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Pain and gastrointestinal dysfunction are significant associations with psychiatric disorders in patients with Ehlers–Danlos syndrome and hypermobility spectrum disorders: a retrospective study

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Abstract

In this retrospective study, we investigate the frequency and types of psychiatric disorders and their relationship to systemic manifestations in a cohort of 391 Ehlers–Danlos syndromes (EDS) and hypermobility spectrum disorder (HSD) patients based on the current 2017 International Classification of EDS diagnostic criteria. A detailed, systematic retrospective chart review was undertaken for patients assessed for HSD or EDS at two Canadian health centres. Patients were diagnosed according to the Villefranche criteria and reclassified for this study according to the 2017 International Classification of EDS. Data validation and statistical analyses were conducted. Psychiatric disorders were very common, with 49.4% of the total cohort affected; 28.9% reported multiple psychiatric diagnoses. Mood (34.5%) and somatoform (28.6%) disorders were most common. Interestingly, attention-deficit/hyperactivity disorder (ADHD) was significantly enriched in the HSD, but not EDS cohort ($p = 0.0002$, 95% CI 3.48–9.00) compared to the general population. There were no differences in the systemic associations with having psychiatric manifestations in the HSD compared to the EDS subsets. Muscle/body pain (OR 1.99) and gastrointestinal dysfunction (OR 2.07) were significantly associated with having mood disorders, and gastrointestinal dysfunction (OR 2.61) and nerve-related pain (OR 3.27) were associated with having somatoform disorders across the cohort. The common systemic associations with the presence of psychiatric manifestations in both HSD and EDS reaffirm that the conditions should be treated as a spectrum rather than as wholly separate entities, particularly with respect to psychiatric management. EDS and HSD patients share common psychiatric presentations, though ADHD is more common with HSD.

Keywords Genetics · Rheumatology · Psychiatry · Pain · Gastrointestinal diseases

Introduction

The Ehlers–Danlos syndromes (EDS) comprise a heterogeneous group of hereditary connective tissue disorders that is primarily characterised by joint and skin hyperextensibility

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and tissue fragility [1]. The various EDS types are caused by mutations in genes encoding various types of collagen or collagen-modifying enzymes [1]. Previously, the Villefranche classification delineated six major types of EDS based on clinical, biochemical and molecular features [2]. The 2017 International classification of EDS provided updated and revised clinical criteria to include 13 subtypes, with the aim of improving standardisation for clinical and research purposes, and incorporating new knowledge on novel EDS subtypes and newly discovered gene associations [3]. The new classification is based on clinical major and minor criteria and molecular confirmation for all subtypes, except hypermobility type EDS (hEDS), for which the genetic basis is still unknown [3]. This new nosology provides more stringent criteria for making a diagnosis of EDS. Based on the 2017 classification, patients who had previously been classified as having EDS may no longer meet criteria for this diagnosis or may have shifted to another EDS classification. Thus, Castori et al. [4] proposed hypermobility spectrum disorders (HSD) as a diagnosis of exclusion for patients with joint hypermobility not corresponding to a specific syndrome. It is now recognised that HSD and EDS are part of a continuous spectrum of phenotypes.

Certain subtypes of EDS patients may present with specific multisystemic manifestations. For example, hEDS patients present with non-traumatic joint dislocations, arthrochalasia-type EDS (aEDS) patients may present with congenital hip dislocation, vascular-type EDS (vEDS) patients have vascular aneurysms, classical-type EDS (cEDS) patients have atrophic scarring and delayed wound healing, classical-like EDS (clEDS) patients have easy bruising and kyphoscoliotic-type EDS (kEDS) patients may present with orbital rupture. Many EDS patients also present with clinical manifestations that are not specific to EDS, such as chronic pain, functional bowel disorders, genitourinary dysfunction and degenerative joint disease [3, 5, 6]. Chronic rheumatological conditions, such as psoriasis, fibromyalgia, ankylosing spondylitis, rheumatoid arthritis and juvenile idiopathic arthritis, can also be associated with hypermobility conditions, including hEDS [7]. Due to the non-specific nature of many of these findings, EDS is often under- or mis-diagnosed [8, 9].

