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Review

Postural tachycardia syndrome and other forms of orthostatic intolerance in Ehlers-Danlos syndrome

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ABSTRACT

Objective: To review the association between orthostatic intolerance syndromes and both joint hypermobility and Ehlers-Danlos syndrome, and to propose reasons for identifying hereditary connective tissue disorders in those with orthostatic intolerance in the context of both clinical care and research.
Methods: We searched the published peer-reviewed medical literature for papers reporting an association between joint hypermobility or Ehlers-Danlos syndrome and orthostatic intolerance.
Results: We identified 10 relevant papers. Although methodological variability between studies introduces some limitations, the published literature consistently identifies a significantly higher prevalence of orthostatic intolerance symptoms in patients with joint hypermobility or Ehlers-Danlos syndrome than in healthy controls, and a significantly higher prevalence of cardiovascular and autonomic abnormalities both at rest and during orthostatic challenge. Postural tachycardia syndrome is the most commonly recognized circulatory disorder. The severity of orthostatic symptoms in those with EDS correlates with impairments in quality of life.
Conclusion: There is a strong association between several forms of cardiovascular dysfunction, most notably postural tachycardia syndrome, and joint hypermobility or Ehlers-Danlos syndrome. We propose that recognition of joint hypermobility and Ehlers-Danlos syndrome among those with orthostatic intolerance syndromes has the potential to improve clinical care and the validity of research findings.

1. Introduction

In the last two decades, postural tachycardia syndrome (POTS) and other forms of orthostatic intolerance have been recognized with increasing frequency in patients with joint hypermobility (JH) and Ehlers-Danlos syndrome (EDS). This review provides an overview of the Ehlers-Danlos syndromes, then examines the evidence regarding orthostatic intolerance in association with joint hypermobility and EDS. We discuss the importance to patients, clinicians, and researchers of making the diagnosis of joint hypermobility or EDS in patients who have orthostatic intolerance.

2. Materials and methods

For this narrative review, we searched the published literature using PubMed and EMBASE for articles on the association of Ehlers-Danlos syndrome or joint hypermobility and syndromes of orthostatic intolerance. The search covered the period from 1988 (the year of publication for the Berlin nosology of connective tissue disorders [Beighton et al., 1988]) to September 2017. We used the following string: (Ehlers-Danlos syndrome OR joint hypermobility) AND (orthostatic OR hypotension OR tachycardia OR syncope OR autonomic). We supplemented these results with references from retrieved papers and from personal literature files. For the association of EDS or JH with orthostatic intolerance, we excluded abstracts, review papers or letters that did not contain primary data, single case reports, and articles in which the primary focus was the association of JH or EDS and pain, gastrointestinal, orthopedic, headache, psychiatric, or obstetrical disorders. One further article was identified during the review process.

3. Overview of the Ehlers-Danlos syndromes

The Ehlers-Danlos syndromes are a heterogeneous group of hereditary connective tissue disorders (Malfait et al., 2017). They share the characteristics of joint hypermobility, skin hyperextensibility, and tissue fragility. Due to advances in clinical and genetic research in the last 30 years, earlier attempts to classify the types of EDS—including the Berlin criteria in 1988 (Beighton et al., 1988) and the Villefranche

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Table 1
Diagnostic features of classical and hypermobile EDS.

Classical EDS (cEDS)
Significant skin hyperextensibility and atrophic scarring
Plus either:
Generalized joint hypermobility[a]
Or
3 of the following 9 minor criteria:
• Easy bruising
• Soft doughy skin
• Skin fragility (or traumatic splitting)
• Molluscoid pseudotumors
• Subcutaneous spheroids
• Hernia (or history thereof)
• Epicanthal folds
• Complications of joint hypermobility (e.g., sprains, luxation/subluxations, pain)
• Family history of a first-degree relative who meets clinical criteria
Hypermobile EDS (hEDS)[b]
Generalized joint hypermobility[a]
And
Two of the following three:
1) Systemic manifestations of a more generalized connective tissue disorder (5 or more must be present):
• Unusually soft or velvety skin
• Mild skin hyperextensibility
• Unexplained striae such as striae distensae or rubrae at the back, groins, thighs, breasts and/or in adolescents, men or prepubertal women without a history of significant weight gain or loss.
• Bilateral piezogenic papules of the heel
• Recurrent or multiple abdominal hernias
• Atrophic scarring involving at least two sites without the formation of truly papyreaceous and/or hemosideric scars
• Pelvic floor, rectal and/or uterine prolapse in children, men or nulliparous women
• Dental crowding and high or narrow palate
• Arachnodactyly
• Arm span-to-height ≥ 1.05
• Mitral valve prolapse
• Aortic root dilatation with Z-score > +2
2) Positive family history, with one or more first-degree relatives meeting the criteria
3) Musculoskeletal complications (must have at least one)
• Musculoskeletal pain in two or more limbs, recurring daily for at least 3 months
• Chronic, widespread pain for ≥3 months
• Recurrent joint dislocations or frank joint instability, in absence of trauma
And
All three of the following:
1) Absence of unusual skin fragility (excessive skin fragility would be more consistent with other forms of EDS)
2) Exclusion of inflammatory connective tissue disorders such as lupus and rheumatoid arthritis[c], and
3) Exclusion of other causes of connective tissue laxity such as Marfan syndrome, neuromuscular disorders, and skeletal dysplasias.

