Original Article

SAGE Open Medicine

SAGE Open Medicine
Volume 12: 1–7

DOI: 10.1177/20503121241287073
journals.sagepub.com/home/smo
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Cardiovascular, autonomic symptoms and quality of life in children with hypermobile Ehlers–Danlos syndrome

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Abstract

Objectives: Hypermobile Ehlers–Danlos syndrome is a connective tissue disorder characterized by joint hypermobility and other systemic manifestations. Cardiovascular, autonomic symptoms and dysautonomia are frequently reported in adults with hypermobile Ehlers–Danlos syndrome and have been shown to have a negative impact on quality of life. However, there is scant literature on autonomic symptoms in pediatric patients with hypermobile Ehlers–Danlos syndrome. This study aims to characterize cardiovascular symptoms and diagnoses in pediatric patients with hypermobile Ehlers–Danlos syndrome and evaluate the impact of autonomic symptoms on quality of life.

Methods: As part of a longitudinal study, a consecutive sample of 70 patients with Ehlers–Danlos syndromes were recruited at routine clinical care visits. Medical history was reviewed, demographics were obtained, and patient-reported outcomes were completed by the patients.

Results: The average age of 70 patients was 15.8 years, and the majority were females (89%) and Caucasian (89%). The most common cardiovascular diagnoses were orthostatic intolerance (59%), dysautonomia (47%), and postural orthostatic tachycardia syndrome (21%). Most patients had an echocardiogram (77%), that was normal (82%). No patients had mitral valve prolapse, and only one patient had mild aortic root dilation (2%). Patient-reported outcomes revealed decreased quality of life associated with autonomic symptoms.

Conclusions: This study shows that most children with hypermobile Ehlers–Danlos syndrome have cardiovascular and autonomic symptoms, which have a negative impact on quality of life. Few patients with hypermobile Ehlers–Danlos syndrome have structural abnormalities on echocardiogram, which suggests that the cardiovascular symptoms experienced by patients are not due to structural cardiovascular disease and possibly reflective of autonomic pathology, though further studies will need to confirm this. This study confirms that cardiovascular and symptoms are prevalent and have a dramatic impact on quality of life in pediatric and young adult patients diagnosed with hypermobile Ehlers–Danlos syndrome.

Keywords

Cardiovascular, Ehlers-Danlos syndrome, quality of life, pediatrics, dysautonomia

Date received: 8 May 2024; accepted: 9 September 2024

Introduction

Ehlers–Danlos syndromes (EDS) are a group of connective tissue disorders that present with skin hyperextensibility, joint hypermobility, and tissue fragility, with the most common subtype being hypermobile Ehlers–Danlos syndrome (hEDS). EDS occurs in 1 in 5000 births, with hEDS accounting for most cases (80%–90%). Unlike other EDS subtypes, the genetic markers of hEDS are unknown and subsequently, hEDS is diagnosed based on the 2017 International Classification of the EDS clinical criteria.[1] Due to the high

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prevalence of hypermobility that may resolve over time in the adolescent aged patients, a new pediatric joint hypermobility framework was developed, which is similar to the 2017 EDS International Classification Criteria for adults and was published in 2023.[2] Many comorbidities are associated with hEDS, which includes autonomic symptoms and dysautonomia such as postural orthostatic tachycardia syndrome (PoTS). The dysautonomia is impairing, frequently reported by adults with hEDS[3] and commonly includes lightheadedness, palpitations, syncope, chest pain, diarrhea, fatigue, and migraines.[4,5] PoTS is a type of dysautonomia that is diagnosed by an increase in heart rate when moving from supine to standing (at least 30 beats per minute (bpm) in adults and 40 bpm in adolescents), autonomic symptoms while in the standing position, and the absence of orthostatic hypotension.[5] Additionally, PoTS is thought to be due to central nervous system dysfunction.[6] This may be one shared mechanism between PoTS and EDS, as those with EDS may be more prone to central sensitization deficits.[7] However, more research is needed to elucidate these mechanisms.[7]