In addition to physical manifestations, psychiatric disorders have been found to be common in individuals with HSD/EDS. While mood and anxiety disorders are most commonly seen, a variety of other disorders have also been reported, including schizophrenia spectrum, neurodevelopmental, eating, personality and substance use/misuse disorders [10–16]. In a previous study, we reported a statistically significant association between pain and the presence of psychiatric manifestations in a group of 106 EDS patients [16]. No disease-specific phenotypes were associated with the increased likelihood of psychiatric impairment, supporting that the psychiatric findings in EDS are likely secondary to pain rather than a primary manifestation of the disorder [16].

In the present study, we examine the clinical phenotypes associated with psychiatric findings in a cohort of 391 patients using the current HSD/EDS classification criteria. We also examine whether there are differences in psychiatric presentations and associations between patients with HSD and EDS.

Methods

Data collection

A detailed, systematic retrospective chart review was undertaken for 252 patients assessed for HSD or EDS at the Fred A. Litwin Family Centre in Genetic Medicine (Toronto, ON, Canada) and 32 patients seen at Kingston Health Sciences Centre (Kingston, ON, Canada) between January 1, 2013 and June 30, 2016. Patients were identified from clinical referral databases using the search terms 'joint', 'joint hypermobility', 'hypermobility', 'connective tissue disorder', 'CTD', 'Ehlers–Danlos syndrome', 'EDS', 'Marfan', 'Stickler', 'collagenopathy', 'collagen vascular disorder', (familial) thoracic aortic aneurysm (dissection), 'FTAA', 'Loeys–Dietz', 'LDS', 'osteogenesis imperfecta', 'OI', as well as referrals for family history of any of the above. The most recent consult letter was reviewed to determine inclusion eligibility for this study. Only the charts of patients diagnosed with EDS or HSD were reviewed further. Patients were diagnosed according to the Villefranche criteria and reclassified for this study according to the 2017 International Classification of EDS. Medical and psychiatric data as reported by the patients and recorded on a standardised intake form during genetics assessments were corroborated by data from the clinical assessment, reports from other specialists, imaging and test reports, and past psychiatric assessments, where available. Data were recorded and coded according to the International Classification of Diseases (ICD-10) [17]. The raw data were reviewed by four research team members, with any coding discrepancies resolved by consensus amongst the four coders and the study lead.

In addition, a cohort of 129 patients previously described in Hershenfeld et al. [16] was reclassified according to the 2017 International Classification criteria and included in this analysis. Of the total 413 patients, sufficient data were available for 391 patients for complete analysis. Research ethics board approval for this project, including waiver of consent, was granted by University Health Network and Mount Sinai Hospital (Toronto, ON, Canada), Kingston Health Sciences Centre and Queen's University (Kingston, ON, Canada).

Statistical analysis

Data validation and statistical analyses were conducted using IBM SPSS v.25 (IBM Corp., Armonk, NY) with Essentials for R add-on (R3.3). Comparisons of continuous variables with normal distribution were made by independent samples *t* test. For non-normal distribution, Mann–Whitney *U* test was utilised. Fisher's Exact test and Chi-square tests were used to determine the association between systemic findings and psychiatric disorders, and presented as odds ratios with associated confidence intervals. To evaluate relationships between dependent categorical variables and mixed predictors (continuous and/or categorical), logistic regression was utilised. A p value of <0.05 was considered statistically significant. All data were assessed for normality and completeness prior to analysis.

