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# Cardiovascular Autonomic Dysfunction in Ehlers–Danlos Syndrome—Hypermobile Type

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Autonomic dysfunction contributes to health-related impairment of quality of life in the hypermobile type of Ehlers–Danlos syndrome (hEDS). Typical signs and symptoms include tachycardia, hypotension, gastrointestinal dysmotility, and disturbed bladder function and sweating regulation. Cardiovascular autonomic dysfunction may present as Orthostatic Intolerance, Orthostatic Hypotension, Postural Orthostatic Tachycardia Syndrome, or Neurally Mediated Hypotension. The incidence, prevalence, and natural history of these conditions remain unquantified, but observations from specialist clinics suggest they are frequently seen in hEDS. There is growing understanding of how hEDS-related physical and physiological pathology contributes to the development of these conditions. Evaluation of cardiovascular symptoms in hEDS should include a careful history and clinical examination. Tests of cardiovascular function range from clinic room observation to tilt-table assessment to other laboratory investigations such as supine and standing catecholamine levels. Non-pharmacologic treatments include education, managing the environment to reduce exposure to triggers, improving cardiovascular fitness, and maintaining hydration. Although there are limited clinical trials, the response to drug treatments in hEDS is supported by evidence from case and cohort observational data, and short-term physiological studies. Pharmacologic therapy is indicated for patients with moderate-severe impairment of daily function and who have inadequate response or tolerance to conservative treatment. Treatment in hEDS often requires a focus on functional maintenance. Also, the negative impact of cardiovascular symptoms on physical and psycho-social well-being may generate a need for a more general evaluation and on-going management and support. 

**KEY WORDS:** Ehlers–Danlos; autonomic; orthostatic; tachcardia; hypotension

**How to cite this article: Hakim A, O'Callaghan C, De Wandele I, Stiles L, Pocinki A, Rowe P. 2017. Cardiovascular autonomic dysfunction in Ehlers–Danlos syndrome—Hypermobile type. Am J Med Genet Part C Semin Med Genet 175C:168–174.**

## INTRODUCTION AND METHODS

There is growing recognition of an association between autonomic dysfunction and Ehlers–Danlos syndrome—hypermobile type (hEDS). While many symptoms of autonomic dysfunction have been observed clinically in hEDS, including cardiovascular, pupil, bladder, sweating dysfunction, and gastrointestinal dysmotility (see "Gastrointestinal Involvement in Ehlers Danlos Syndrome," by Aziz et al. in this issue), the purpose of this review is to explore

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DOI 10.1002/ajmg.c.31543

Article first published online 4 February 2017 in Wiley Online Library (wileyonlinelibrary.com).

what is known of the association between cardiovascular autonomic dysfunction and hEDS; provide guidance on the assessment and management of these in the context of hEDS; and, consider areas for further research in this field.

The committee on Cardiovascular Dysautonomia of the International Ehlers–Danlos Syndrome Consortium met by teleconference or through electronic correspondence throughout 2015 and 2016 to discuss the associations of cardiovascular autonomic dysfunction with hEDS and its assessment and management. The following reflects the Committee's literature review and professional experience as well as insights from various contributing members of the international effort on EDS through the Consortium.

## LITERATURE REVIEW

There has been no general hEDS population cohort study of cardiovascular autonomic dysfunction, and there has been one published case-control study of symptom reporting. Equally the causal relationships in hEDS are unclear though there are plausible mechanisms, and the evidence for the management in hEDS is lacking in that there are no published clinical trials.

That said tachycardia and hypotension are recognized complications in hEDS [Rowe et al., 1999; Gazit et al., 2003; Hakim and Grahame, 2004; Mathias et al., 2011; Wallman et al., 2014; De Wandele et al., 2014a, 2016]. Typically one of the following four presentations may arise:

- Postural tachycardia syndrome (POTS),
- neurally mediated hypotension (NMH), also referred to as vaso-vagal syncope or neuro-cardiogenic syncope,
- orthostatic hypotension (OH) or delayed orthostatic hypotension,
- orthostatic intolerance (OI).

