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High prevalence of gastrointestinal disorders in a large cohort of patients with joint hypermobility

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Abstract

The gastrointestinal (GI) manifestations in children with hypermobile Ehlers–Danlos syndrome/joint hypermobility syndrome (hEDS/JHS) are not well described. We investigated the prevalence of GI disorders in children and young adults with hEDS/JHS through a single-center retrospective review. Demographic data, clinical history, symptoms, and diagnostic studies were reviewed. Of 435 patients with hEDS/JHS, 66% were females (age 5–28 years). We noted a high prevalence of constipation (61%), dysphagia (32%), dyspepsia and/or gastroparesis (25%), eosinophilic esophagitis (EoE) (21%), and celiac disease (4%) in our cohort. Upper endoscopy and gastric emptying scans had the highest yield to detect abnormalities. Motility studies were abnormal in 31% of the 80 patients who underwent them. Dysphagia symptoms are significantly associated with EoE. Thirty-three percent of dysphagia patients had EoE, versus 16% of non-dysphagia patients ($p < 0.001$). Screening hEDS/JHS patients for GI issues should be routine, with further investigations and referrals guided by identified symptoms.

Prior abstracts:

Comprehensive evaluation of children with hypermobility and gastrointestinal symptoms, Digestive Diseases Weekly Annual Conference in May 2018. Comprehensive evaluation of gastrointestinal disorders in children with joint hypermobility, Third Meeting of the Federation of Neurogastroenterology and Motility, Amsterdam, Netherlands in August 2018; Midwest Gut

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CONFLICT OF INTEREST STATEMENT

Dr. Vincent A. Mukkada is a consultant for Shire/Takeda, Sanofi, Regeneron, and Allakos. He is on the Adjudication board for Alladapt. The remaining authors declare no conflict of interest.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Club Annual Meeting in September 2018; North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) Annual Conference in October 2018.

Keywords

constipation; gastrointestinal; hypermobile Ehlers–Danlos syndrome; joint hypermobility; motility

1 | INTRODUCTION

Hypermobile Ehlers–Danlos syndrome (hEDS) and joint hypermobility syndrome (JHS) are characterized by generalized joint hypermobility and musculoskeletal symptoms, as well as skin and soft tissue involvement.[1] The diagnosis is largely based on clinical criteria. There is no genetic test or biological marker to confirm the diagnosis. Generalized joint hypermobility is screened using a 9-point Beighton score, which considers the flexibility of the spine/hips, paired knees, and elbows, fifth metacarpophalangeal joint, thumb, and wrists.[2] A score of 5 or greater for adults and 6 or greater for prepubertal children and adolescents is suggestive of hypermobility. Definitive diagnosis requires fulfilling criteria, which include Beighton scores and other features such as joint pain, dislocations, and soft tissue lesions, as well as overlap features of connective tissue disorders (Supporting Information Digital Content 1).[3] The 2017 International consensus statement states that hEDS and JHS share similar features and are considered part of a continuum of hypermobility spectrum disorders.[4] We have used the term hEDS/JHS to describe our cohort. The gastrointestinal (GI) involvement in hEDS/JHS patients can have functional and organic manifestations.[5–9] Adult patients with JHS have significantly increased Gl symptoms such as dyspepsia, gastro-esophageal reflux disease (GERD), irritable bowel syndrome (IBS), and conditions such as abdominal hernia, diaphragmatic hernia, and rectal prolapse.[10,11]

We describe the Gl symptoms and related evaluation in a large cohort of children and young adults with hEDS/JHS.

2 | METHODS

This is a single-center retrospective study approved by the Cincinnati Children's Hospital Medical Center (CCHMC) Institutional Review Board (IRB # 2017–4366). We identified patients with GI symptoms seen at the CCHMC Gastroenterology Clinics who had a prior diagnosis of hEDS/JHS. hEDS/JHS was diagnosed by rheumatology or genetics based on established clinical criteria, including the Beighton scoring system.[3] The electronic medical records of patients were screened using the International Classification of Diseases-10 code Q 79.6 (Ehlers–Danlos syndrome) or M 35.7 (hypermobility syndrome) as well as the search terms "hypermobility syndrome, joint hypermobility, and hypermobile Ehlers–Danlos syndrome" from March 2011 to December 2017. Data on demographics, clinical history, symptoms, comorbidities, and diagnostic work-up done at our center was collected. Studies were classified as normal versus abnormal based on clinical definitions (Supporting Information Digital Content 2).