The prevalence of PoTS in the general population is 0.2%.[5] In patients with hEDS, the prevalence of PoTS is around 30% (150 times higher than in the general population).[4] PoTS has been well-studied in adult patients.[5] Additionally, dysautonomia and PoTS are frequently reported in adults with hEDS and have been linked with lower quality of life (QoL), increased pain, and fatigue.[8] However, there is scant literature on PoTS, dysautonomia, and cardiovascular autonomic symptoms in pediatric patients[9] despite half of all patients with PoTS receiving the diagnosis during adolescence.[10] This represents a gap in the medical literature that needs to be addressed.[11] This study aims to characterize cardiovascular diagnoses and symptoms in pediatric patients with hEDS and evaluate the impact of autonomic symptoms on QoL.

Methods and materials

Study population

As part of a longitudinal study, a clinic-based, consecutive, convenience sample of 70 patients diagnosed with EDS were recruited at routine clinical care visits from a pediatric multidisciplinary EDS clinic at one tertiary care center between May 2022 and December 2022. All patients were recruited from the multidisciplinary EDS clinic. This sample size included all patients who enrolled in the study and completed the initial surveys. The decision to use the sample size was made on the basis that this is a rare disease population. Patients were eligible if they were <22 years of age and had a diagnosis of EDS as defined by the 2017 International Classification for the Ehlers–Danlos Syndromes.[1] Patients were excluded if they did not have a diagnosis of EDS or did not complete all surveys. Of all patients approached for this study, 82% agreed to participate, and 43% completed all surveys. Medical history, which included cardiovascular symptoms, and diagnoses, was reviewed and demographics were obtained from patients' Electronic Medical Record (EMR). From the EMR, cardiovascular symptoms and diagnoses were collected from the cardiology medical notes, while additional medical history was obtained from other specialties documentation. Orthostatic testing was performed on all patients that reported autonomic symptoms as part of the cardiovascular evaluation at the clinic visit and the cardiologist made the diagnosed of dysautonomia and PoTS based on the results of their evaluation. Finalized echocardiogram results/impressions were obtained from the EMR. Patient-reported outcomes (PROs) were completed electronically by the patients via REDCap data collection forms. Institutional review board (IRB) approval was obtained (IRB Study ID: 00001628 and formal informed consent was not required for this study. This work was conducted in accordance with the Declaration of Helsinki.

Measures

Clinical assessments

Echocardiogram results and clinical cardiac symptoms and diagnoses were abstracted from the medical record.

Composite autonomic symptom score-31

The composite autonomic symptom score-31 (COMPASS-31) is an instrument used to assess autonomic symptoms and was developed by the Mayo Clinic based on a statistical analysis of the 169-question Autonomic Symptom Profile (ASP) and its scoring instrument, the COMPASS, in a cohort of controls (age range = 8–79).[12] The original ASP was simplified into 31 questions under six domains, forming the COMPASS-31. The six domains include Orthostatic Intolerance (OI), Vasomotor (VM), Secretomotor (SM), Gastrointestinal (GI), Bladder (BL), and Pupillomotor (PM).[12] It has since been used in many studies evaluating dysautonomia.[13–15] COMPASS-31 scores range between 0 and 100, with higher scores indicating worse dysautonomia.[12]

Patient reported outcomes measurement information system (PROMIS) pediatric profile-25, version 2.0 (PROMIS Pediatric-25 Profile v2.0)

The PROMIS Pediatric-25 Profile v2.0 assesses QoL and general health across diseases. It is a set of six four-item short forms that measure domains of anxiety, depressive symptoms, fatigue, pain interference, peer relationships, and physical function.[16] Each item is rated on a five-point Likert scale with a total of four questions per sub-scale.[16] The total sub-scale scores were calculated as the straight sum score of the four questions with each question ranging from 0 to 4 points. Similarly, the total PROMIS measure was scored using a straight sum score from the raw values of each

subsection. Higher PROMIS scores represent more of the domain of interest. The PROMIS Pediatric-25 Profile v2.0 covers health-related QoL (HRQoL) domains and may be applied to pediatric populations with demonstrated reliability in other pediatric groups with joint and muscle pain.[17] Post hoc power calculation for a sample size of $n=70$, probability cut-off of $\alpha=0.05$, and a correlation of $r=0.4$, was $\beta=0.95$. This study was adequately powered at $\beta=0.80$ for correlations above $r=0.32$.