Symptoms can be highly debilitating in hEDS [Rowe et al., 1999; Hakim and Grahame, 2004; Mathias et al., 2011; De Wandele et al., 2014b]. There is recognition of an association of POTS with fatigue [Schondorf et al., 1999], reduced quality of life [Benrud-Larson et al., 2002], and a greater incidence of migraine and syncope with POTS in patients with joint hypermobility syndrome compared to those without [Kanjwal et al., 2010]. When poorly controlled, these symptoms may also restrict treatment strategies for other symptomatic management including physical therapies.

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In the general literature on the management of autonomic dysfunction there is evidence for the effectiveness of treatment strategies. This and the definitions of the different cardiovascular presentations are discussed later. Such treatments have been applied to individual cases of hEDS, based on physiological findings. However, there are no clinical trials of treatment in hEDS, either in general or in specific subgroups based on pathophysiology.

## CAUSAL ASSOCIATIONS WITH hEDS

The causes of cardiovascular autonomic dysfunction in hEDS are unclear. Suggested mechanisms include (listed based on clinical experience and in order of most common occurrence):

- Low blood pressure,
- increased peripheral venous dilation and blood pooling,
- low circulating blood volume,
- medications with side effects that trigger or impair autonomic responses, for example tricyclics,
- elevated circulating catecholamines,
- auto-immunity, particularly auto-antibodies directed against receptors which play a role in the regulation of heart rate and blood pressure, and other autonomic functions,
- excess systemic levels of histamine, and
- rarely, brainstem or cervical cord impingement from Chiari malformation or cranio-cervical instability.

## EVIDENCE FOR UNDERLYING MECHANISMS IN hEDS

Handler et al. [1985] identified through continuous wave Doppler ultrasound measurement increased aortic wall compliance in 10 of 13 study cases with joint hypermobility syndrome. Rowe et al. [1999] suggested that in some cases the association of OI with hEDS could be attributed to abnormal connective tissue in dependent blood vessels with veins distending excessively in response to ordinary hydrostatic pressures. This in turn leads to increased venous pooling and its hemodynamic and symptomatic consequences. Studies by Mathias et al. [2011] and De Wandele et al. [2014a] suggest that neuropathy, connective tissue laxity, and vasoactive medication play a role in development of cardiovascular dysfunction in hEDS.

Gazit et al. [2003] identified evidence of alpha-adrenergic and beta-adrenergic hyper-responsiveness. In support of the hypothesis that this is one mechanism in hEDS, a study by Thieben et al. [2007] identified a hyperadrenergic state in 29% of cases of POTS from a general cohort though cases of hEDS were not specifically identified. Also in the general literature, research has identified potentially pathogenic adrenergic [Fedorowski et al., 2016], muscarinic [Yu et al., 2012; Dubey et al., 2016], and other neural autoantibodies [Thieben et al., 2007; Li et al., 2014; Singer et al., 2016] in a significant percentage of cases with POTS and a subset of those

with OH. Current, ongoing research may identify this as applicable to patients with hEDS.

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Histamine can induce hypotension and tachycardia [Frieri et al., 2013]. More recently mast cell activation, and excessive histamine release has been identified in cases of hEDS [Louisias et al., 2013; Cheung and Vadas, 2015] and an intriguing association reported between multi-systemic pathologies including autonomic disturbances and germline duplications and triplications of the TSPAB1 gene encoding alpha 1 tryptase [Lyons et al., 2016]. High circulating levels of histamine may be another mechanism contributing to cardiovascular dysfunction (see also "Mast Cell Activation Syndrome in Ehlers–Danlos syndrome" by Seneviratne et al. in this issue).

