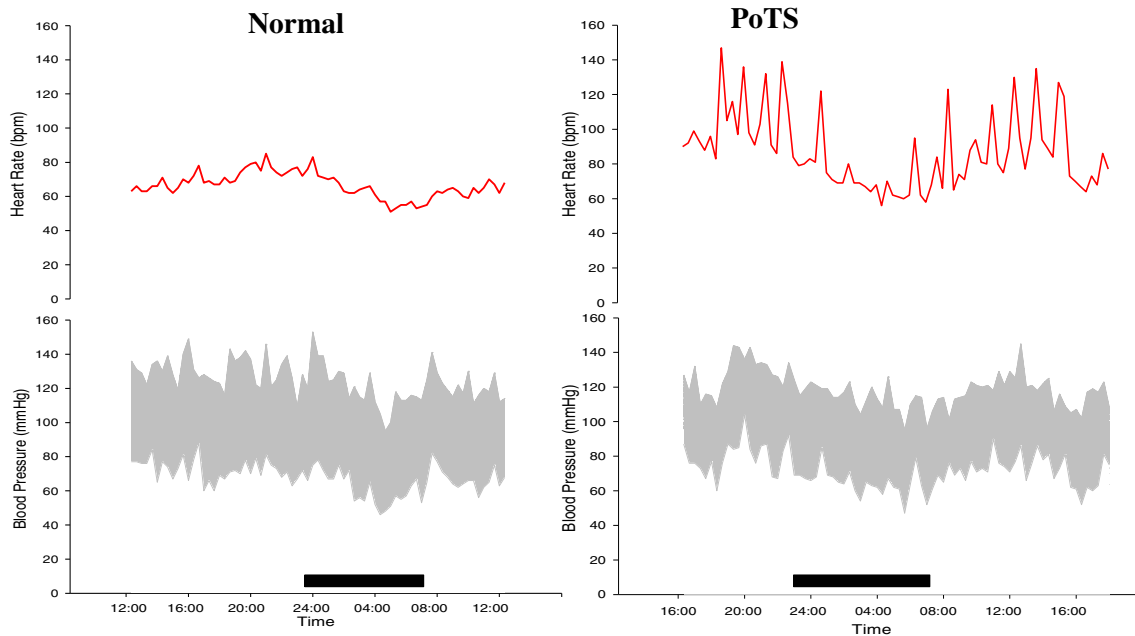


FIGURE 3 Ambulatory blood pressure/heart rate (BP/HR) autonomic profiles using the Mathias et al. autonomic protocol (MAP) recorded during different activities and essential stimuli (postural change, food exertion and modest exertion) during a 24-hr period. There are expected changes in BP and HR in the normal subject with the expected circadian fall in BP and HR at night when asleep. In postural tachycardia syndrome (PoTS), there is a definite tachycardia in the day when position changed to standing, without a fall in BP. At night while supine this is not present

symptoms and affected systems. A precise and individually targeted treatment is desirable, appropriate, and can be effective. Some individuals may have been subjected to a delay in diagnosis that may be substantial, with a delay greater in females (Bourne et al., 2021). There may be an erroneous diagnosis with a psychiatric label and associated psychological concerns may need additional consideration.

The key goals are to prevent the symptoms associated with postural change and exertion, and to reduce postural tachycardia a readily measured biomarker of the syndrome. Raising the resting BP (if it is low), and reducing peripheral vascular pooling when upright, often is beneficial.