Statistical analysis. Descriptive statistics were calculated for patient demographic data and PROs. All patient-reported subscales and total scores were evaluated for skew and kurtosis via measures of central tendency. Subscale scores were evaluated for nonnormality and kurtosis, and Pearson's statistical correlations were conducted between subscale scores. The statistical analysis was performed using IBM SPSS Statistics 24 software.

Results

Respondent characteristics

Of 70 patients that had a diagnosis of EDS and completed all surveys, the mean age was 15.8 years (SD = 2.9), the majority were female (89%) and Caucasian (89%), and all had a diagnosis of hEDS. The most common cardiovascular diagnoses were OI (59%), dysautonomia (47%), and PoTS (21%). Cardiovascular symptoms reported included tachycardia (31%), palpitations (13%), chest pain (14%), and dizziness (9%). While most patients reported two or more cardiovascular symptoms (92.9%), a minority had no cardiovascular involvement (7%) (Table 1).

Most patients had an echocardiogram (77%), and the majority were normal (82%). Specific to hEDS, no patients had mitral valve prolapse (MVP), and only one patient had mild aortic root dilation (ARD) (2%). Additionally, some patients had trivial regurgitation per official interpretation of the echocardiogram (15%) (Table 1).

Relationships between autonomic symptoms and HRQOL

Having tachycardia was correlated with a higher total COMPASS-31 score ($r=0.31$, $p=0.02$) and higher total PROMIS score ($r=0.31$, $p=0.02$). Additionally, a diagnosis of PoTS was also correlated with a higher total PROMIS score ($r=0.32$, $p=0.01$) (Table 2).

The average total COMPASS-31 score was 41.9 (SD = 13.8), the OI sub-domain score was 24.00 (SD = 9.49), and the pupillomotor sub-domain score was 1.96 (SD = 0.86). The average total PROMIS score was 3.1 (SD = 0.6). Higher sub-domain scores of the COMPASS-31 correlated with higher total PROMIS scores ($r=0.59$, $p=0.0002$). The pupillomotor ($r=0.59$, $p\leqslant 0.0001$) and OI ($r=0.47$, $p\leqslant 0.0001$) COMPASS-31 subdomains had the highest correlations with total PROMIS score. Additionally, the total PROMIS score correlated with the secretomotor ($r=0.40$, $p=0.0006$),

Table 1. Demographics and cardiovascular history in pediatric patients with hypermobile Ehlers-Danlos syndrome.

Demographics ($n=70$)	Freq	%
Sex		
Female	62	89
Male	8	11
Race		
Caucasian/White	58	89
More than one race	7	11
Ethnicity		
Non-Hispanic	58	89
Hispanic	7	11
Cardiovascular history ($n=70$)	**Freq**	**%**
Orthostatic intolerance	41	59
Dysautonomia	33	47
POTS	15	21
Aortic root dilation	1	1
Mitral valve prolapse	0	0
Tachycardia	22	31
Palpitations	9	13
Chest pain	10	14
Dizziness	6	9
Syncope	5	7
Shortness of breath	5	7
Chest tightness	1	1
Costochondritis	1	1
Exercise-induced bronchospasm	1	1
Recurrent pneumonia	1	1
Chronic pulmonary dysplasia	1	1
Chronic lung disease	1	1
Tracheomalacia	1	1
Number of cardiovascular symptoms and diagnoses		
0	5	7
1	14	20
2	11	16
3	7	10
4	12	17
5	9	13
6	7	10
7	1	1
Echocardiogram findings ($n=54$)		
Normal	44	82
Trivial regurgitation (all types)	8	15
Tricuspid	4	7
Mitral	3	6
Aortic	3	6
Pulmonic	1	2
Aberrant right subclavian artery	2	4
Stable mild aortic root dilation	1	2
Doming and thickened aortic valves	1	2
Patent foramen ovale	1	2
Mitral valve prolapse	0	0

gastrointestinal ($r = 0.29$, $p = 0.01$), and bladder ($r = 0.28$, $p = 0.02$) subdomains. However, the total PROMIS score did not correlate to the vasomotor subdomain ($r = 0.08$, $p = 0.52$) (Table 2).