[a] Generalized Joint Hypermobility (GJH) is evaluated according to the Beighton scale. The diagnosis of GJH requires a Beighton score of ≥6 for pre-pubertal children and adolescents, ≥5 for pubertal men and women to age 50, or ≥4 for men and women over the age of 50. If past surgery, amputations, or other circumstances cause joint limitations that affect the Beighton score calculation, the assessment can include a five-point questionnaire (5PQ) regarding historical information (Hakim and Grahame, 2003). If the Beighton score is 1 point below the specific cut-off but the 5PQ is positive, a diagnosis of GJH can be made (see text).

[b] A useful checklist for the diagnosis of hEDS is available on the Ehlers Danlos Society website: https://www.ehlers-danlos.com/heds-diagnostic-checklist/.

[c] In those with an acquired inflammatory connective tissue disorder, hEDS can be diagnosed if the criteria for "Systematic manifestations of a more generalized connective tissue disorder" and a "Positive family history, with one or more first-degree relatives meeting the criteria" are present; the musculoskeletal complications cannot be used in this setting.

criteria a decade later (Beighton et al., 1998)—have now been superceded by the 2017 international classification (Malfait et al., 2017). The new classification recognizes 13 subtypes of Ehlers-Danlos syndrome, 12 of which result from mutations in genes encoding fibrillary collagen, the collagen-modifying enzymes, or enzymes involved in glycosaminoglycan synthesis. The most common EDS subtypes are the classical (cEDS) and hypermobile (hEDS) forms. Mutations in the COL5A1 and COL5A2 genes are found in > 90% of cEDS (Bowen et al., 2017). Less commonly, mutations in the COL1A1 and COL1A2 genes can be associated with cEDS phenotype, but confer a greater risk of vascular and heart valve abnormalities. The diagnosis of hEDS remains clinical in nature, as there is no identified genetic etiology.

Table 1 illustrates the diagnostic criteria for cEDS and hEDS. While both conditions require evidence of generalized joint hypermobility, the degree of skin hyperextensibility is substantial in the classical form and relatively mild in the hypermobile form. Similarly, those with cEDS have more prominent skin findings such as atrophic scarring, hemosiderin deposition (often along the tibial surface), molluscoid pseudotumors, and subcutaneous spheroids (Bowen et al., 2017). Unusual skin fragility is common in cEDS and absent in hEDS. Widespread pain and fatigue are more common in the hypermobile type (Malfait et al., 2017).

The 2017 EDS criteria recognize that joint hypermobility occurs along a wide spectrum: it can be symptomatic or asymptomatic, and can be either isolated or occur in multiple joints. For *asymptomatic* individuals, the terms localized joint hypermobility (LJH), peripheral joint hypermobility (PJH), or generalized joint hypermobility (GJH) are used. Individuals with *symptomatic* joint hypermobility are now classified as (1) patients with an underlying heritable connective tissue disorder (e.g. hEDS) or (2) patients with a "hypermobility spectrum disorder" (HSD). The diagnosis of hEDS is made when joint hypermobility is generalized, symptomatic, and accompanied by multiple signs of tissue fragility, or multiple external signs of a connective tissue disorder (Table 1). Patients who have symptomatic hypermobility, but who do not meet the criteria for hEDS, are classified as having HSD (Castori et al., 2017).

Some clarification is needed regarding the benign joint hypermobility syndrome (JHS) (Grahame et al., 2000), the criteria for which had included major criteria of joint hypermobility and arthralgia, and multiple minor criteria that are similar to the 2017 definition of hEDS. Because of this substantial and often indistinguishable clinical overlap between JHS and hEDS (Tinkle et al., 2009), and the recognition that both JHS and hEDS can co-exist within the same pedigrees, the 2017 classification of EDS abandons use of the label JHS, instead considering it to be part of the clinical spectrum from generalized JH to hEDS (Tinkle et al., 2017; Castori et al., 2017).

Generalized joint hypermobility is usually evaluated using the 9-point Beighton score (Beighton et al., 1973). The methods of measuring the Beighton score are illustrated in Fig. 1. Conducting this examination usually takes < 2 min.

For adults, if the Beighton score is one point below the age specific values, GJH can be diagnosed if two of the following five questions are answered in the affirmative (Hakim and Grahame, 2003):

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"?*

A limitation of relying exclusively on the Beighton score is that it does not ascertain for hypermobility in the temporomandibular joint, spine, shoulders, hips, wrists, or ankles, and it measures angular hypermobility in only one plane, without ascertaining for rotatory or translational mobility, thus emphasizing the importance of incorporating more complete data from the history and physical

Maneuver (1 point for each positive)	L	R	Score
a. Passive dorsiflexion of the fifth finger at the metacarpophalangeal joint > 90º			
b. Passive apposition of the thumb to the flexor aspect of the forearm			
c. Extension of the elbow > 190º			
d. Extension of the knee > 190º			
e. Forward flexion of the trunk with the knees straight so the palms rest flat on the floor			
Beighton score (maximum score=9)			

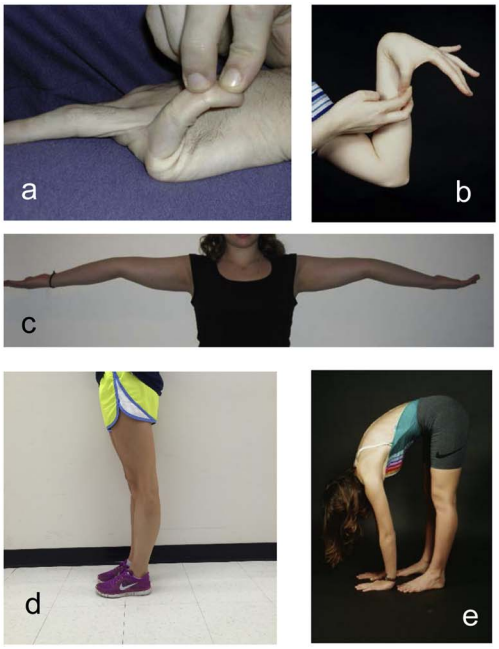


Fig. 1. Measuring the Beighton score.
Examples of each maneuver in the Beighton score are shown in Fig. 1a–e, and the points are assigned as in the scoring sheet. A goniometer is required to accurately measure elbow and knee hyperextension.

examination.

