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Prevalence of Hypermobile Ehlers-Danlos Syndrome in Postural Orthostatic Tachycardia Syndrome

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Abstract

Despite well-established clinical associations between Hypermobile Ehlers-Danlos syndrome (hEDS) and postural orthostatic tachycardia syndrome (POTS), the precise prevalence is unknown. We therefore evaluated for hEDS in 91 POTS participants using the 2017 hEDS diagnostic checklist, which has three major criteria: 1) generalized joint hypermobility (Beighton score), 2) systemic features, family history, and 3) absence of exclusion criteria. Overall, 28 out of 91 POTS participants (31%) met clinical criteria for hEDS. An additional 24% of participants had generalized joint hypermobility without meeting hEDS criteria. Identifying the prevalence of hEDS in POTS is important for understanding possible mechanisms connecting these two syndromes.

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DISCLOSURES

On behalf of all authors, the corresponding author states that there is no conflict of interest.

INTRODUCTION

Hypermobile Ehlers-Danlos Syndrome (hEDS) is a heritable disorder of connective tissue that is characterized by joint hypermobility and instability, chronic widespread pain, mildly stretchy skin, and soft tissue manifestations.(Malfait et al., 2017) Many other symptoms are described in hEDS that are more debilitating than joint manifestations, even though they are not included in diagnostic criteria. These features include but are not limited to sleep disturbances, fatigue, functional gastrointestinal disorders, and orthostatic intolerance (OI), most commonly postural orthostatic tachycardia syndrome (POTS).(Tinkle et al., 2017) POTS is characterized by excessive orthostatic tachycardia in the presence of daily orthostatic symptoms such as lightheadedness, fatigue, and nausea. The tachycardia in POTS is defined by an increase in heart rate from the supine posture of at least 30 beats/min in adults and 40 beats/min in adolescents within 10 minutes of standing or head-up tilt. (Sheldon et al., 2015)

It is estimated that two-thirds of individuals with hEDS have OI, with 41–49% of these individuals having POTS.(Roma et al., 2018). Despite an anecdotal clinical association, the precise prevalence of hEDS in POTS is unclear, with most studies to date relying on self-report or retrospective chart review and not specifying EDS subtype.(Deb et al., 2015; Kavi, 2016; Wallman et al., 2014) In addition, in the 2017 reclassification, the diagnostic guidelines for hEDS were made more stringent.(Malfait et al., 2017) The goal of the present study was to investigate the prevalence of hEDS using current diagnostic criteria in a large convenience sample of people with POTS.

METHODS

The Penn State Hershey Medical Center Institutional Review Board approved all procedures. A convenience sample of 100 people with POTS was recruited from the 2018 Dysautonomia International Conference, which was held in June in Nashville, TN and had 600 attendees. Dysautonomia International is a non-profit organization that supports dysautonomia awareness and research. Dysautonomia International hosts an annual national educational conference primarily directed to patients and caregivers. Participants with POTS who were 13–60 years of age and had previously been diagnosed with POTS by a clinician were invited to participate in this study. Participants who were ≥18 years of age provided written informed consent. Participants who were <18 years of age signed an assent form, with a parent or guardian signing the consent form. The study was advertised during the patient conference as a project to assess co-morbidities of POTS, with EDS not specifically mentioned, to prevent volunteer bias favoring participation by people with POTS who had known or suspected EDS.

Following the informed consent process, participants were asked to fill out a comorbidities questionnaire and scheduled to return for a study visit. Participants were evaluated for hEDS by physicians (authors: C.A.F, R.B, H.P.L) using the hEDS diagnostic checklist that was developed by the International Consortium on EDS and Related Disorders as part of the 2017 classification.(Malfait et al., 2017) The hEDS diagnostic checklist includes three criteria: 1) Generalized Joint Hypermobility, 2) Systemic Features and Family History, and