Discussion

This is the first study to evaluate the impact of autonomic symptoms on QoL using the COMPASS-31 and PROMIS Pediatric-25 Profile v2.0 in pediatric patients with hEDS and addresses a gap in the literature.[11] This study shows a high percentage of autonomic diagnoses seen in pediatric patients with hEDS and shows that cardiovascular and autonomic symptoms have a negative impact on QoL for patients with hEDS.

Most patients (93%) in this study reported at least one cardiovascular symptom, which is similar to the adults with hEDS (89%).[4] Therefore, cardiovascular symptoms appear to be a common feature in hEDS and are similar in magnitude for both pediatric and adult populations. This is not a universal feature in hEDS, as some patients reported no cardiovascular symptoms. Further, PoTS has been reported in 30% of adult patients with hEDS,[4] while 21% of pediatric patients with hEDS had a PoTS diagnosis in this study. Both adult and pediatric percentages are significantly higher than the prevalence of PoTS in the general population (0.2%).[5] Differences in the adult and pediatric diagnostic criteria for PoTS (adults $>$ 30 bpm vs pediatrics $>$ 40 bpm increase in heart rate with standing)[5] could be one explanation for the difference in percentage observed between these two groups. Reports have shown the prevalence of dysautonomia in patients with hEDS to be between 31% and 94%,[18] which encompasses the 47% diagnosed with dysautonomia in this study. Therefore, the rate of PoTS, dysautonomia, and autonomic symptoms is high in both the adult and pediatric hEDS populations. This further supports the idea that clinicians need to be knowledgeable about hEDS[19] and associated comorbidities so that early screening can be performed and treatment delays can be avoided when patients with hEDS or autonomic symptoms present to care.

The results of this study also indicate some differences in cardiac findings between children and adults. The 2017 International Classification of the EDS includes both MVP and ARD as potential diagnostic criteria for hEDS.[1] Studies in adult patients with hEDS have found ranges of 6%–8% for MVP[4,20] and 0%–2% for ARD.[4,20] While our ARD frequency is consistent with these findings, we had no patients with MVP. One explanation is that MVP primarily impacts middle-aged adults with a prevalence of less than 1% in children and young adults.[21] These rates and the percentage of patients with trivial regurgitation are similar to the general population.[4] Other echocardiogram findings in this study include aberrant right subclavian artery, doming and thickened aortic valves, and patent foramen ovale, none of which have been reported routinely in hEDS. The frequencies of these other echocardiogram findings are no greater than what is found in the general population.[22–24] In summary, few patients had structural abnormalities on echocardiogram, and those seen were consistent with prevalence percentages in the general population. This suggests that the cardiovascular symptoms experienced by adult and pediatric patients with hEDS are primarily due to underlying autonomic symptoms rather than structural cardiovascular abnormalities. As none of the patients in this study had MVP and only one had mild ARD, both echocardiogram findings in the diagnostic criteria for hEDS, the role of echocardiogram in diagnosing hEDS in the pediatric and young adult population may be less relevant. However, we would still encourage routine echocardiograms to screen for cardiovascular structural disease, which appears to be rare but could have clinical treatment implications if identified.