4. Association of orthostatic intolerance and circulatory dysfunction with JH/EDS

EDS has long been recognized to be associated with a high prevalence of chronic fatigue, which in turn is a cardinal feature of various forms of orthostatic intolerance. The literature review identified 10 studies that addressed the association between various forms of circulatory dysfunction and JH or EDS. The main findings of these studies are described in this section.

Rowe and colleagues reported an association between EDS, chronic fatigue syndrome (CFS), and orthostatic intolerance (Rowe et al., 1999). Of 100 adolescents evaluated in a pediatric CFS clinic over a one-year period, 12 patients (11 female) were identified as having EDS, a significantly higher prevalence than the estimated prevalence of EDS in the general population. All 12 satisfied the Fukuda criteria for the diagnosis of CFS (Fukuda et al., 1994). Fatigue had been present for a median of 37 months (range, 12–62) before the EDS was recognized. The median Beighton score was 7 (range, 5 to 9). All 12 patients had a history of joint dislocation, 3 of whom had required joint surgery. All patients had acrocyanosis and localized skin hyperextensibility, and 6 had papyraceous scars. After formal genetic and ophthalmologic evaluations, six satisfied the 1997 Villefranche criteria for hypermobile EDS and six for classical EDS. Five had at least 3 episodes of syncope and the remaining 7 had recurrent lightheadedness. Objective orthostatic tolerance was assessed using either a 10-minute standing test or a 3-stage tilt test. Ten patients met criteria for POTS, 7 of whom also developed neurally mediated hypotension (NMH) at a later point in the test. Two further patients had isolated NMH. Regardless of the hemodynamic phenotype, all patients reported an exacerbation of their usual symptoms during the first 10 min of the orthostatic testing.

It has been recognized that orthostatic intolerance is present in up to 96% of adolescents with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) (Rowe et al., 1995; Stewart et al., 1999; Institute of Medicine, 2015), and in a somewhat lower but more variable proportion of adults with ME/CFS (IOM, 2015). Given the overlap between EDS, ME/CFS, and orthostatic intolerance, Barron and colleagues assessed whether non-syndromic joint hypermobility was more common in 58 adolescents with ME/CFS than in 58 healthy controls (Barron et al., 2002). Beighton scores ≥ 4 were identified in 60% of CFS patients, compared to 24% of healthy adolescents ($P < 0.001$). The odds ratio for JH in those with ME/CFS versus healthy controls was 3.5 (95% CI, 1.6–7.5; $P < 0.001$). Given the high prevalence of orthostatic intolerance in pediatric ME/CFS, this study thus indirectly provides further support for the association between joint hypermobility and orthostatic intolerance.

Gazit and colleagues provided a more explicit demonstration of the association between joint hypermobility and dysautonomia (Gazit et al., 2003). Their study population consisted of 48 consecutive adult patients (44 women, 4 men; mean age 32 years; range, 18 to 69 years) who satisfied the 1998 criteria for joint hypermobility syndrome as well as 30 healthy controls (29 women) of similar age. All 48 JHS patients had 5 or more orthostatic symptoms present for at least 6 months, compared with only 3/30 (10%) in the control group ($P < 0.001$). Symptoms reported significantly more frequently by the JHS group included lightheadedness (88 vs. 20%), syncope (56 vs. 10%), and impaired concentration (71 vs. 27%). A subset of 27 JHS and 21 controls completed a maximum duration of 20 min of standing. The mean [SD] change in heart rate upon standing was significantly greater in JHS patients than controls (22 [9] vs. 15 [7]; $P = 0.04$). Standing tolerance was significantly lower in the JHS group (14.5 [6] vs. 19 [3.5] minutes; $P = 0.004$). In all, 6 of 27 (22%) with JHS who underwent the standing test met criteria for orthostatic hypotension compared to none of the controls, and a further 34% had postural tachycardia, with the remainder of the JHS population having uncategorized orthostatic intolerance. Those with JHS required both significantly lower doses of isoproterenol to raise their heart rates by 15 beats per minute and significantly lower doses of phenylephrine to increase their systolic blood pressures by 15 mm Hg, interpreted as being consistent with adrenoreceptor hypersensitivity.

Hakim and Grahame provided further evidence to support the association between JHS and autonomic dysfunction (Hakim and Grahame, 2004). One hundred seventy adult female JHS patients attending a rheumatology hypermobility clinic and 50 controls completed a questionnaire asking about symptoms experienced on a regular basis.

Symptoms were grouped into five categories: (pre)syncope, cardiorespiratory, gastrointestinal, common JHS concerns, and non-specific symptoms. Forty-one percent of JHS patients experienced at least one pre-syncopal symptom in comparison with 15% of the control group. Pain and fatigue were both more common in JHS patients (91% and 71% respectively) than in controls (30% for both symptoms).