2.1 | Statistical analysis

Ordinal and categorical data were collected. Counts and percentages were computed to estimate the prevalence of Gl disorders and investigations in subjects with hEDS/JHS (Tables 1 and 2). Associations and relative risks of various Gl manifestations in subjects with hEDS were performed using χ^2 tests. A $p < 0.05$ was considered statistically significant. Data analyses were performed using SAS version 9.4 (SAS Institute).

3 | RESULTS

A total of 435 hEDS/JHS patients with GI symptoms were identified. Ages ranged from 5 to 28 years (median age of 16 years [13.0–20.0], 76%: ≤18 years, 50%: 12–18 years). Most patients were female (66%) or Caucasian (94%). The most reported symptom was constipation (61%), followed by dysphagia (32%). A total of 25% of patients reported symptoms of abdominal pain, post-prandial nausea, vomiting, early satiety, or weight loss indicative of dyspepsia with and without gastroparesis. Since dyspepsia and gastroparesis are now considered a spectrum of disorders,[12] we have mentioned them collectively throughout the manuscript.

Of the 435 symptomatic patients, 79% underwent evaluation with imaging, endoscopy, and/or motility testing based on the nature and presentation of their symptoms. Table 1 presents the yield of diagnostic tests in our cohort. Upper endoscopy and gastric emptying scans had the highest yield to diagnose abnormalities. Details of investigations are presented below.

3.1 | Endoscopy

Upper endoscopies were performed in 67% (293/435) of patients, and 34% of the endoscopies had histological abnormalities. Eosinophilic esophagitis (EoE) was the most common diagnosis, followed by celiac disease, reflux esophagitis, and chronic gastritis (Table 2). Colonoscopies were performed in 111 patients, of which 24% had abnormal histological results. The most common biopsy findings were eosinophilic colitis (some of these also fulfilled the histologic criteria for EoE), followed by microscopic colitis and inflammatory bowel disease.

3.2 | Radiographic studies

Fourteen of 39 patients undergoing video fluoroscopic swallow study had abnormalities identified (Table 2). Delayed initiation of swallowing and oropharyngeal dysphagia were the most common findings. None of the patients demonstrated evidence of aspiration or penetration. Contrast imaging of the upper GI tract was abnormal in 14/108 patients. Esophageal dysmotility was the most reported abnormality. Water soluble contrast enema studies were abnormal in 14/38 patients with constipation. Common findings included dilated and redundant recto-sigmoid colon and partial evacuation of contrast. Gastric scintigraphy was abnormal in 50/80 patients with delayed gastric emptying at 4 h while none had accelerated gastric emptying.

3.3 | Motility studies

Motility studies were performed for 80 (18%) patients, of whom 25 had an abnormal test result (31% of 80 patients, 6% of the total sample, Table 2). Results were abnormal for high-resolution esophageal manometry in 4/11 patients, pH-impedance (pH-MII) in 4/16, anorectal manometry (ARM) in 6/13, antroduodenal manometry in 8/17, and colonic manometry (CM) was abnormal in 3/24 patients. Ineffective esophageal motility, GERD, antral hypomotility, and colonic dysmotility were the most prevalent findings in the limited subset of patients undergoing motility evaluation. Details of abnormalities are presented in Table 2.

EoE was more often diagnosed in patients who reported dysphagia versus those who did not (33% vs. 16%: $p < 0.001$). Thus, EoE was 2.15 times more likely to be diagnosed in patients with dysphagia than those without (RR: 2.15 [95% Cl: 1.51–3.07]). The associations of constipation with dyspepsia and celiac disease were not significant ($p > 0.05$).

4 | DISCUSSION

The presence of GI symptoms in hEDS/JHS patients is being increasingly recognized,[7,13] and a number of disorders of the GI tract, including but not limited to inflammatory bowel disease, celiac disease, eosinophilic GI disease, complex abdominal pain, IBS, and constipation have been reported in children and adults with joint hypermobility.[5,6,8,10,14]

Our study demonstrated an increased prevalence of eosinophilic disorders and celiac disease in our cohort of pediatric hEDS/JHS patients. The overall prevalence of EoE is currently estimated at 1 in 1000,[15] while in our cohort (differing from the general population in that they had symptoms prompting referral to GI), 21% of patients had EoE, and 4% had eosinophilic colitis. This higher prevalence of EoE in our hEDS/JHS cohort is similar to previous work by Abonia et al. that demonstrated that patients with connective tissue disorders that resembled Marfan syndrome, hypermobile EDS, or JHS with other atopic diseases had a higher prevalence of EoE (RR: 8.1; Cl: 5.1–12.9) compared to the general population.[15]

Our study also revealed an increased prevalence of celiac disease in 4% of our patients. However, this is much lower than the prevalence of 16% in adult hEDS patients reported by Danese et al.[16] A population-based cohort from Sweden demonstrated a 49% increased risk of hEDS/JHS in patients with celiac disease with an estimated hazard ratio of 1.34 and 2.43 for JHS and EDS, respectively.[17] This difference may be secondary to under-diagnosis in our study since not all patients underwent an EGD or serologic testing for celiac disease, particularly as the celiac disease may be relatively asymptomatic or may develop during later years of life.