Patients in this study exhibited a significant autonomic symptom burden, similar to other studies in both adults and children with PoTS and hEDS.[25] Additionally, the OI and pupillomotor subdomains were found to have the greatest contribution to the overall COMPASS-31 score in this study. A previous study found the subdomains with the greatest difference when comparing patients with PoTS to healthy controls were the OI and pupillomotor domains.[13] Additionally, other studies have reported that the OI subdomain has the greatest contribution to the total COMPASS-31 score in patients with PoTS.[14,15] The OI and pupillomotor subdomains should be evaluated further as they may have the potential to be used in place of the full COMPASS-31 to assess autonomic symptom burden in patients with hEDS, which may be more expeditious in a clinical setting. However, further research is needed to confirm these findings.

In all COMPASS-31 subsections, except for the vasomotor subdomain, higher subdomain scores in the COMPASS-31 correlated with higher total PROMIS scores. This suggests that higher autonomic symptom burden, correlates with a more negative impact on QoL. Additionally, results from this study align with previous literature that the pupillomotor and OI subdomains of the COMPASS-31 had the greatest correlation with total PROMIS scores. Thus, pupillomotor and OI symptoms most negatively impact HRQoL. This information could be beneficial to clinicians as they can focus more on the OI and pupillomotor subdomains of the COMPASS-31 when monitoring the autonomic symptom progression in patients with hEDS or PoTS. However, the secretomotor, gastrointestinal, and bladder subdomains may also have utility in evaluation as they also correlated with total PROMIS scores, but not as highly as pupillomotor and OI sub-domains.

Limitations to this study include a small sample size and cross-sectional design, which precludes more sophisticated data analysis, including structural equation modeling and subgroup analysis of patients based on cardiovascular symptoms and diagnoses; however, this is a reasonable sample

Table 2. Composite autonomic symptom score-31 (COMPASS-31) and patient reported outcomes measurement information system (PROMIS) correlations and total scores.

Subdomains	C-OI	C-VM	C-SM	C-GI	C-BL	C-PM	C-TOT	P-MOB	P-ANX	P-DEP	P-FA	P-PAIN	P-PEERS	P-TOT	Hx	OI	Dys	Tach	Palp	PoTS
COMPASS-31 orthostatic intolerance (C-OI)	1.00																			
COMPASS-31 vasomotor (C-VM)	0.12	1.00																		
COMPASS-31 secretomotor (C-SM)	0.25*	0.11	1.00																	
COMPASS-31 gastrointestinal (C-GI)	0.09	0.11	0.27*	1.00																
COMPASS-31 bladder (C-BL)	0.16	0.24*	0.25*	0.44**	1.00															
COMPASS-31 pupillomotor (C-PM)	0.45**	0.07	0.34**	0.48**	0.47**	1.00														
COMPASS-31 total (C-TOT)	0.84**	0.28*	0.56**	0.53**	0.49**	0.66**	1.00													
PROMIS mobility (P-MOB)	0.53**	0.21	0.38**	0.21	0.14	0.44**	0.58**	1.00												
PROMIS anxiety (P-ANX)	0.37**	0.10	0.15	0.13	0.17	0.50**	0.40**	0.40**	1.00											
PROMIS depression (P-DEP)	0.28*	0.13	0.41**	0.31**	0.34**	0.54**	0.48**	0.45**	0.68**	1.00										
PROMIS fatigue (P-FA)	0.40**	0.16	0.42**	0.26*	0.34**	0.54**	0.55**	0.63**	0.49**	0.59**	1.00									
PROMIS pain interference (P-PAIN)	0.37**	−0.04	0.33**	0.22	0.22	0.37**	0.44**	0.64**	0.34**	0.33**	0.62**	1.00								
PROMIS peer interactions (P-PEERS)	−0.26*	−0.28*	−0.26*	−0.07	−0.24*	−0.28*	−0.34**	−0.35**	−0.36**	−0.45**	−0.36**	−0.19	1.00							
PROMIS total (P-TOT)	0.47**	0.08	0.40**	0.29*	0.28*	0.59**	0.59**	0.76**	0.73**	0.74**	0.83**	0.76**	−0.23	1.00						
Any cardiovascular history (Hx)	0.19	−0.07	−0.13	0.20	0.04	0.11	0.17	0.05	0.21	−0.05	−0.01	0.02	0.10	0.09	1.00					
Orthostatic intolerance (OI)	0.21	0.20	0.20	0.13	0.26	0.17	0.30*	0.03	0.09	0.18	0.17	0.12	−0.23	0.11	—	1.00				
Dysautonomia (Dys)	0.33*	0.13	0.24	0.29*	0.26	0.31*	0.44**	0.17	0.16	0.28*	0.26	0.08	−0.01	0.25	—	0.12	1.00			
Tachycardia (Tach)	0.24	0.22	0.05	0.20	0.23	0.25	0.31*	0.23	0.27*	0.30*	0.28*	0.22	−0.18	0.31*	—	0.20	0.28*	1.00		
Palpitations (Palp)	0.15	0.04	0.08	0.19	−0.05	0.11	0.18	0.15	0.10	0.09	0.03	0.06	−0.16	0.07	—	0.11	0.21	0.41*	1.00	
Postural orthostatic tachycardia syndrome (PoTS)	0.15	0.18	−0.08	0.15	0.08	0.09	0.17	0.34*	0.19	0.24	0.34*	0.12	−0.02	0.32*	—	−0.01	0.20	0.29*	0.09	1.00
Mean score	24.00	1.68	3.77	9.48	1.06	1.96	41.94	2.75	2.76	2.52	3.37	3.49	3.77	3.11						
SD	9.49	1.39	3.33	4.19	1.76	0.86	13.79	0.86	1.02	1.02	0.95	1.00	0.86	0.58						