Results

Demographic data and systemic findings

A cohort of 391 patients with HSD or EDS diagnosis were included in the analysis. Demographic data are presented in Table 1. The mean age for patients was 36.2 years and most patients were female (85.6%). Most had a diagnosis of HSD (79.8%) under the 2017 International Classification criteria. The most common subtype of EDS was cEDS (11.3%). There were notably no patients who met the current criteria for a diagnosis of hEDS. Median Beighton score was 6.0 out of 9. The most common systemic manifestations were musculoskeletal findings (96.9%) and pain (85.7%). Other common systemic manifestations included haematological, gastrointestinal (GI), dermatological and neurological symptoms. Two EDS patients, but none with HSD, had comorbid rheumatologic conditions; one cEDS patient had rheumatoid arthritis and one clEDS patient had systemic lupus erythematosus. Frequencies of systemic manifestations are presented in Fig. 1. Statistical analysis did not identify any significant associations between any of the systemic categories, including no associations between any EDS-suggestive features, such as joint hypermobility, recurrent joint dislocations and skin hyperextensibility, with any other systemic findings (data not shown).

Table 1 Demographic characteristics of the HSD/EDS study cohort

Characteristics	Mean (± SD)	*N* (%)
Mean age (years)	36.1 ± 14.4	
Female		334 (85.2)
HSD		312 (79.8)
cEDS		44 (11.3)
clEDS		31 (7.9)
Other EDS (a, v, k)		4 (1.0)
Median Beighton score	6.0 (range: 0–9)	

Frequencies and types of psychiatric disorders

The frequency of psychiatric disorders in the total HSD/EDS cohort was 49.4%, with 28.9% of these patients having two or more psychiatric diagnoses (Fig. 2a). A variety of psychiatric diagnoses were reported (Table 2), with the most common being mood (34.5%) and somatoform disorders (28.6%).

Comparison of the frequency of various psychiatric disorder categories and diagnoses in the EDS and HSD cohorts compared to the general population is shown in Fig. 2b. Compared to the general population, EDS ($p<0.0001$, 95% CI 39.11–62.04) and HSD ($p=0.0002$, 95% CI 25.08–43.84) patients had significantly higher frequency of psychiatric disorders, including mood (EDS