3) Exclusion Criteria. All three criteria must be simultaneously present to diagnose hEDS. (Malfait et al., 2017) Criterion 1 includes the Beighton Scale and five questions to assess joint hypermobility.(Juul-Kristensen et al., 2017) Goniometers were used by all evaluators to confirm that the degree of joint hyperextension. Criterion 2 includes three parts, A) Systemic features of EDS including skin features, hernias, prolapse, arm span > height, and echocardiographic findings, B) family history, and C) chronic pain and joint instability. Two out of the three parts (A, B, and C) must be met to fulfill Criterion 2. Criterion 3 is exclusion criteria to rule out other types of EDS, other connective tissue disorders, and neuromuscular diseases. Criterion 3 also notes that if a patient has a known autoimmune disease, then Criterion 2C (chronic pain and joint instability) cannot be counted. In the setting of the research study, slight modifications to the diagnostic checklist were necessary. We did not evaluate or perform echocardiography in Criterion 2A and relied on self-reported previous diagnosis of mitral valve prolapse (after 2014) or aortic root dilation. For Criterion 3, participants filled out a form after providing consent; the questionnaire asked them to identify previous diagnoses that they subsequently discussed with their physician-evaluator. We did not review medical records or perform further tests to rule out Criterion 3 conditions. Participants were sent a copy of their checklist following their study to discuss with their care providers, if desired. No clinical diagnosis was provided to participants by the study physicians.

Following the study, participants were emailed a link to a questionnaire to complete in the online database, REDCap. The questionnaire included questions about POTS onset, comorbidities, current medications, and standard scales to assess quality of life and autonomic and orthostatic symptoms including the RAND 36-item Short Form Health Survey (SF36) which includes mental and physical health scores, composite autonomic symptom score (COMPASS 31), and the orthostatic grading scale.

Questionnaire data and hemodynamic data were compared between POTS participants with versus without hEDS using Mann-Whitney U nonparametric tests. The proportions of POTS participants with versus without hEDS that were female and currently taking common medications were compared using Chi-square analysis tests. Data were analyzed using GraphPad Prism (Version 8.3.0), with significance level set at $p < 0.05$ for all tests.

RESULTS

Demographic Data for POTS Participants

One hundred POTS participants signed the consent form for the study, with 91 returning to complete the study visit. Of these participants, 77 (85%) completed the questionnaire in REDCap following the study. Demographic and questionnaire data are shown in Table 1. POTS participants were 93% female, 96% Caucasian, and 14–59 years of age (median age: 26 years).

Hypermobile Ehlers-Danlos Syndrome Evaluations

The number and percentage of POTS participants fulfilling each criterion for the 2017 hEDS diagnostic criteria is shown in Table 2. Fifty participants (55%) met Criterion 1 for

generalized joint hypermobility. Of these participants, 45 were positive for Criterion 1 based solely on the Beighton score cutoffs for their age range, and 5 participants (age 18–31 years) scored 4/9 on the Beighton scale and gained an extra point through the 5-point questionnaire for assessing generalized joint hypermobility.(Juul-Kristensen et al., 2017) Criterion 2 was fulfilled by 37 participants (41%), with most participants meeting this criterion based on systemic features (criterion 2A, 47%) and pain/joint instability (criterion 2C, 69%). Only 6 participants (7%) had a positive family history of hEDS based on 2017 criteria (criterion 2B). Criterion 3, absence of exclusion criteria, was fulfilled by 77 participants (86%). Overall, based on the physician evaluations, 28 participants (31%) met all three hEDS criteria.

Differences between POTS Participants with versus without hEDS

Beighton scores were higher in POTS participants with versus without hEDS (Table 1). There were no differences in mental or physical quality of life (SF-36) or orthostatic grading scale scores between POTS with hEDS and POTS without hEDS. There was a trend towards higher COMPASS 31 total and OI scores in POTS participants with hEDS suggesting more severe autonomic symptoms, but this did not reach statistical significance (p=0.064). Current use of beta-blockers was lower in POTS participants with versus without hEDS (38% versus 55%, respectively; p=0.040), with no differences in other commonly used medications between groups.