Arnold Chiari malformation may also trigger cardiovascular autonomic disturbances that resolve following decompressive surgery [Ireland et al., 1996]. Milhorat et al. [2007] demonstrated an association between Arnold Chiari and hEDS. In some cases this may also be a contributing factor (see also "Neurologic Manifestations in Ehlers–Danlos Syndrome" by Henderson et al. in this issue).

## CONTROVERSIES

### Screening for Mitral Valve Prolapse

Mitral valve prolapse (MVP) can be associated with excessive catecholamines, orthostatic intolerance, and occasionally with dysrhythmias. MVP is not common (approx. 6%) in patients with hEDS [Dolan et al., 1997; McDonnell et al., 2006; Atzinger et al., 2011], and in most cases this is unlikely to be of clinical significance. Also, normal cardiac anatomy does not rule out cardiovascular dysfunction. Screening for MVP in hEDS is not indicated. Echocardiography should be limited to those in whom there is concern regarding cardiac function, or a personal or family history of cardiac or aortic root/arch disease [Atzinger et al., 2011].

### The Role of Physical Therapy in Improving POTS, OI, and OH

Physical deconditioning and poor aerobic fitness are common findings in patients chronically unwell with hEDS. A history of onset of symptoms of cardiovascular dysfunction following a prolonged period of reduced physical activity is not uncommon.

OI has been related to deconditioning [Fu et al., 2010; Parsaik et al., 2012]. However, as to which is the cause and which is the consequence remains open to debate. Increased physical fitness may counteract OI. Fu et al. [2011] and George et al. [2016] have shown that after a 3-month training programme, moderate gradual endurance and strength training can decrease upright heart rate, improve baroreflex sensitivity and heart rate variability, and improve quality of life.

The extent to which physical deconditioning triggers cardiovascular dysfunction, and to which physical reconditioning has a fundamental role in managing symptoms related to OI, OH, and POTS, warrants further research and long-term follow up.

## MANAGEMENT AND CARE GUIDELINES

Using the standard nomenclature for guidelines Level I to III evidence for the management of cardiovascular autonomic dysfunction in hEDS is lacking; there are no published clinical trials. Level IV evidence of the associations with EDS arises from small cohort studies, case reports, and expert opinion. Even where evidence exists, it is confounded by imprecision in definitions and diagnostic methods that further confound extrapolation from data to individual patients. As such guidance is principally based on expert consensus, but draws on Level I to III guidance published by international groups on the assessment and management of POTS and OI per se [Grubb et al., 2006; Lahrmann et al., 2006; Sheldon et al., 2015].

### History, Examination, and Investigations

*History*

The clinical history should focus on defining the symptoms, triggers, modifying factors, impact on daily life, chronicity of the condition, possible causes, and family history.

Many of the common symptoms relate to changes in posture. They occur when changing from a lying or sitting to a standing position, or with maintaining upright posture, and are improved but not always completely relieved by sitting or lying down.

The more common symptoms and signs that suggest cardiovascular dysfunction are:

- Fast heart rate (palpitations),
- light-headedness, sometimes with a sense of being about to blackout (pre-syncope),
- visual impairment including altered acuity, partial or complete visual loss, and light sensitivity due to pupillary dilation,
- cognitive complaints including word-finding difficulties, limited concentration and poor memory (often described in lay terms as "brain fog"),
- chest pain,
- tremulousness,
- chronic fatigue,
- exercise intolerance and post exercise malaise,

- swelling and/or discolouration (dusky purple/red) in the legs after standing for only relatively short (e.g., 5 min) periods of time (as seen in OI),
- peripheral vasoconstriction (cold, dusky hands, and feet),
- fainting (syncope),
- temperature dysregulation,
- sleep disturbance.

The history may reveal states that trigger or exacerbate symptoms. Such things include:

- Medication side effects,
- dehydration,
- hot environments,
- exercise or after exercise,
- valsalva manouevers for example lifting a heavy object, defecation,
- after alcohol or caffeine intake,
- after eating, particularly carbohydrate,
- during other illness including infection,
- stressful situations for example blood tests, arguments, exams,
- painful stimuli,
- high altitude (aircraft travel, etc.),
- after long periods of rest,
- surgery involving general anesthesia,
- allergic reactions (histamine reactions).