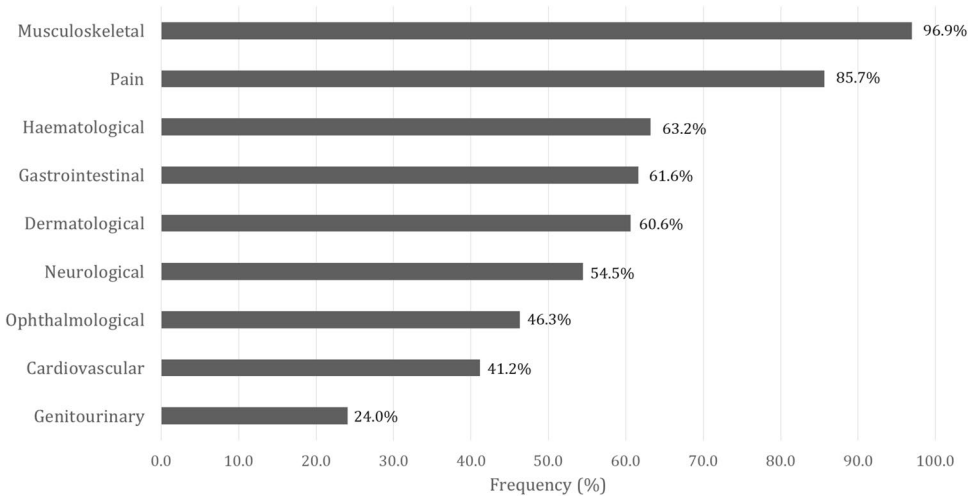

Fig. 1 Frequencies of systemic findings in the HSD/EDS study cohort

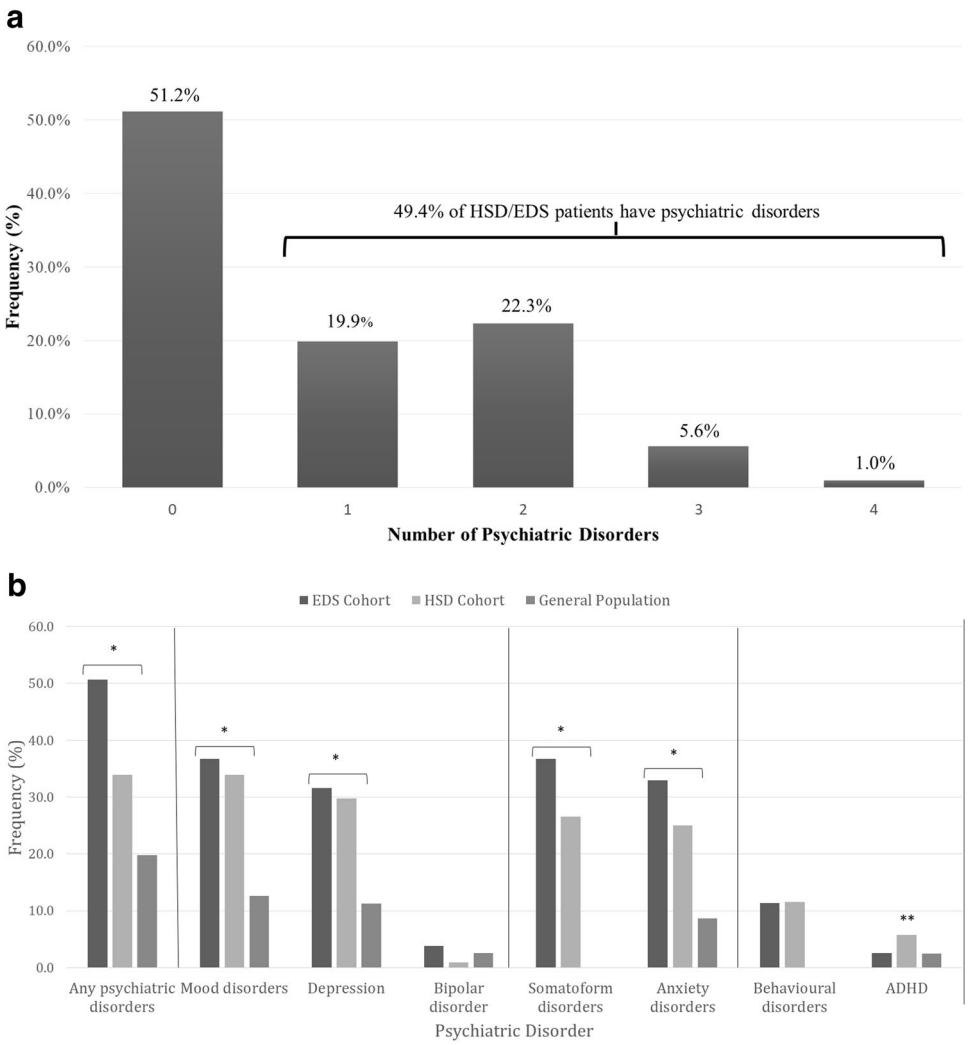

Fig. 2 Frequency of psychiatric disorders in the HSD and EDS cohort. **a** Frequencies of psychiatric disorders by number of disorders in the HSD/EDS cohort. **b** Frequency of psychiatric disorders in the HSD and EDS study cohort subsets compared to the general Canadian population. Frequency of any psychiatric disorder is reported from the Mental Health Commission of Canada Report on the Life and Economic Impact of Major Mental Illnesses in Canada (2011). Frequencies of mood disorders and anxiety are reported from the 2012 Canadian Community Health Survey—Mental Health (CCHS-MH) conducted by Statistics Canada. Mood disorders include depression and bipolar disorders. Frequency of ADHD is reported from Simon et al. [28]. Population statistics were unavailable for somatoform disorders and behavioural disorders. *Statistically significant difference between EDS and HSD subsets compared to the general population ($p < 0.05$). **Statistically significant difference between the HSD cohort and the general population ($p < 0.05$). *MDD* major depressive disorder, *GAD* generalised anxiety disorder, *ADHD* attention-deficit/hyperactivity disorder