The most comprehensive examination of the association between hEDS and autonomic dysfunction thus far has been conducted by De Wandele et al. (2014a). Eighty patients classified using the Villefranche criteria as having hypermobile type EDS were compared to patients with the classical form (n = 11), the vascular form (n = 7), fibromyalgia (n = 34), and healthy controls (n = 43). Participants completed the Autonomic Symptom Profile (ASP) and the Checklist of Individual Strength (CIS). Of the hypermobile EDS patients, 75 of 80 (94%) reported symptoms of orthostatic intolerance. Patients with hypermobile EDS had the highest autonomic symptom burden compared to all EDS groups and the controls (all $P < 0.001$), and had similar values to those with fibromyalgia (57.9 [21.57] vs. 51.3 [22.36]; $P = 0.296$). Hypermobile EDS patients also had a higher mean ASP total score than controls and those with other forms of EDS (total mean scores: hEDS, 57.9 [21.57]; cEDS, 32.3 [19.47]; vEDS, 29.12 [19.18]; healthy, 12.3 [10.73]; all $P < 0.001$). Fig. 2 illustrates the ASP subscores in the various groups of participants. Among those with hEDS, there was a significant negative correlation between ASP scores and energy, pain, and the physical function subscale of the SF-36, but not with the mental component score. There was no significant association between the ASP score and measures of affective distress or physical activity. Similar findings were present using the CIS.

De Wandele and colleagues also performed autonomic testing in a group of 39 female hEDS adults and 35 female controls of similar age (De Wandele et al., 2014b). Testing included resting heart rate variability and baroreflex sensitivity, quantitative sudomotor axon reflex testing (QSART), deep breathing, Valsalva maneuvers, and head-up tilt table tests. In addition, the Orthostatic Grading Scale (OGS) questionnaire was completed. At rest, patients had a significantly higher heart rate, lower heart rate variability, and lower baroreflex sensitivity. QSART tests showed lower sweat volumes at all testing sites in hEDS patients, with only 35% having normal results. The Valsalva ratio in hEDS patients was significantly higher due to a higher heart rate in phase 2. In addition, the blood pressure drop during phase 2 of the Valsalva maneuver was significantly larger than controls. During tilt testing, those with hEDS manifested orthostatic intolerance earlier (3 min 38 s vs. 8 min 22 s; $P = 0.017$), and overall orthostatic intolerance was more common in hEDS patients (74% vs. 34%; $P = 0.001$). The most common hemodynamic phenotype was POTS, which was identified in 41% with hEDS versus 11% of controls ($P = 0.003$). Higher Beighton scores were correlated with lower blood pressure and with a larger heart rate increase during tilt. OGS scores for patients were significantly higher for both frequency and severity of orthostatic symptoms when compared to controls. Composite Autonomic Severity Scores (CASS) reflected mild (47%), moderate (33%) or severe (3.33%) dysautonomia in hEDS patients. In conclusion, the results suggest a higher sympathetic tone at the heart (higher heart rates) and reduced sympathetic reactivity at the peripheral blood vessels (insufficient blood pressure increases in response to disturbances such as Valsalva or tilt) among those with hEDS.

Wellman and colleagues performed a retrospective chart review from a referral neurology clinic with an interest in EDS and POTS. Eligible patients were those with at least one POTS symptom (Wellman et al., 2014). The chart review identified two subgroups with some form of autonomic dysfunction: those with a chart diagnosis of POTS after tilt table testing, and those without POTS. A clinical diagnosis of EDS was confirmed in all cases by a geneticist. The prevalence of EDS was 7/39 (18%) in those with POTS, and 3/70 (4%) in those without ($P = 0.033$). The authors acknowledge that the comparison group with non-POTS autonomic dysfunction did not always undergo tilt testing to exclude POTS, and caution that this group might not be representative of non-POTS autonomic dysfunction in general.