*Physical examination*

A detailed examination is always warranted. Other common causes of low blood pressure or palpitations should be considered in an assessment. These include:

- Anaemia,
- hyperthyroidism (e.g., tachycardia and heat intolerance),
- hyper adrenergic states (e.g., tachycardia and flushing),
- addison's disease (e.g., low blood pressure and fatigue).

There are a number of causes of autonomic neuropathy, many of which are rare and more pertinent to the older adult population. It is not the purpose of this guideline to describe these. Some of the more common conditions to consider in the younger adult population are:

- Diabetes mellitus,
- coeliac disease,
- Sjögren syndrome and other autoimmune rheumatic conditions,
- pregnancy,
- toxicity (e.g., alcohol),
- trauma (e.g., surgery),
- vitamin deficiencies: vitamin E, B1 (thiamine), B3 (niacin) B6 (pyridoxine), and B12.

*Investigations*

POTS, OH, and some forms of OI can be diagnosed in clinic without the need for complex tests. The diagnosis of NMH that is associated with recurrent syncope can be made clinically, and in most cases does not require formal tilt table testing. A simple clinic room standing test can help assess whether a brief period of standing can provoke orthostatic symptoms in those with NMH, but provocation of hypotension usually requires more prolonged tilt table testing.

Orthostatic testing should take place in a quiet room, ideally at a temperature between 20 and 24°C. The patient should rest while supine for 5 min before testing. Emptying the bladder before testing is recommended.

The following consensus definitions[1] [Freeman et al., 2011; Sheldon et al., 2015] are applied:

- POTS: is a clinical syndrome usually characterized by: (i) frequent symptoms that occur with standing, such as lightheadedness, palpitations, tremor, generalized weakness, blurred vision, exercise intolerance, and fatigue; (ii) a sustained increase in heart rate of $\geq$30 beats per minute (bpm) within 10 min of standing or head-up tilt (or $\geq$40 bpm in individuals 12–19 years of age); and (iii) the absence of orthostatic hypotension (>20 mm Hg drop in systolic blood pressure).
- OH: a sustained reduction of systolic blood pressure by at least 20 mm Hg systolic or diastolic blood pressure of at least 10 mm Hg within 3 min of standing or head-up tilt to at least 60° angle on a tilt table.
- NMH: requires the reproduction of orthostatic symptoms and a 25 mm Hg drop in systolic BP during standing or tilt testing. The drop in blood pressure can be associated with junctional rhythm (recognized by a loss of P waves on an electrocardiogram) at the time of pre-syncope or syncope. Syncope need not be present to make the diagnosis of NMH, as individuals with this hemodynamic pattern have daily lightheadedness and other symptoms but have adopted habits such as sitting or lying down, or tensing the calf muscles to avoid losing consciousness.
- OI: the development of symptoms during 10 min upright posture which improve upon lying down and do not meet the above criteria for POTS, OH, or NMH.

If orthostatic signs are normal on testing in the clinic but the clinical suspicion of autonomic dysfunction remains high, or signs are present and simple, non-pharmacologic treatments have not helped, for most individuals a haematocrit, electrocardiogram, blood pressure monitoring, and echocardiogram are sufficient to screen for a potential cardiovascular or systemic disorder.

***If orthostatic signs are normal on testing in the clinic but the clinical suspicion of autonomic dysfunction remains high, a haematocrit, electrocardiogram, blood pressure monitoring, and echocardiogram may be sufficient further screening.***

Symptoms of OI can overlap with some features of cardiac dysrhythmias.

[1]The authors are aware of limitations of the criteria that have been traditionally used to classify the types of cardiovascular disease that are seen in hEDS. This document uses definitions already proposed by international consensus and published in the general literature.