$p < 0.0001$, 95% CI 26.13–48.30; HSD $p < 0.0001$, 95% CI 28.76–39.55) and anxiety (EDS $p < 0.0001$, 95% CI 22.74–44.39; HSD $p < 0.0001$, 95% CI 20.29–30.19) disorders. Specific disorders that were more frequent include depression in both EDS ($p < 0.0001$, 95% CI 21.59–43.03) and HSD ($p < 0.0001$, 95% CI 24.78–35.21), and attention-deficit/hyperactivity disorder (ADHD) in HSD patients only ($p = 0.0002$, 95% CI 3.48–9.00).

Association between psychiatric disorders and systemic findings

When controlled for age and gender, several types of pain and GI conditions were found to be significantly associated with mood and somatoform disorders in the total HSD/EDS cohort (Table 3). Muscle/body pain and GI dysfunction were significantly associated with having mood disorders,

Table 2 Types and frequencies of psychiatric disorders in the HSD/EDS study cohort

Psychiatric disorder	*N* (%)
All psychiatric disorders	196 (50.1)
Mood disorders	135 (34.5)
Depression	118 (30.2)
Bipolar disorder	7 (1.9)
Somatoform Disorders	112 (28.6)
Anxiety disorders*	104 (26.6)
Behavioural disorders	45 (11.5)
Attention-deficit/(hyperactivity) disorder	18 (4.6)
Disorders of psychological development	25 (6.4)
Dyslexia/speech difficulties	11 (2.8)
Other**	7 (1.8)
Self-harm/suicide	2 (0.5)
Schizoaffective disorder	1 (0.3)
Schizotypal disorder	1 (0.3)

*Anxiety disorders include general anxiety disorder and unspecified anxiety disorder

**Includes not otherwise specified

particularly depression. GI dysfunction and nerve-related pain were significantly associated with having somatoform disorders, with GI dysfunction significantly associated with anxiety, specifically. Joint hypermobility, recurrent joint dislocations and skin hyperextensibility were not associated with psychiatric disorders in the patient cohort. No significant associations were found between psychiatric disorders and the presence of cardiovascular, respiratory, dermatological, genitourinary, gynaecological, endocrine, dental, autoimmune, infectious, inflammatory or autonomic conditions.

Discussion

In this study of 391 HSD and EDS patients categorised according to the 2017 International Classification criteria, we found a significantly increased frequency of psychiatric disorders across the entire cohort, most prominently mood and somatoform disorders, which were associated primarily with the presence of pain and GI symptomatology.

Despite reclassification of the patient cohort under the new EDS classification criteria, the results replicate findings from our previous study, showing a high frequency of psychiatric disorders in HSD/EDS patients, particularly mood and somatoform disorders [16]. These results are consistent with previous studies of psychiatric disorders in EDS patients [9, 13, 16, 18–23]. A recent review article by Bulbena et al. [18] concludes that there is a growing body of evidence suggesting higher rates of depression amongst HSD/EDS patients, especially when comorbid anxiety disorders are present. For example, severe fatigue and depression have been found to be significantly higher in high-anxious hEDS patients compared to low-anxious hEDS patients [24]. Other studies have identified comorbid anxiety disorders such as generalised anxiety, panic, and phobic and obsessive–compulsive disorders in patients with joint hypermobility [12, 15, 25]. Depression and anxiety in the EDS population may arise from challenges due to the chronic nature and