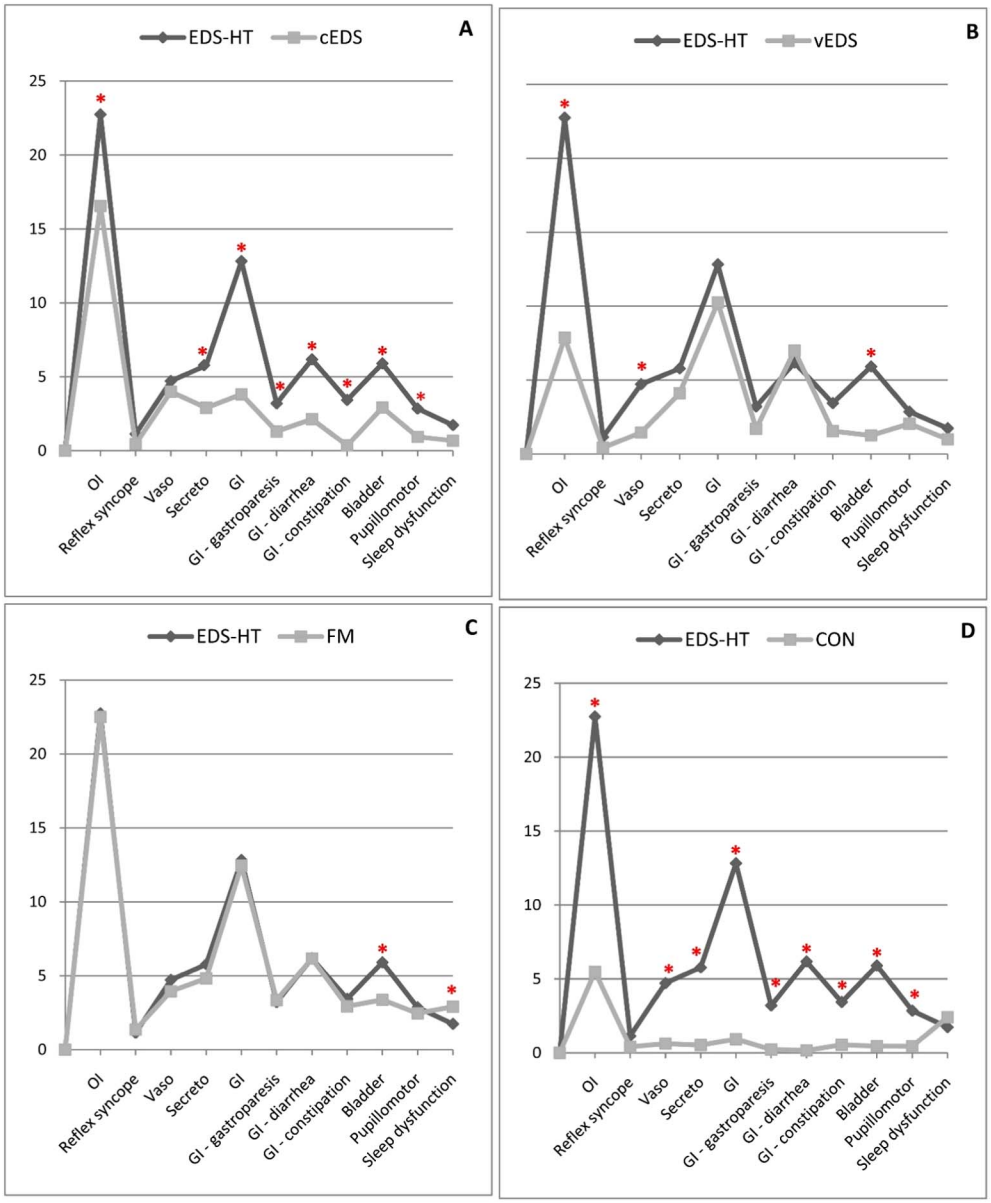
De Wandele and colleagues also evaluated whether orthostatic intolerance was a predictor for fatigue among 80 hEDS patients (21–56 years) and 52 healthy controls of similar age (De Wandele et al., 2016). Fatigue severity on the CIS was associated with an increased orthostatic symptom burden, as previously noted. The main new finding in this study was that a numerical rating of the severity of fatigue (ranging from 0 = not at all tired, to 10 = extremely fatigued/exhausted) increased significantly more in those with hEDS during the tilt test itself. This study confirmed the earlier observations of OI as an important predictor for fatigue.

In a relatively small study, Cheng and colleagues examined the cardiovascular profile in 9 adults with POTS and hEDS and 9 age- and sex-matched controls (7 female, 2 male; range, 18–65 years) (Cheng et al., 2016). After 10 min of rest, cardiovascular assessments were performed in the supine position. Patients were permitted to continue taking their usual medications in order to obtain a cardiovascular profile that represented day-to-day conditions. Applanation tonometry was performed at the carotid and femoral arteries to identify the pulse transit time with a 5- to 30-Hz bandpass filter. Foot-to-foot transit time waveform analysis was used to assess the pulse wave velocity (PWV) (PWV = 80% carotid-femoral distance/pulse transit time). Common carotid artery (CCA) distensibility was measured by using simultaneous applanation tonometry on the left CCA and B-mode ultrasound imaging on the right. Cardiac function and structure were analyzed with standard two-dimensional M-mode echocardiography. The results showed no significant differences between patients and controls in cPWV, CCA distensibility, or resting cardiac differences. The small sample size in this study limits confidence regarding the absence of a true difference, and it remains to be seen whether differences would emerge under conditions of orthostatic stress (Blitshteyn and Fries, 2017).

Celletti and colleagues investigated cardiovascular autonomic involvement in JHS or hypermobile EDS with a group of 35 adults (29 female; mean age 35 ± 14 years) (Celletti et al., 2017). Cardiovascular reflex tests included deep breathing, Valsalva maneuver, 30/15 ratio, handgrip test and a 20-minute head-up tilt table test. The 30/15 ratio and the deep breathing results were normal in all patients. The Valsalva ratio was normal in patients who completed the test, although 13 (31.4%) could not complete this autonomic measure. No hEDS patient was able to complete the handgrip test. Tilt table testing confirmed that 17 (49%) met the criteria for POTS, 11 (31%) others had orthostatic intolerance, and seven (20%) had normal hemodynamic results. The 80% prevalence of objective orthostatic intolerance is similar to the findings of Gazit and colleagues and De Wandele and colleagues, although no healthy controls participated in this component of the study. Baroreflex sensitivity was significantly higher for those with JHS/hEDS compared to 23 controls exposed to the same tilt table testing.