If there is clinical concern that a dysrhythmia is present, a 24-hr Holter monitoring is indicated. If these tests are normal but clinical suspicion remains high, a tilt-table test might be helpful as it assesses the patient over a more prolonged period than a standing test. The test may also be used to provoke syncope in a controlled environment and where there is doubt as to the diagnosis.

More extensive evaluation by an expert Autonomic Unit might be required. An extended approach to evaluation might include:

- Thermoregulatory sweat test or QSART testing to detect autonomic neuropathy,
- supine and upright plasma epinephrine and norepinephrine level tests,
- 24-hr urine sample to assess sodium intake.

Tests of autonomic function may identify autonomic neuropathy that is not usually a component of the cardiovascular dysfunction of EDS.

## Treatment

None of the treatments available is universally effective, and several treatments, used together, are likely to be needed. There is no evidence that specific treatments should be targeted at subgroups of patients with hEDS.

Education, advice, and non-pharmacologic treatments should be offered first in all patients, and include education on:

- Avoiding or reducing exposure to triggering factors,
- withdrawing medications that might worsen symptoms,
- maintaining good hydration and electrolyte balance,
- reducing venous pooling by lower limb elevation or by abdominal and/or lower limb compression garments,
- increasing exercise adapted where necessary for the presence of joint hypermobility, instability, and injury.

When prescribing exercise, the program might be adapted to account for OI in several ways that include the:

- Exercise modality: in general, aerobic activities with a local resistive component for the lower limbs are preferred, such as (reclined) cycling and swimming.
- Type of exercise: dynamic exercise may be better tolerated than isometric exercise. The latter is more prone to provoke valsalva manoeuvers, which decrease blood pressure.
- Prevention of peripheral blood pooling: exercising in the supine position is better tolerated than the upright position. Exercising in water may also help decrease peripheral blood pooling, because of the greater pressure exerted by the water on the lower limbs. However, an over-heated pool may cause venous dilation and be poorly tolerated.
- Intensity and frequency: training at a target heart rate of 75% of the estimated maximal heart rate for about 30 min per session, 2–3 times per week is advised [Fu et al., 2011; George et al., 2016]. This should be adapted according to level of disability.
- Increase of fluid intake, preferably with added sodium, and if helpful, the use of pressure garments during and after exercise.
- Avoidance of meals 1 hr prior to an exercise session, because vasodilatation in the gastrointestinal tract lowers the capacity of the circulatory system.
- Prevention of sudden drop in blood pressure after a training session by engaging in low-intensity cooling-down activity.

In those with moderate-severe impairment of daily function, and poor response to or tolerance of non-pharmacologic treatments, pharmacologic treatments are available [Grubb et al., 2006; Lahrmann et al., 2006; Sheldon et al., 2015]. These include:

- Fludrocortisone is a first line drug therapy for OI at doses of 100–200 mg daily (Level III evidence).
- Midodrine significantly reduces POTS symptoms and reduces the frequency of neurally mediated syncope (Level I evidence). The initial dosage is 2.5 mg orally every 4 hr while awake, usually for two to three doses daily, increasing gradually up to 10 mg every 4 hr while awake if needed. Midodrine may also be used with fludrocortisone.
- Beta blockers can help with management of recurrent syncope, NMH, POTS, and OI (Level I evidence). Lower doses tend to be better tolerated, but there is substantial inter-individual variability.
- Ivabradine slows sinus heart rate without affecting blood pressure, and has been reported to be helpful in those with POTS (Level III evidence).