Table 3 Association between psychiatric and systemic findings

Systemic findings	Mood disorders ($n=135$)		
	OR	95% CI	*p* value
Muscle/body pain	1.99	1.25–3.18	0.004
Gastrointestinal dysfunction	2.07	1.33–3.25	0.001
Systemic findings	Depression ($n=118$)		
	OR	95% CI	*p* value
Gastrointestinal dysfunction	1.68	1.07–2.66	0.026
Muscle/body pain	1.83	1.13–2.97	0.014
Systemic findings	Somatoform disorders ($n=112$)		
	OR	95% CI	*p* value
Gastrointestinal dysfunction	2.61	1.62–4.19	<0.001
Nerve-related pain	3.27	1.30–8.20	0.012
Systemic findings	Anxiety ($n=104$)		
	OR	95% CI	*p* value
Gastrointestinal dysfunction	2.26	1.39–3.67	0.001

disability of the condition [26]. High anxiety levels may lead to pain catastrophising, somatosensory amplification, as well as poorer social functioning and general health [24, 27]. The ever-growing body of evidence showing a large psychological burden in HSD/EDS patients supports the importance of considering psychosocial factors and the need for a biopsychosocial approach in the management of patients with this chronic condition.

ADHD was more frequent (4.6%) in the total HSD/EDS cohort than in the general adult population (2.5%) [28], though, interestingly, the rate of ADHD was only significantly higher in HSD, and not EDS, patients. Numerous studies have shown a higher prevalence of ADHD amongst hEDS and joint hypermobility populations [16, 29–33]. Cederlöf et al. [34] reported that both EDS and hypermobile patients have an increased risk of having ADHD, although the subtype of EDS was not specified. Glans et al. [35] have observed that Swedish women from the general population who scored > 3 out of 5 on the five-point questionnaire for joint hypermobility had higher hyperactivity and impulsive ADHD traits. A recent review article by Baeza-Velasco et al. [14] highlights the unexpected association between joint hypermobility and ADHD, and suggests possible pathophysiological and psychopathological connections between the two conditions. In a genome-wide association study on ADHD, *TLL1* and *TLL2* genes were among the top genes associated with the ADHD phenotype [36]. Both of these genes encode metalloproteases that cleave collagen and are expressed in multiple tissues in the brain [37–39]. Interestingly, we did not find any direct association between ADHD and joint hypermobility in this study, suggesting that the connection between the two may be indirect. As our EDS cohort had no patients meeting current criteria for hEDS and previous studies reported patients classified prior to the 2017 International Classification criteria, further studies are warranted to explore the association of ADHD in hEDS and potentially other EDS types. It may be worthwhile to examine whether previous studies on ADHD in EDS patients classified using the Villefranche criteria would reveal differences between HSD and EDS patient populations if classified under the new criteria. In our study, 90% of ADHD patients in the current cohort are classified as HSD, while the majority (65.0%) were classified as hEDS under the old nosology (data not shown).

The vast majority (85.7%) of HSD/EDS patients in our study experienced pain, including muscle/body, joint, nerve-related, cardiovascular, genitourinary and gynaecological and GI pain, which is consistent with the results from previous studies [40, 41]. While our previous study identified muscle, abdominal and neuropathic pain, as well as migraines to be associated with having a mood or anxiety disorder in EDS patients [16], the current study, with a larger sample size, and controlling for age and gender, was able to differentiate between types of pain associated with different psychiatric disorders. Muscle/body pain was significantly associated with having a mood disorder, while nerve-related pain, a type of pain commonly found in EDS patients [42], was significantly associated with somatoform disorders. This suggests that the prevalence of specific types of pain can be a contributing factor to the increased frequency of specific types of psychiatric disorders. Previous studies support the interaction between pain and mental health, wherein the presence of chronic pain can lead to psychological symptomatology, such as negative emotions, increased awareness of body sensations, depression and anxiety, and vice versa, with the psychological factors perpetuating pain chronicity and disability [43–45]. The interaction between specific types of pain and psychiatric disorders in HSD/EDS patients should be further explored to provide appropriate, tailored chronic pain and psychosocial management.