4.1. Literature summary

The current literature on the association of orthostatic intolerance with joint hypermobility/EDS is limited by variability in several methodological factors, including the age of the participants, the intensity with which studies ascertain for orthostatic intolerance symptoms, the duration and type of orthostatic challenge (standing versus upright tilt), whether medications for treating orthostatic intolerance were continued during the orthostatic challenge, and the preparation for and conduct of the test (duration of pre-test fast, prior sodium intake, time of day for testing, and degree of movement allowed during the test). All published studies have enrolled patients who were being evaluated in academic medical centers or specialty clinics. It is therefore unclear how much referral bias influences the findings. Enrolling individuals with joint hypermobility or EDS who were not presenting for medical care would help address questions about the representativeness of the current literature.



OI: Orthostatic intolerance domain, Vaso: vasomotor domain, Secreto: Secretomotor domain, GI: gastrointestinal domain, EDS-HT: hypermobility type of Ehlers-Danlos Syndrome, cEDS: classical type, vEDS: vascular type, FM: fibromyalgia, CON: healthy controls.

The mean ASP domain scores are compared between groups. The values shown are corrected for age. Domains that significantly differ between groups are indicated by an asterix (*). The scores are connected by a line in order to facilitate the comparison of domain scores within one group.

Fig. 2. Comparison of the autonomic symptom profile between groups.
Reprinted with permission from Seminars in Arthritis and Rheumatism, 44(3), De Wandele I, Calders P, Peersman W, Rimbaut S, De Becker T, Malfait F, et al., Autonomic symptoms burden in the hypermobility type of Ehlers-Danlos syndrome: a comparative study with two other EDS types, fibromyalgia, and healthy controls, 353–361, 2014.

Nonetheless, in all studies with > 10 patients, the data are consistent with clinically important and statistically significant increases in the prevalence of orthostatic symptoms and objective hemodynamic abnormalities in those with joint hypermobility or EDS, with the highest prevalence being found among those with hEDS. Between 41 and 100% with JH/EDS report orthostatic symptoms on a regular basis, with higher prevalence rates being reported in studies using more comprehensive ascertainment methods for those symptoms. Hemodynamic abnormalities are identified in 56–80% of JH/EDS patients in published studies, with higher prevalence rates being reported when the orthostatic testing duration exceeds 20 min. The available evidence is consistent with higher sympathetic tone in JH/EDS, and with a strong association between decreased overall quality of life and the degree of autonomic dysregulation.

The mechanism for the increased prevalence of orthostatic intolerance in joint hypermobility and EDS is not well established. It has been hypothesized that the generalized connective tissue laxity in ligaments and skin also affects vascular wall compliance, allowing increased pooling of blood in dependent vessels during upright posture, with secondary elevations in heart rate and drops in blood pressure (Rowe et al., 1999). A second mechanism may be a peripheral neuropathy affecting sympathetic fibers in joint hypermobility and EDS patients (Gazit et al., 2003; De Wandele et al., 2014b). Other potential mechanisms for the cardiovascular abnormalities in EDS—such as

Table 2
Reasons to look for EDS and JH in POTS/OI patients.

Reasons to look for EDS and JH in the clinical care of POTS and other forms of orthostatic intolerance
1. To improve general clinical management
2. To detect rare forms of EDS
3. To ensure provision of appropriate physical therapy care
4. To provide a unifying diagnosis for patients

Reasons to look for EDS and JH in studies of POTS and other forms of orthostatic intolerance
1. To accurately describe the clinical features of study populations
2. To reduce biased assignment to subgroups in pathophysiology studies
3. To reduce enrollment of potential non-responders in treatment studies
4. To prevent incorrect causal inferences

adrenergic hyper-responsiveness, excessive histamine release or mast cell disorders, deconditioning, and the higher prevalence of neuroanatomic abnormalities in EDS—are discussed elsewhere (Hakim et al., 2017). Further research is needed to test the proposed etiologic hypotheses and to determine whether other underlying risk factors influence the expression of circulatory problems.

5. Reasons to look for EDS and joint hypermobility in individuals with orthostatic intolerance (OI)

Until recently, few autonomic or cardiovascular studies have compared groups with and without JH/EDS. In Table 2, we enumerate several reasons for doing so, and in the section that follows we describe in more detail the potential benefits to clinicians and patients of distinguishing groups on the basis of connective tissue laxity, as well as the potential advantages to researchers of doing so in studies. The strength of these proposals will need to be evaluated as the research on the topic expands.

5.1. Reasons to look for EDS and JH in the clinical care of POTS and other forms of orthostatic intolerance

5.1.1. To improve general clinical management

Knowing that a given patient with orthostatic intolerance has hEDS would be important for the clinical assessment of other family members and also has implications for genetic counseling. Recognition of JH and EDS affects general management due to connective tissue laxity and fragility itself, and to the presence of co-morbid conditions (reviewed by Tinkle et al., 2017). For example, during pregnancy, surgery, and vascular procedures, hEDS patients have a higher risk of delayed wound healing and a higher risk of wound dehiscence, as a result of which they require longer periods of pressure at venipuncture sites and reinforcement of suture lines. Some experts recommend twice the waiting time before suture removal (Castori, 2012b). Intubation can be problematic for hEDS patients due to temporomandibular joint laxity or spinal ligamentous laxity and early intervertebral disc degeneration (Henderson et al., 2017).