Self-Reported Ehlers-Danlos Syndrome Prevalence

Based on the online REDCap questionnaire, the self-reported rate of EDS was 46% and the self-reported rate of hEDS subtype was 42% (Table 1). Only 19 out of 32 participants (56%) who self-reported previous hEDS diagnosis, met hEDS criteria during the study evaluation. The remaining 13 participants self-reporting previous hEDS diagnosis were not classified as having hEDS during this study, with 9 out of 13 of these participants having a Beighton score >5. Furthermore, 7 participants did not report previous hEDS diagnosis, but met hEDS criteria in this study.

DISCUSSION

This is the first cross-sectional study to evaluate the prevalence of hEDS in a large sample of POTS participants using the updated 2017 hEDS diagnostic criteria. We found that 31% of POTS participants were classified as having hEDS, with 55% exhibiting generalized joint hypermobility.

Previous Estimates of EDS Prevalence in POTS

The connection between EDS and OI was first recognized in 1999, when Rowe and colleagues found that 12 out of 100 of patients presenting in their clinic for OI had EDS. (Rowe et al., 1999) Since then, several retrospective chart review studies have reported a prevalence of EDS in POTS between 12 and 22%. One study found 7 out of 39 (18%) POTS patients evaluated had EDS, compared with 4% of autonomic patients without POTS and an estimated 0.02% prevalence in the general population.(Wallman et al., 2014) Another study reported that 6 out of 38 (16%) POTS patients from one clinic had EDS.(Deb et al., 2015)

These prior studies did not differentiate between EDS subtypes, however, and it is unclear whether all study participants were evaluated for EDS and what criteria were used. A study by Boris et al. observed 57% prevalence of joint hypermobility, with 22% diagnosed with hEDS and the other 35% diagnosed with hypermobility spectrum disorders, in a large single center pediatric POTS cohort (n= 708).(Boris et al., 2018) It is possible that some participants in this study did not have POTS since heart rate criteria used (increase in heart rate >30 beats/minute within 10 minutes of standing) were inconsistent with current consensus diagnostic criteria for pediatric POTS (increase in heart rate >40 beats/minute within 10 minutes of head-up tilt).(Boris et al., 2018; Sheldon et al., 2015) All previous estimates of the prevalence of EDS in POTS based on retrospective analysis confirmed that participants had OI or POTS by review of medical records but relied on older diagnostic criteria for EDS that were imprecise, inconsistently used, and often did not identify EDS subtype.

An advantage of the current study is that we investigated the prevalence of hEDS in a diverse cohort of adolescent and adult POTS participants using current and more stringent criteria. Our finding that 31% of POTS participants evaluated had hEDS, and an additional 24% had generalized joint hypermobility, support the high prevalence of joint hypermobility and in particular, hEDS, among people with POTS. The rate of hEDS in our study is higher than previous estimates from retrospective analyses.

Online questionnaire-based studies estimate that 26–50% of people with POTS have been previously diagnosed with EDS.(Deb et al., 2015; Kavi, 2016; Shaw et al., 2019) In the largest published survey of POTS patients (n=4,835), 26% of respondents reported they had been previously diagnosed with EDS; this survey was distributed worldwide but 80% of participants were in the United States.(Shaw et al., 2019) In two survey-based studies from the United Kingdom, 26% of 136 (Deb et al., 2015) and 50% of 779 survey respondents with POTS reported being previously diagnosed with EDS.(Kavi, 2016) These previous survey-based studies relied on self-report of POTS and EDS diagnoses, did not differentiate EDS subtypes, and it is unclear whether all respondents were evaluated for EDS and what criteria were used.