5.1 | Nonpharmacological measures

Nondrug measures are an initial step to be implemented even if drugs are being considered (Table 4). These are similar to those used for other causes of orthostatic intolerance, including orthostatic hypotension. Hypovolemia may worsen symptoms, especially at times such as on changing posture after first waking in the morning. An adequate fluid intake is needed in most cases, avoiding excessive consumption of caffeine containing beverages, which can increase diuresis and contribute to hypovolemia. In some cases, comorbid concerns such as gastroparesis or bladder dysfunction may limit ability to tolerate higher fluid intake. Some individuals may be on a low-salt diet as part of promoted lifestyle changes (such as to prevent hypertension), and salt repletion is needed especially with a low

TABLE 4 An outline of nonpharmacological approaches

To be avoided

- Sudden head-up postural change (especially on waking)
- Prolonged recumbency
- High environmental temperatures (including hot baths)
- Large meals (especially of refined carbohydrate)
- Alcohol
- Undue exertion
- Medication with vasodepressor properties

To be introduced

- High salt intake
- Water repletion (especially in the morning on waking)
- Small, frequent meals
- Judicious regular exercise (including swimming)
- Raising the head end of the bed at night
- Physical maneuvers to activate autonomic activity (such as sustained hand grip)

To also be considered

- Compression stockings and hosiery
- Abdominal binders

BP. Those with a low-salt appetite may need salt supplementation (Garland et al., 2021), the target being at least 6 g/day as recommended in the general population. These measures should be

combined with appropriate physical exercises, even in those who are not deconditioned.

Preventative measures in situations in daily life include activation exercises such as sustained hand grip which increase sympathetic activity and raise the BP for a short period and using the calf muscle pump to reduce peripheral pooling (Smit et al., 2004; van Lieshout, ten Harkel, & Wieling, 1992). These exercises can help if done before changing position, from supine or sitting to standing such as in the morning on waking, after food ingestion and after exertion. Compression hosiery with Grade 2 stockings or tights, and in some abdominal binders can provide further benefit.

Certain foods (often refined carbohydrates), large meals, and even small amounts of alcohol can worsen symptoms through splanchnic vasodilatation. Small meals at frequent intervals and attention to the composition of food can help. Exertion, even if modest, can worsen tachycardia, especially after food ingestion, hot weather, and in those who are deconditioned. Exercise while semi-recumbent such as swimming, rowing, or recumbent cycling has advantages in PoTS in reducing orthostatic stress as compared to the upright position (Fu & Levine, 2018).

5.2 | Pharmacological measures

Autonomic medication is needed when nonpharmacological measures alone are not effective (Table 5). Treatment needs to be individualized depending on the clinical features and circumstances, the underlying pathophysiological basis, the resting supine BP, and the initial response to medication. Hence, the need for objective assessment

TABLE 5 Some of the more common used pharmacological treatments for PoTS

Therapeutic strategy	Drug class or mechanism of action	Agent
Reducing salt loss and/or aid plasma volume expansion	Mineralocorticoid	Fludrocortisone
Vasoconstriction	Alpha-adrenoceptors on resistance vessels	Midodrine
Reducing tachycardia	β_2 -Adrenoreceptor blockers, ideally cardioselective Selective sinus node blockade	Bisoprolol Ivabradine
Preventing postprandial tachycardia	Vasoactive peptide release inhibitors—somatostatin analogues	Octreotide
Ganglionic nicotinic receptor stimulation	Anticholinesterase inhibitors	Pyridostigmine
Reducing raised blood pressure/heart rate	Central sympatholytic	Clonidine Moxonidine

Abbreviation: PoTS, postural tachycardia syndrome.

before and if required later, ideally with a domiciliary BP/HR autonomic profile. It is important that associated disorders or conditions are treated satisfactorily, such as urinary tract infection, which often can worsen PoTS features.

In those with a low supine BP, a drug of choice is fludrocortisone, in doses that ideally do not exceed 300 μg daily to avoid adverse effects such as a low plasma potassium level. Fludrocortisone should not be used in those with a tendency to retain fluid. An alternative is midodrine, a sympathomimetic that induces vasoconstriction, prevents pooling, and can raise BP, which reduces compensatory tachycardia. Sympathomimetics that increase HR, such as Ephedrine should be avoided. Adverse effects of midodrine that include scalp pruritus and cutis anserina (goose bumps) are often transient. In PoTS, supine hypertension does not occur, unlike in many with orthostatic hypotension, and the advice to not be supine for 4 hr after this medication should not apply this group. midodrine can cause urinary retention in older men with prostatic hypertrophy, an unlikely occurrence in PoTS subjects who are typically young. midodrine should be initiated at a dose of 2.5 mg three times daily (tds) before meals, and titrated upwards if needed by 2.5 mg increments tds after 7–10 days depending on BP and HR responses, both lying and standing. The recommended maximum dose is 30 mg daily.

