Gastrointestinal Symptoms in Marfan Syndrome and Hypermobile Ehlers-Danlos Syndrome.


Laura Scheufele PT, DPT, WCS
December 5, 2018

Introduction: Ehlers-Danlos syndrome (EDS) is a group of inherited noninflammatory connective tissue disorders primarily caused by a defect in the synthesis of collagen, with hypermobility being one of its characteristics. Hypermobile EDS (hEDS) is the most common, but all types have some component of joint laxity, soft skin, and easy bruising. Diagnosis is primarily done using Beighton criteria, skin histopathology and molecular genetics. Marfan syndrome (MS) a multisystem disorder caused by mutation in FBN1 gene on chromosome 15. One trait that MS shares with EDS is joint hypermobility. Some prior research has suggested an association between connective tissue hypermobility and functional gastrointestinal disorders (FGD’s). No prior study has compared prevalence of GI symptoms between these 2 groups.

Aim of Study: Determine the prevalence of gastrointestinal symptoms in patients with hEDS and Marfans.

Study Design: Case controlled study

Methods:
Participants: Subjects previously diagnosed with hEDS or MS at St. George’s Hospital invited to participate. Additional recruitment with help from Marfan Association UK. Controls recruited from fracture clinic at same facility. One control per hEDS/MS recruited and age matched by gender and age (+/-10 yrs). Excluded if organic gastrointestinal disease diagnosed. Study protocol approved by South West-Central Bristol Research Ethics Committee and NHS Research Authority UK.

Questionnaires & Measurements: All participants completed:
1) SF36 RAND-Mean scores out of 100 for each of the 8 categories.
2) Rome IV Diagnostic questionnaire, 89 question screen for functional gastrointestinal disorders. Scoring algorithm for adults used and a functional gastrointestinal disorder noted to be present if criteria met. Presence of abdominal pain, constipation, and diarrhea investigated separately even if criteria for FGID not met. Article outlined many definitions associated with questionnaire: see page 2.
3) Additional questions re: ethnicity, smoking, alcohol use, other medical conditions, medication also asked, using previously validated questionnaire. Also asked specifically if they had used antisecretory/antacid therapy or laxatives, either regularly or as needed basis in last 6 months.
4) Potential control subjects screened with Beighton criteria for hypermobility and included as a control if score of 4 or less was achieved.
Statistical Power and Analysis: Analysis performed using IBM Statistical Package for the Social Science (SPSS) software version 25. Fisher’s exact test and Chi-squared test used for comparing categorical variables. Independent sample t-test values used to compare mean scores in different modalities of SF 36.

Results: 90 subjects (45 hEDS: 6 males and 39 females between age 18-32, mean 24 years and 45 MS: 12 males and 33 females, age 19-41, mean 28 years) and 90 controls included.

1. Gastrointestinal symptoms in hEDS/MS patients compared to normal controls: See Table One.
   a. Bowel disorders: All categories were significantly greater in hEDS/MS subjects with highest level of statistical difference (p<0.001) for Functional constipation, Functional abdominal bloating/distension and Unspecified functional bowel disorder, and the other 2 categories of IBS, Functional diarrhea achieving statistical difference of p<0.01.
   b. Esophageal disorders: Only functional heartburn and functional dysphagia achieved statistical difference at p<0.01 and p<0.05 respectively.
   c. Gastroduodenal disorders: Functional dyspepsia reached the p<0.001 significance and belching p<0.05.
   d. No clinically difference prevalence of Centrally mediated abdominal pain syndrome, Functional biliary pain and Anorectal disorders identified.
   e. The overall symptoms of Abdominal pain, Diarrhea, and Constipation all significantly greater (p> 0.001) in hEDS/MS population as compared to controls and they were also medicating with either antisecretory/antacids and/or laxatives in the hEDS/MS significantly more (p<0.001).

2. Gastrointestinal symptoms in MS patients compared to controls. See Table Two.
   a. The only category that achieved statistical difference was the Symptom of Abdominal pain and it was only p<0.05.

3. Gastrointestinal symptoms in hEDS patients compared to controls. See Table 3
   a. Mostly, the significant difference was exactly the same as combined comparisons with a few exceptions.
   b. Functional dyspepsia reduced from p<0.001 to p<0.05 when combined comparison modified and hEDS compared to controls in isolation and Belching disorders no longer significantly greater than controls. A reduction in clinical significance from p<0.001 to 0.01 in the Functional constipation and Functional abdominal bloating also noted.

4. Quality of Life scores comparing MS and control groups. See Table Four. Six of the eight categories of QoL significantly lower than controls.

5. Quality of Life scores comparing hEDS and control groups. See Table Five. All 8 categories statistically lower in hEDS group. All achieved highest level of significance except pain, which was p< 0.05.

Discussion: The connective tissue syndromes of hEDS and Marfans are associated with higher rates of gastrointestinal symptoms when compare to matched controls. Although these two syndromes both involve hypermobility, the hEDS group was impacted more significantly with symptoms and quality of life scores when compared to controls. Since
2015 there have been several articles published that have identified functional GI symptoms in up to 75% of EDS patients, and structural abnormalities in up to 20%. Bolasco, et al published a study with matched controls compared to hEDS and JHS subjects and reported all GI symptoms were more common in the hypermobile groups. This association between hypermobility and functional GI symptoms is increasingly being recognized, although the reasons remain unclear.

Weaknesses: Small sample size. Potentially undiagnosed organic GI causes of symptoms may have skewed the study. The fact that the subjects were recruited from rheumatology may have biased the study to recruit the more severe hEDS subjects. This could partially explain the more severe symptoms of this group when compared to Marfans subjects.

**Summary:** A greater understanding of functional GI symptoms in the hypermobile population may help to better understand the etiology of these issues. Also, medical professionals who treat Functional GI symptoms may be able to identify the hypermobility pathology in unsuspected women and men. With all areas of quality of life impacted in the hEDS patients and a majority of the categories in the Marfan group, there is the potential for significantly improving their quality of lives if the GI symptoms are treated.

**Discussion Questions:**
1. Do you routinely screen for hypermobility with functional constipation patients?
   If so, which screening tool do you use?
2. Does anyone regularly see patients with Marfan syndrome? Any unique presentations?
3. Are there any other typical findings with this group of patients? Posture, gait, strength/muscle function of trunk and LE’s, etc?
4. Do your hypermobile GI patients respond to your treatments similar to non-hypermobile?

**Resources:**


89 question screening questionnaire.

Sample questions:
45. How often did your pain start or get worse after eating a meal? (Percent of time with pain) 0. ___0% (never); 1. ___10%; 2. ___20%; 3. ___30%, 4. ___40%, 5. ___50% 6. ___60%; 7. ___70%; 8. ___80%, 9. ___90%; 10. ___Always

63. In the last 3 months, how often did you have to rush to the toilet to have a bowel movement? (Percent of bowel movements) 0. ___0% (never); 1. ___10%; 2. ___20%; 3. ___30%, 4. ___40%, 5. ___50% 6. ___60%; 7. ___70%; 8. ___80%, 9. ___90%; 10. ___Always
Summary of revised Ghent criteria for diagnosis of Marfan syndrome: https://www.marfan.org/dx/rules