*p-value < 0.05; **p-value < 0.01.

size for a rare disease. Limitations also include response bias as not all patients that were approached agreed to participate, and we did not collect data on subjects that did not agree to participate. Further, while an echocardiogram was ordered for all participants, not all participants obtained an echocardiogram, which led to incomplete data for cardiovascular evaluation. Additionally, orthostatic testing was not obtained on participants who did not endorse any autonomic symptoms, and a validated questionnaire for cardiovascular symptoms was not used to collect data; however, a standard cardiovascular review of symptoms was completed by all participants as part of their cardiovascular evaluation. Despite the limitations, this is the largest cohort of pediatric patients with hEDS and documentation of their cardiovascular and autonomic symptoms and diagnoses and the impact on QoL. Future studies in a larger population will allow a more detailed exploration of PROs and cardiovascular variables.

Conclusion

This study shows that many children with hEDS have cardiovascular and autonomic symptoms, which have a significant impact on QoL. The rate of PoTS and dysautonomia are high in adult and pediatric hEDS populations, and clinicians managing patients with autonomic symptoms or hEDS need to be aware of these comorbidities so they can screen and initiate treatment sooner for these conditions. Interestingly, few patients with hEDS have structural abnormalities on echocardiogram, which suggests that the cardiovascular symptoms experienced by patients are due to autonomic symptoms. Orthostatic intolerance and pupillomotor symptoms are the strongest predictors of poor HRQoL. Based on these results, the OI and pupillomotor subdomains of the COMPASS-31 may be considered as a proxy for QoL in pediatric patients with hEDS and dysautonomia as they relate to cardiovascular and autonomic symptoms. This study confirms that cardiovascular conditions and autonomic symptoms are prevalent and do impact QoL in pediatric and young adult patients diagnosed with hEDS, and further research is needed to evaluate the long-term effect of cardiovascular symptoms on QoL.

Acknowledgements

The authors would like to thank Ariana Coker (University of Kansas School of Medicine) for organization and acquisition of clinical data used for this project.

Author contributions

AKH, WRB, LMW, and JTJ equally contributed to the conception, drafting, and final version of the whole manuscript. AL, EC contributed to acquisition, analysis, and interpretation of data, revising final version of manuscript. All authors read and approved the final manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics approval

Ethical approval for this study was obtained from the Institutional Review Board from Children's Mercy Kansas City (IRB Study ID: 00001628).

Informed consent

Formal informed consent was not required for this study.

Trial registration

Not applicable.

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