Other agents include:

- Stimulants: medications such as methylphenidate [Grubb et al., 1996] and dextroamphetamine [Susmano et al., 1993] have vasoconstricting properties, and can help reduce peripheral pooling of blood. They can be particularly helpful if inattention is a prominent symptom.
- Hormonal contraceptives can help manage OI symptoms in young women. This option can be first line therapy for OI in those who have comorbid dysmenorrhea, menstrual irregularity, heavy periods, or worse fatigue and OI symptoms during the menstrual cycle [Boehm et al., 1997].
- Desmopressin may be given as nasal spray (10–40 μg) or orally (100–200 μg) at night to prevent volume loss due to frequent urination at night [Raj, 2006]. Additional doses of 100–200 μg during the day may be beneficial as well, but must include monitoring for hyponatremia. At 200 ug orally it may also reduce tachycardia [Coffin et al., 2012].
- Pyridostigmine is a peripheral acetylcholinesterase inhibitor that increases synaptic acetylcholine in the autonomic ganglia and at peripheral muscarinic receptors [Raj et al., 2005]. The drug can be effective for neurally mediated syncope and for POTS (Level I evidence).
- Clonidine is a central sympatholytic agent that can be useful if there is comorbid anxiety, and can be useful in patients with the central hyper adrenergic form of POTS [Robertson et al., 1983].

- Selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors can be helpful in some patients with OI, and can be beneficial in the setting of co-morbid pain, anxiety, or depression [Di Girolamo et al., 1999]. Dihydroxyphenylserine titrated 100–200 mg three times daily reduces OH (Level I evidence).
- Octreotide given subcutaneously in doses of 25–150 μg for 30 min before a meal may be used to reduce postprandial OH.
- Tolerance of upright posture and autonomic tone may improve after the administration of 1–2 L of intravenous normal saline infused over 1–2 hr [Burklow et al., 1999; Takenaka et al., 2002], or other forms of sodium loading [Rosen and Cryer, 1982]. Some physicians use IV saline to manage acute episodic exacerbations of OI [Moak et al., 2016]. The use of IV saline on a weekly basis can help improve function for selected individuals who are intolerant of or unresponsive to medications. The administration of IV saline via indwelling central catheters creates a risk of bacteremia and thrombosis, and should be avoided if at all possible.
- Ruscus aculeatus (butcher's broom) [Altern, 2000].

## WHAT WE NEED TO KNOW

The incidence, prevalence, and natural history of cardiovascular autonomic dysfunction in the hEDS population are unknown, as are the distribution and types of (co-associated) mechanisms that may trigger or influence these phenomena.

Subgroup (by risk factors/mechanism of disorder) clinical trials of efficacy and safety of treatments are required to move beyond the limitations of case study and expert opinion evidence. Studies also need to assess the effect of treatment on quality of life and fatigue.

## SUMMARY

Individuals with hEDS can develop cardiovascular autonomic dysfunction. Its manifestations include symptoms related to inadequate cerebral perfusion and symptoms of heightened adrenergic tone. Specific conditions include POTS and NMH.

The diagnosis is predominantly based upon taking a detailed personal and family history of symptoms, provoking circumstances, and accompanying complaints.

Simple clinic room tests can provide support for the diagnosis and other tests may be useful to exclude other diseases that can present in a similar manner.

Consideration should also be given to the possibilities that symptoms are due to medications and supplements, cardiac valvular disease, venous pooling, allergy, autoimmunity, or rarely Chiari malformation.

Although pharmacological therapies are often required, non-drug treatments should always be employed. Foremost amongst these are education about the causes of symptoms and physical measures that might be used to control them. Other non-pharmacological measures include increased dietary salt intake, use of compression garments and graded exercise therapy.

Pharmacological therapy begins with minimizing or removing medications that are either ineffective or producing deleterious effects. Drug treatments include volume expansion (e.g., fludrocortisone, saline infusion), vasoconstriction (e.g., midodrine), modulators of autonomic tone including beta-blockade, and others.

The prognosis remains uncertain with the outcomes ranging from virtually complete resolution of symptoms to long-term disability, which may be so severe as to affect education, employment, or socialization.

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## ACKNOWLEDGMENTS

We want to thank the international experts of the Consortium, and in particular Dr. Brad Tinkle, for their contributions to the development of this review.

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