Constipation and dysphagia were the most reported symptoms in our cohort. This is consistent with prior studies reporting constipation as the most prevalent and the earliest reported GI symptom in patients with hEDS/JHS with a higher prevalence of IBS-C than IBS-D.[6] Of the patients with constipation in our cohort that underwent ARM, half had manometric evidence of rectal evacuation dysfunction, similar to adult studies.[7,18,19]

Interestingly, we did not see evidence for rectal hyposensitivity or a high prevalence of colonic dysmotility in the subset of our patients who underwent anorectal or CM testing for constipation. This may reflect a general trend that children with constipation more commonly demonstrate dyssynergic defecatory disorders than colonic dysmotility.

Dysphagia and reflux symptoms are commonly reported in patients with JHS and can affect up to 39% of patients, with previous reports showing over half of patients having increased esophageal acid exposure time and reflux episodes, and 40% having esophageal dysmotility (mostly ineffective esophageal dysmotility).[8,20] In our sample, in the small group of patients undergoing esophageal manometry or impedance probe testing, 25% showed evidence of GER, and 36% had esophageal dysmotility.

A quarter of our cohort had dyspepsia, congruent with previous work showing an increased prevalence of functional dyspepsia in hEDS/JHS.[8] There is a wide range of reported data on delayed gastric emptying in adults with hEDS/JHS, with rates ranging from 12% to 71%.[7,8]

While some symptoms suffered by patients with hEDS/JHS may be functional in nature, investigations may be necessary in symptomatic patients to evaluate other diseases requiring specific treatment. The authors would recommend a low threshold for upper endoscopy when symptoms such as dysphagia, nausea/vomiting, or abdominal pain are present, given the greater than 20% prevalence of eosinophilic disorders or celiac disease in our cohort, with consideration for secondary testing such as imaging, pH/impedance testing, or manometry studies generally reserved for those with persistent symptoms despite a normal endoscopy.

Our study was limited by its retrospective nature and the lack of age and gender matched non-hEDS/JHS controls to allow for adequate comparisons of GI symptoms. We did not universally screen all hEDS/JHS patients to detect all potential disorders, so not all patients received all testing for identified conditions, and the patients that did have testing were symptomatic. There may also be a selection bias toward a severe phenotype of our cohort since our institution is a large tertiary referral center for both connective tissue disorders and pediatric gastroenterology. To attempt to minimize bias, we included all patient records meeting our inclusion criteria within a predetermined study period. Our study had the advantage of a large sample size and the availability of extensive information about the workup. This study enabled us to identify clinical associations with hEDS/JHS, such as EoE and celiac disease, and may provide direction for future studies exploring shared pathophysiologic mechanisms between these seemingly unrelated disorders.

To conclude, this study presents the prevalence of GI conditions in pediatric and young adult patients with hEDS/JHS. We demonstrated a high prevalence of constipation, dysphagia, dyspepsia, celiac disease, and EoE in our cohort of patients with hEDS/JHS, suggesting that screening these patients for GI symptoms should be routine. Identified symptoms should then guide further referrals and investigations with a low threshold for endoscopy and further investigations such as gastric emptying studies or manometry reserved for refractory and persistent symptoms. Future prospective trials to determine the natural history

of symptom progression, treatment outcomes, and translational studies analyzing connective tissue dynamics involved in GI disorders are needed in this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ADM	antroduodenal manometry
ARM	anorectal manometry
CM	colonic manometry
EGD	esophagogastroduodenoscopy
EoE	eosinophilic esophagitis
GERD	gastroesophageal reflux disease
GES	gastric emptying scan
GI	gastrointestinal
HAPC	high amplitude propagating contractions
hEDS	hypermobile Ehlers–Danlos syndrome
HREM	high resolution esophageal manometry
JHS	joint hypermobility syndrome
LAPC	low amplitude propagating contractions
pH-MII	pH and multiluminal impedance study
UGI	upper gastrointestinal series
VFSS	video fluoroscopic swallow study
WSCE	water soluble contrast enema

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What is Known

- Structural and functional gastrointestinal (GI) disorders have been reported in adults with hypermobile Ehlers–Danlos syndrome/joint hypermobility syndrome (hEDS/JHS).
- Pediatric studies have explored the association of disorders of gut–brain interaction in hEDS/JHS.
- Data on GI and motility disorders in pediatric patients have not been fully established, and they may remain overlooked, misdiagnosed, and untreated.