A novel association was revealed between GI dysfunction and the presence of mood and somatoform disorders, particularly depression and anxiety, in the total HSD/EDS cohort. This is consistent with numerous studies that have found a high frequency of comorbid psychiatric conditions in patients with GI disorders [46, 47]. GI health-care professionals should be aware of the increased risk for psychiatric disorders when evaluating patients with comorbid joint hypermobility and GI disturbance.

It is notable that nearly all patients previously identified with hEDS were classified as HSD under the new classification criteria; in fact, no patients met the classification for hEDS (Supp. Fig. 1). This may reflect that the new criteria are too stringent, that hEDS is rarer than previously thought or that the new classification may require further validation. As in the case of the association of ADHD with HSD and EDS, it will be important to re-examine studies which classified EDS patients under the Villefranche criteria to determine if previously reported associations are still valid when patients are reclassified under the current criteria, and whether there is any difference between EDS and HSD patients.

Although our patient cohort is large with respect to studying a rare genetic disorder, the sample size is still relatively small. This limits the ability to generalise the results outside of the sample population. Additionally, the retrospective nature of the study may result in an underestimation of phenotypes due to lack of patient reporting, documentation or investigation. Therefore, it is possible or even likely that the frequencies of psychiatric disorders are underestimated. Systematic prospective screening for psychiatric disorders could aid in identifying overlooked psychiatric conditions in HSD/EDS patients. There may also be sampling bias in the recruitment of patients for this and other studies. Patients with psychiatric conditions may be underrepresented in the population seen by various

specialists due to misattribution of EDS symptoms (e.g. pain, GI symptoms) to the psychiatric disorder, resulting in lack of further scrutiny [48]. Patient registry initiatives, comprehensive phenotyping and the use of standardised ontology, such as in our study, will aid in reducing these limitations in further studies.

This study of 391 HSD/EDS patients classified according to the 2017 International Classification of EDS criteria demonstrates that psychiatric disorders are frequent, diverse and strongly associated with pain, validating the results of our previous study [16]. The most common psychiatric disorders were mood and somatoform disorders, which were variably associated with different types of pain, as well as with GI dysfunction. Apart from ADHD, which was more frequent in HSD, psychiatric findings and their systemic associations were similar across the spectrum of HSD and EDS, suggesting that the management of both patient groups should be similar regardless of diagnosis. ADHD may be specifically associated with joint hypermobility; this association warrants further examination, particularly in light of the new classification criteria for EDS, to determine whether it is specifically associated with the hEDS and HSD patient populations. These results support the importance of screening for mental health disorders in HSD and EDS patients, particularly those with pain and GI symptoms. Awareness of associations between multisystemic manifestations of HSD/EDS and psychiatric disorders will aid physicians in providing optimal management for patients and to identify those at higher risk for mental health disorders.

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Author contributions SW contributed to study design, data analysis and interpretation, and revision of the work. JSS contributed to data interpretation, and drafting and revision of the work. MP contributed to data acquisition, and drafting and revision of the work. SL, BH and AG contributed to data acquisition and revision of the work. JS contributed to study conception and design, data acquisition and interpretation, and drafting and revision of the work. All authors gave final approval of the version to be published and agree to be accountable for all aspects of the work.

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Compliance with ethical standards

Conflict of interest All authors declare no conflicts of interest.

Ethical approval Ethics approval for this study was obtained from University Health Network (Research Ethics Board (REB) #: 16-5634; date of approval: July 22, 2016), Mount Sinai Hospital (REB #: 16-0180-C; date of approval: August 8, 2016) and Queen's University (REB #: PAED-406-16; date of approval: September 27, 2016).

Informed consent Waiver of informed consent was obtained from the University Health Network, Mount Sinai Hospital and Queen's University REBs.

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