The combination of medication with different mechanisms of action such as fludrocortisone and midodrine can result in lower dosage, reduced adverse effects, and sometimes summative beneficial effects.

If the HR remains elevated and symptoms remain when upright, cardioselective beta-blockers such as bisoprolol, can be added. Non-selective beta-blockers such as propranolol may lower BP, leading to orthostatic side effects. The selective cardiac sinoatrial node blocker, ivabradine is an alternative (McDonald, Frith, & Newton, 2011), a recent meta-analysis confirming its benefit in lowering HR and providing symptomatic relief in PoTS (Gee, Watkins, Brown, & Young, 2018).

Other drugs include pyridostigmine, an acetylcholinesterase inhibitor, which increases ganglionic activity (S. R. Raj, Black, Biaggioni, Harris, & Robertson, 2005). Its adverse gastrointestinal effects (causing loose stools) may be of benefit in those with impaired lower bowel motility and constipation.

In those with an elevated BP, pressor agents such as fludrocortisone and midodrine, should not be used. Beta-adrenergic blockers that include bisoprolol or propranolol, could be considered. Clonidine, a short-acting centrally active sympatholytic agent, or the longer acting moxonidine can reduce tachycardia and lower BP.

In individuals with marked postprandial features, especially when other treatments have been ineffective, subcutaneous octreotide can be beneficial in small doses of 25–50 μg , twice or three times daily before food ingestion (Hoeldtke, Bryner, Hoeldtke, & Hobbs, 2006). A rapid-acting formulation initially should be used, starting with a single trial dose, and titrated upwards as required. Adverse effects include gastrointestinal disturbances and, in a minority of individuals, hypoglycemic features. These disadvantages need to be considered before

using intramuscular preparations with a long duration of action of 30 days.

Some individuals are considerably worse in the morning, possibly owing to increased fluid loss overnight while supine. When fluid replacement alone, especially on waking, does not help nocturnal desmopressin at doses prescribed for patients with autonomic failure (Mathias & Young, 2003) may have a therapeutic role (Coffin et al., 2012). In addition, intravenous infusion of saline has been reported to be beneficial in some (Ruzieh et al., 2017).

There is recent and increasing evidence both on measurement of antibody levels and in response to immunotherapy that autoimmune mechanisms may be causative or contributory (Al-Ansari & Robertson, 2021; Gunning et al., 2019; Vernino & Stiles, 2018; Watari et al., 2018). The response to immunotherapy with intravenous immunoglobulin has also been reported in PoTS and other forms of dysautonomia in subsets of individuals with evidence of autoimmunity (Schofield & Chemali, 2019; Weinstock, Brook, Myers, & Goodman, 2018).

Finally, drug interventions for underlying conditions may also improve PoTS symptoms. Treatment of migraine headache with beta-blockers can have dual benefits. Orthostatic intolerance can worsen during the menstrual period, and the introduction of a contraceptive agent, or a change if such therapy is already present, may need consideration with a specialist.

6 | CONCLUSION

Dysautonomia may occur in EDS and HSD, and most often manifests as PoTS. However, there may be other autonomic or allied conditions, independent and regardless of EDS or HSD, which should be considered for completeness. In addition, systemic hypotension even when supine and with peripheral vasodilatation when upright also may contribute further to compensatory tachycardia. PoTS can cause considerable morbidity, with a negative impact on quality of life even greater when there is involvement of other systems. This is compounded if the condition is missed, leading to prolonged exposure to symptoms, and/or if the symptoms solely are attributed to a primary psychological disorder, as often can be the experience of individuals with EDS or HSD during their diagnostic journey. A holistic and multidisciplinary approach to both assessment and treatment is often the most appropriate and effective means of providing optimum care.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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