What is New

- We found a higher prevalence of constipation (61%), dysphagia (32%), dyspepsia (25%), eosinophilic esophagitis (21%), and celiac disease (4%) in our cohort of patients with hEDS/JHS.
- Screening hEDS/JHS patients for GI issues should be routine, with further investigations and referrals guided by identified symptoms.

TABLE 1

Diagnostic yield of investigations.

Symptom	Fraction of cohort with symptom	Workup modality	A fraction of symptomatic patients who underwent this modality	Diagnostic yield
Dysphagia/reflux	140/435	UGI/esophagram	108/140	13% (14/108 abnormal)
		VFSS	39/140	36% (14/39 abnormal)
		EGD	113/140	58% (65/113 abnormal)
		HREM	11/140	36% (4/11 abnormal)
		pH-MII	16/140	25% (4/16 abnormal)
Upper GI symptoms/dyspepsia	107/435	EGD	71/107	28% (20/71 abnormal)
		GES	84/107	59% (50/84 abnormal)
		ADM	17/107	47% (8/17 abnormal)
Lower GI symptoms/constipation	265/435	WSCE	38/265	37% (14/38 abnormal)
		Colonoscopy	111/265	24% (27/111 abnormal)
		CM	23/265	13% (3/23 abnormal)
		ARM	13/265	26% (6/23 abnormal)

Note: Refer to Supporting Information Digital Content 2 for the definition of abnormal studies. Note that patients may have overlapping symptoms, and the number of investigations may differ per symptom group.

Abbreviations: ADM, antroduodenal manometry; ARM, anorectal manometry; CM, colon manometry; EGD, esophagogastroduodenoscopy; GES, gastric emptying scan; GI, gastrointestinal; HREM, high resolution esophageal manometry; pH-MII, pH and multichannel intraluminal impedance study; UGI, upper gastrointestinal series; VFSS, video fluoroscopic swallow study; WSCE, water-soluble contrast enema.

TABLE 2

Details of investigations and abnormalities.

Number of hEDS/JHS patients with GI symptoms	Gastrointestinal investigations completed (*n*)	Abnormal investigations (#*n*)	
Dysphagia/reflux (140/435)	Upper GI study/esophagogram	14/108	Esophageal dysmotility (8), hiatal hernia (2), esophageal reflux (3), esophageal stricture (1)
	Video fluoroscopic swallowing study	14/39	Delayed swallowing with pharyngeal residue and abnormal feeding pattern (14), velopalatine insufficiency (1)
	Esophagogastroduodenoscopy	65/113	Eosinophilic esophagitis (93), reflux esophagitis (13), Candida esophagitis (2), esophageal stricture (1 with EoE and 1 erosive esophagitis)
	(pH-MII) pH and multichannel intraluminal impedance study	4/16	Increased number of reflux episodes (4), rumination (1)
	High-resolution esophageal manometry	4/11	Esophageal hypoperistalsis (3), hypercontractile pattern (1)
Upper GI symptoms/ dyspepsia (107/435)	Esophagogastroduodenoscopy	20/71	Celiac disease (18), chronic gastritis (17), *H. pylori* gastritis (3), chronic duodenitis (7)
	Gastric emptying scan	50/84	Delayed gastric emptying (50)
	Antroduodenal manometry	8/17	Antral hypomotility—post-prandial and provocative phase (8), neuropathic small bowel dysmotility (3)
Lower GI symptoms/ constipation (265/435)	Water soluble contrast enema	14/38	Dilated and redundant colon with partial clearance of the contrast (14), non-rotated colon with midline cecum (1)
	Colonoscopy	27/111	Eosinophilic colitis (16), microscopic colitis (5), chronic active colitis (3), Crohn's disease (2), juvenile polyp (1)
	Colonic manometry	3/23	Colonic dysmotility—absent high amplitude propagating contractions (3), low amplitude propagating contractions (2)
	Anorectal manometry	6/13	Dyssynergic defecation (6), elevated resting anal sphincter pressures (4)

Abbreviations: GI, gastrointestinal; hEDS/JHS, hypermobile Ehlers–Danlos syndrome/joint hypermobility syndrome; pH-MII, pH and multichannel intraluminal impedance study.

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