Individuals with EDS have an increased risk of spontaneous cerebrospinal fluid leaks, which in turn can contribute to worsening of headaches in positions of upright posture (Mokri et al., 2002). Orthostatic headaches are common in POTS and other forms of orthostatic intolerance (Mack et al., 2010). Orthostatic headaches due to spinal fluid leaks and intracranial hypotension would require entirely different management than orthostatic headaches due to POTS alone. Although the clinical features discriminating orthostatic headaches due to POTS from those due to spinal fluid leaks have not been clearly enumerated, one might expect orthostatic headaches due to POTS to be more responsive to the usual POTS or headache treatments, whereas headaches due to spinal fluid leaks would be more refractory. Recognizing EDS and the higher risk of spinal fluid leaks might prevent a delay in diagnosis of this less common cause of orthostatic headaches. Other problems that occur more commonly in EDS are described elsewhere (Castori, 2012a; Tinkle et al., 2017). Thus far, no studies have identified differences in the pharmacological management of orthostatic intolerance for those with and without JH or EDS, but this topic warrants further study.

5.1.2. To detect rare forms of EDS and other hereditary connective tissue disorders

Screening for hereditary connective tissue disorders is important for dysautonomia patients because it can lead to the detection of conditions that have a higher mortality risk, including Marfan syndrome (Van Dijk et al., 2008) and vascular EDS (vEDS). Although those with vascular EDS are less likely than cEDS and hEDS to have autonomic symptoms (De Wandele et al., 2014a), it would be important to diagnose vEDS because of the increased risk of arterial aneurysms and hollow organ rupture (Byers et al., 2017). The major criteria for vEDS are a family history of vEDS with documented causative variant of COL3A1, arterial rupture at a young age, spontaneous sigmoid colon perforation, uterine rupture during the third trimester without history of a previous C-section, severe peripartum perineum tears and carotid-cavernous sinus fistula (CCSF) formation in the absence of trauma. The minor criteria for vEDS include easy bruising in the absence of trauma, translucent skin, vascular visibility, acrogeria, early onset varicose veins, congenital talipes, and characteristic facial features (large, protruding eyes, thin lips, thin and pinched nose, hollow cheeks, and small earlobes) (Byers et al., 2017).

5.1.3. To ensure provision of appropriate physical therapy care

The avoidance of complete inactivity is important in POTS to prevent reductions in blood volume that can accompany complete bed rest (Takenaka et al., 2002). Graded increases in exercise have been proposed as a means of counteracting the reduction of blood volume that can be seen in association with POTS (Fu et al., 2010). However, in patients with joint hypermobility, training protocols need to be adapted for tissue fragility (Engelbert et al., 2017). Patients with EDS often report exacerbation of pain and fatigue after exercise, and the recovery from physical exertion can be protracted. Rigid advancement of high impact exercise that places excessive strain on hypermobile joints has the potential to cause harm in those with hEDS.

For these patients, EDS experts recommend starting aerobic training at a very low training intensity. Low impact exercises (cycling, leg press, hydrotherapy, etc.) are better suited than exercises that contains a high impact component on the joints (e.g., running). In patients with POTS, increasing the muscle mass of the lower limbs has been recommended to improve the 'muscle pump function' (Sheldon et al., 2015; George et al., 2016). To avoid subluxations and pain complaints, EDS experts prefer symmetrical strengthening exercises that cause joint compression (e.g. leg press with a theraband around the knees) over asymmetrical exercises, open chain movements, and exercises that contain a distraction component (e.g. lifting the leg in a standing position with a weight around the ankle).

In addition, the advancement of exercise is often more successful in EDS after the incorporation of manual therapy techniques (as opposed to exercise-based treatment) to restore normal biomechanics, address areas of neurodynamic dysfunction, increase joint stability, and address dysfunctional posture and body mechanics (Russek, 2000; Simmonds and Keer, 2007; Simmonds and Keer, 2008; Engelbert et al., 2017). Ring splints to prevent excessive hyperextension of the fingers during writing, or splints to protect other hypermobile joints, might be needed. In this population, high velocity manual thrust treatments are generally avoided because of the potential to increase hypermobility in the treated segment.

5.1.4. To provide a unifying diagnosis for patients

Identifying joint hypermobility or hEDS in those with POTS and orthostatic intolerance can help to provide a unifying diagnosis for the other chronic symptoms. Instead of a long and seemingly disconnected series of separate co-morbid diagnoses, the recognition of JH or EDS allows clinicians to be attentive to potential complications of connective tissue laxity and, in many instances, to initiate preventive measures. As one patient stated: "The diagnosis of EDS made it all make sense… it glued all of the problems together and showed that there was an underlying cause for the different issues."

5.2. Reasons to look for EDS and JH in studies of POTS and other forms of orthostatic intolerance

5.2.1. To accurately describe the clinical features of study populations

Screening for JH and hEDS can improve the description of study populations and thereby allow readers to draw more accurate inferences about the representativeness of study findings. For example, in a study to address the prevalence of anxiety in those with POTS, it would be important to distinguish between those with and without hypermobility given the reports of an elevated prevalence of anxiety in those with joint hypermobility (Smith et al., 2014). In a large systematic review of 1006 with joint hypermobility syndrome and 2951 controls, those with joint hypermobility had higher odds of anxiety (OR = 4.4) and panic disorder (OR = 6.7). There has been speculation that brain structure in EDS might contribute to some of this risk (Mallorqui-Bague et al., 2014). Conversely, studies of anxiety in EDS would benefit from analyzing the independent contribution of POTS and its accompanying hyperadrenergic state, particularly in light of older evidence that isoproterenol can provoke panic and anxiety in experimental settings (Rainey et al., 1984; Balon et al., 1990; Pohl et al., 1988; Pohl et al., 1990).