In the current study, the self-reported rate of EDS of all variants was 46%, which is consistent with higher estimates in questionnaire-based studies.(Deb et al., 2015; Kavi, 2016; Shaw et al., 2019) The self-reported rate of the hypermobile type of EDS in our study was 42%, which is higher than the 31% of participants who met the diagnostic criteria for hEDS through physician-based evaluation in our study. This finding is consistent with previous literature discussed above in which the self-reported prevalence of EDS in POTS is generally higher compared to estimates from evaluation-based studies. There are several possibilities for the divergence in self-reported and objectively measured hEDS in this study. First, it is unclear how patients were previously evaluated for hEDS. The hEDS evaluation may have been incomplete (by just including the hypermobility criteria only for example) or based on older diagnostic criteria which were less specific than the 2017 diagnostic criteria. (Malfait et al., 2017) Some of the patients who would have previously been diagnosed with hEDS, may fall into the category of hypermobility spectrum disorders based on the new criteria.(Juul-Kristensen et al., 2017) It is also possible that some participants who were

previously diagnosed with hEDS, were not diagnosed correctly in our study given our rapid evaluation and lack of echocardiography data in the research setting.

Significance of Overlap between hEDS and POTS

Despite an established clinical association, it remains unclear there are any pathophysiology that connects EDS and POTS. Rowe, et al. first postulated that the mechanism underlying this association is that generalized connective tissue laxity in hEDS increases vascular and venous compliance, leading to insufficient vasoconstriction and venoconstriction when upright to predispose to OI.(Rowe et al., 1999) This theory has become widely accepted despite there being no evidence to support it.(Roma et al., 2018) There is also an increased prevalence of small fiber neuropathy in EDS, which may contribute to autonomic dysfunction.(Cazzato et al., 2016) The current study helps identify a phenotype of patients and future research is needed to explore possible mechanism(s) linking POTS to hEDS. We did not observe many differences between POTS participants with and without hEDS. However, less POTS with hEDS participants were taking beta-blockers. While beyond the scope of the study, it is possible that hEDS patients are more intolerant to beta-blockers or that treatments to increase vasoconstriction, such as midodrine and stimulants, are preferentially prescribed for POTS patients with hEDS since that is the leading theory on how POTS and EDS are related.

Limitations

There are several potential limitations to this study. First, it is important to note that the study population may not reflect the entire population of POTS patients since participants were recruited from attendees of the 2018 Dysautonomia International patient conference and many patients are not able to travel for financial or health reasons. However, this is a limitation of most research studies that require an in-person study visit. Dysautonomia International offers several need-based scholarships to help patients attend the conference which helps mitigate a socioeconomic bias in this study. It is possible there was a volunteer bias in which POTS participants with suspected or diagnosed hEDS were more motivated to volunteer for the study in order to obtain the hEDS evaluation. We attempted to mitigate this bias by advertising this study as a co-morbidity of POTS evaluation, in which EDS was just one condition. We did not formally evaluate for POTS in this study due to the need to keep participants on medications, and therefore relied on self-report of prior POTS diagnosis. The demographics questionnaire was administered post-study, with approximately 15% of participants not completing this component, thus making the self-reported EDS data incomplete. We did not evaluate or perform echocardiography data in criterion 2A and therefore could have missed classifying some participants with hEDS. We did not include a control group in this study; the estimated prevalence of hEDS is 0.0002% and symptomatic generalized joint hypermobility is 2% in the general population.(Tinkle et al., 2017)

CONCLUSIONS

Overall, this study represents the first cross-sectional study examining prevalence of hEDS in a large sample of participants with POTS using the 2017 diagnostic checklist for hEDS. Previous estimates of hEDS prevalence in POTS were based on retrospective chart reviews

or self-report with inconsistent screening. These data will inform future research on potential mechanisms that connect these syndromes and treatment approaches.

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ABBREVIATIONS

(EDS)	Ehlers-Danlos syndromes
(hEDS)	Hypermobile Ehlers-Danlos syndrome
(OI)	Orthostatic Intolerance
(POTS)	Postural orthostatic tachycardia syndrome

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Table 1.