The potential benefits of separating those with and without hypermobility are illustrated in a paper comparing 39 with POTS alone and 26 with POTS and preexisting JH (age range 10–53 years) who had been referred for evaluation of orthostatic intolerance symptoms (Kanjwal et al., 2010). Those with JH and POTS presented at a significantly younger age than those with isolated POTS and had a higher prevalence of co-morbid syncope (62 vs. 30%). None of the JH patients had experienced a viral infection as a precipitant of POTS, compared to 15% of the POTS only group, but this difference did not reach statistical significance. The overall rate of migraines in a group of 65 patients with POTS was 46%. However, Kanjwal and colleagues found that 73% of patients with POTS and hEDS had migraines, compared to 28% of patients with isolated POTS ($P = 0.001$). Whether differences in rates of co-morbid diagnoses are present at all ages has been challenged in a small study (Chelimsky et al., 2016). In a retrospective review of pediatric patients with chronic functional pain disorders, 11 with JHS and 10 without, there were no differences in migraines or other co-morbid disorders including orthostatic intolerance. The authors conclude that JHS is not the driving factor for the autonomic and co-morbid disorders, although the small sample size limits confidence in these conclusions.

Studies of health related quality of life (HRQOL) in individuals with POTS risk misrepresenting the true quality of life of affected patients unless the independent effects of joint hypermobility or EDS are measured. To illustrate, HRQOL was measured using the SF-36 questionnaire both in a study of POTS (Benrud-Larson et al., 2002) and in a study of EDS (Rombaut et al., 2010). Accounting for some differences in the method of reporting the central tendency of the data (means versus median values), and for error in extrapolations from a figure, the mean or median scores for the SF-36 physical function subscale are similar in healthy controls (90–95 range) between the two studies, but appear to differ substantially for patients. The mean physical function subscale score was 55 in POTS and the median value in hEDS was 35, with lower scores indicating worse QOL. The bodily pain subscale scores also appear to differ substantially, 60 in POTS and 35 in hEDS. If a POTS study included a large proportion of EDS participants, the results would be biased towards lower HRQOL than might be true for those with POTS but without EDS. The magnitude of these apparent differences emphasizes the importance of reporting data on symptoms and HRQOL separately for those with and without joint hypermobility in future studies.

5.2.2. To reduce biased assignment to subgroups in pathophysiology studies

Distinguishing POTS plus JH/hEDS versus POTS without JH/hEDS would help prevent unbalanced assignment to subgroups in pathophysiology studies. Take, for example, a hypothetical study designed to examine the prevalence of beta-receptor hypersensitivity in those with POTS. The data from Gazit and colleagues describe an increased sensitivity to isoproterenol among those with JH. If a new study did not ascertain for JH/EDS among the POTS population, then a chance recruitment of a study population that overrepresented JH/EDS would lead to an overestimate of the prevalence of beta-receptor hypersensitivity among those with POTS.

5.2.3. To reduce enrollment of potential non-responders in treatment studies

Screening for joint hypermobility and EDS has the potential to improve the interpretation of responses to study interventions. In addition to the other conditions already mentioned, individuals with hEDS have a higher risk of a wide variety of co-morbid problems, including gastrointestinal motility disorders, scoliosis, varicose veins, Chiari malformation, craniocervical instability, painful joint dislocation, and others (Castori, 2012a; Zarate et al., 2010; Milhorat et al., 2007; Henderson et al., 2017). A coincidental exacerbation of any of these conditions at the time a study medication was introduced could increase the background noise of general symptoms, potentially obscuring the signal from an effective intervention. This methodologic threat to internal validity could be addressed through stratifying study patients based on the presence or absence of joint hypermobility or hEDS or on the number or severity of co-morbid conditions.

5.2.4. To prevent incorrect causal inferences

Screening for joint hypermobility and hEDS in POTS patients has the potential to reduce the risk of drawing incorrect causal inferences. For example, Durham and colleagues evaluated the prevalence of temporomandibular disorders (TMD) among 36 adults with POTS (Durham et al., 2015). They identified 17 (47%) as having TMD and concluded that this elevated prevalence "adds further support to the conditions having a similar underlying dysautonomic pathophysiology." Other studies, however, suggest that joint hypermobility likely precedes and predisposes to both TMD (De Coster et al., 2005; Kavuncu et al., 2005; Deodato et al., 2006; Pasinato et al., 2011) and POTS (Rowe et al., 1999). Kavuncu and colleagues found that 87% of patients with systemic joint hypermobility (SJH) and localized condylar hypermobility (LCH) also suffer from TMD, compared to only 30% of controls (Kavuncu et al., 2005). The odds ratio for hypermobility syndromes in TMD were 11.2 for SJH, 7.5 for LCH and 15.3 for both. This study showed that the risk of TMD was significantly higher if both LCH and SJH were present ($P < 0.001$). Although the presence of co-morbid dysautonomia might influence the expression of pain and related symptoms in those with TMD, we would suggest that POTS is a confounder for the relationship between joint hypermobility/hEDS and TMD, and that the true causal pathway leads from connective tissue laxity to both POTS and TMD, rather than from a dysautonomic state to both POTS and TMD.

6. Conclusion

There is a strong association between joint hypermobility and Ehlers-Danlos syndrome and several forms of orthostatic intolerance, most strikingly postural tachycardia syndrome. A proportion with hEDS report frequent orthostatic symptoms that correlate with impairments

in quality of life. Increased attention to the prevalence of joint hypermobility and EDS in those with orthostatic intolerance syndromes has the potential to improve clinical care and to enhance the validity of research results.

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