Demographic and Questionnaire Data for POTS Participants

Study Visit Data	All Participants (n = 91)	POTS without hEDS (n = 63)	POTS with hEDS (n = 28)	p-values
Age, median (range)	26 (14–59)	27(14–59)	26 (17–40)	0.944
Sex, female n (%)	86 (93)	59 (90)	27 (96)	0.257
Beighton Score, median (range)	4 (0–9)	3 (0–8)	6 (4–9)	0.001*
REDCap Questionnaire Data	All Participants (n = 77)	POTS without hEDS (n = 51)	POTS with hEDS (n = 26)	p-values
Race, Caucasian (%)	96%	94%	100%	0.298
Hispanic, (%)	4%	6%	0%	0.298
Education years, median (range)	16 (8–22)	16 (8–22)	14 (11–20)	0.959
Age at POTS symptom onset, median years (range)	16 (5–52)	15 (5–52)	18 (10–32)	0.938
SF-36 Physical Functioning (0–100%), median (IQR)	40% (25–65)	40% (25–55)	38% (24–66)	0.955
SF-36 Emotional Well Being (0–100%), median (IQR)	68% (52–80)	64% (48–80)	68% (55–81)	0.754
Orthostatic Grading Scale (0–20), median (IQR)	13 (9–15)	13 (13–14)	14 (8–16)	0.287
COMPASS 31 Orthostatic Intolerance Score (0–40), median (range)	24 (20–28)	24 (20–28)	28 (24–29)	0.064
COMPASS 31 Total Score (0–100), median (IQR)	46 (36–55)	45 (34–52)	51 (40–62)	0.065
Self-reported diagnosis of Ehlers-Danlos Syndromes, n (%)	35 (46%)	16 (31%)	19 (73%)	
• Classical	3 (4%)	3 (6%)	0 (0%)	
• Hypermobile	32 (42%)	13 (25%)	19 (73%)	
• Vascular	0 (0%)	0 (0%)	0 (0%)	
• Other	0 (0%)	0 (0%)	0 (0%)	
Common Current Medications, n (%)				
• Beta blockers	38 (49%)	28 (55%)	10 (38%)	0.040*
• Vitamin B12 supplements or injections	23 (30%)	15 (29%)	8 (31%)	0.961
• Fludrocortisone	22 (29%)	16 (31%)	6 (23%)	0.274
• Midodrine	21 (28%)	13 (25%)	9 (35%)	0.383
• Intravenous Saline	20 (26%)	12 (24%)	8 (31%)	0.571
• Ivabradine	11 (14%)	6 (12%)	5 (19%)	0.340
• Steroids	10 (13%)	6 (12%)	4 (15%)	0.710
• Pyridostigmine	9 (12%)	5 (10%)	4 (15%)	0.450
• Narcotics	4 (5%)	2 (4%)	2 (8%)	0.396
• Intravenous Immunoglobulin	4 (5%)	3 (6%)	1 (4%)	0.674

Postural orthostatic tachycardia syndrome (POTS), Hypermobile Ehlers-Danlos Syndrome (hEDS), Interquartile range (IQR). Data are shown as median (range or IQR) or percentages. p values represent either Mann-Whitney U nonparametric tests between POTS participants with versus without hEDS, or chi-square analysis for proportions of POTS participants with versus without hEDS that were female or currently taking common medications.

* represents p value < 0.05.

Table 2.

Prevalence of hypermobile Ehlers-Danlos Syndrome (hEDS) in volunteers with Postural Orthostatic Tachycardia Syndrome (POTS)

	Number of Participants who fulfilled criteria (n = 91)	Percentage of Participants who fulfilled criteria (%)
Criterion 1:	50	55
Joint Hypermobility		
Beighton Scale only	45	49
Beighton scale plus 5-point questionnaire	5	6
Criterion 2:	37	41
2a: Systemic Features	43	47
2b: Family History	6	7
2c: Pain and Joint Instability	63	69
Criterion 3:	77	86
Exclusion Criteria		
hEDS Diagnosis	28	31