Gastrointestinal Complications of Ehlers-Danlos Syndrome
Gastrointestinal Complications of Ehlers-Danlos Syndrome

“All disease begins in the gut.”

“Bad digestion is the root of evil.”

“Death sits in the bowels.”

- Hippocrates (c. 400 BC)
Isn’t Ehlers-Danlos Syndrome (EDS) all about:
  • hypermobility?
  • musculoskeletal issues?
  • pain?
  • skin issues?
  • vascular issues?

What do gut functions have to do with EDS?
Conditions / symptoms caused by gastrointestinal connective tissue abnormalities in EDS include:

- structural / anatomic issues.
- dysmotility.
- Functional Gastrointestinal Disorders.
- dysbiosis.
- inflammation.
- increased permeability.
- malabsorption (malnutrition).
- gut-related immune dysregulation.
- pain.

The autonomic nervous system abnormalities common in EDS may cause additional GI symptoms.
Gastrointestinal complications of EDS are:

- common.
- potentially disabling.
- well-documented in existing literature.
- under-appreciated by clinicians.
Teenager, 18, is fed through her heart via a drip after being diagnosed with life-threatening tissue disorder

By Larisa Brown

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“Jodie, of Carlisle, Cumbria, has Ehlers-Danlos Syndrome Hypermobility Type III (EDS), a disorder that affects the collagen in the body and can also interfere with the way internal organs, nerves and muscles work.”

“Jodie has severe complex intestinal failure, has had her large bowel removed and a permanent stoma bag fitted, her small intestine has stopped working, her stomach doesn't function and her bladder has failed. It was hoped she would be able to get a five-organ transplant but doctors have said she would not survive the surgery. As the teenager cannot tolerate food she has not eaten since 2009 and is fed intravenously into the heart by a Total Parental Nutrition tube (TPN), however, this comes with serious risks including septicaemia and liver disease.”
Gastrointestinal complications of the Ehlers-Danlos syndrome

PETER H. BEIGHTON1, J. LAMONT MURDOCH2, AND THEODORE VOTTELER3

From Johns Hopkins Hospital, Baltimore, USA

SUMMARY The gastrointestinal abnormalities encountered in 125 patients with the Ehlers-Danlos syndrome have been described. Spontaneous perforation of the intestine and massive gastrointestinal haemorrhage are uncommon but potentially lethal complications of the Ehlers-Danlos syndrome. Less dangerous abnormalities, such as external hernia, hiatus hernia, eventration of the diaphragm, intestinal diverticula, and rectal prolapse were all encountered in patients in the series. Abdominal surgery in affected patients may be made difficult by fragility of tissues and a bleeding tendency. In the postoperative period, tearing out of sutures and wound dehiscence may occur.
Gastrointestinal Complications of Ehlers-Danlos Syndrome: Well-documented in Existing Literature

GI Manifestations of Ehlers-Danlos Syndrome.
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Although once though to be extremely rare, more and more cases of EDS are being reported, and it is conceivable that patients may present in nonaca-
demic settings without a known diagnosis. EDS can have manifestations from mouth to anus, some of which are benign, and others can be lethal. A thor-
ough knowledge of the GI manifestations of Ehlers-Danlos and their management is mandatory to pre-
vent unnecessary morbidity and mortality. The app-
ropriate management of such patients begins with the realization that there is a systemic illness, EDS, present that may involve multiple organ systems.
Gastrointestinal Complications of Ehlers-Danlos Syndrome: Well-documented in Existing Literature

Program Nr: 362 from the 1999 ASHG Annual Meeting

**Gastroesophageal reflux and irritable bowel syndrome in classical and hypermobile Ehlers Danlos syndrome (EDS).**
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Rupture of the GI tract is a known manifestation of vascular EDS (type IV), and diverticuli and hiatal hernia have been reported without specification of EDS subtype. However, the spectrum and frequency of GI complications in classical (types I and II) and hypermobile (type III) EDS have not been established.

We reviewed the charts of 51 EDS patients for GI findings. 38 patients had classical, and 13 had hypermobile EDS. Age range was 8 to 78 years. Sex ratio was biased, with F:M=41:10 (30:8 classical and 11:2 hypermobile). Gastroesophageal reflux (GERD) was suspected clinically in 26 of 45 patients [58%] for whom data was available (17 of 32 classical [53%] and 9 of 13 hypermobile [69%]). Irritable bowel syndrome (IBS), defined as chronic intermittent diarrhea and/or constipation, with or without abdominal cramps, was reported by 24 of 43 patients (56%) for whom data was available (18 of 30 classical [60%] and 6 of 13 hypermobile [46%]). Also, 4 patients (2 classical, 2 hypermobile) had endoscopic diagnoses of non-specific inflammatory bowel disease (IBD); thus 28 of 47 informative patients [60%] had IBS or IBD. Overall, 34 of 47 patients [72%] had any combination of GERD, IBS & IBD. If all missing data was considered negative, the overall prevalence would be 26 of 51 [51%] for GERD and 28 of 51 [55%] for IBS/IBD.

EDS patients may have **chronic pain**, leading to NSAID-induced gastritis mimicking GERD or narcotic-induced symptoms mimicking IBS. Alternatively, EDS may cause reduced lower esophageal sphincter tone, increased distensibility, and/or decreased GI motility, resulting in **GERD and/or IBS**. **Autonomic dysfunction** could cause both GERD and IBS. 10 patients had suspected or confirmed cardiovascular autonomic dysfunction; 9 also had GI complications.

We conclude that GERD and IBS are common **complications of classical and hypermobile EDS**, and should be sought and treated in these patients.
Letters to the Editor

Rheumatology 2004;43:1194–1195
doi:10.1093/rheumatology/keh279

Non-musculoskeletal symptoms in joint hypermobility syndrome. Indirect evidence for autonomic dysfunction?

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Accepted 19 May 2004

Fig. 1. Bar chart showing the percentage proportions of patients and controls reporting symptoms.
Ehlers-Danlos syndromes (EDS) are a heterogeneous group of hereditary disorders of connective tissue that are characterized by joint, skin, and vascular abnormalities.

Most literature reports of gastrointestinal (GI) involvement in EDS have been limited to patients with vascular EDS. Patients with vascular EDS have abnormalities of type III collagen, a constituent of the bowel wall, and thus prone to GI complications and bowel rupture. Patients with other types of EDS, however, also report GI dysfunction.

Complete physicals and medical histories were obtained from 90 patients with hypermobile or classical types of EDS enrolled in the National Institutes on Aging protocol 2003-086, “Clinical and Molecular Manifestations of Heredity Disorders of Connective Tissue.”

We found a high prevalence of GI manifestations in this cohort of patients, including severe chronic constipation (17%), irritable bowel syndrome (12%), acid reflux or gastroesophageal reflux disease (14%), and/or chronic abdominal pain (22%). Gastroparesis was noted in four subjects. The prevalence of each of these disorders was significantly higher in our cohort (P<.0001) compared with the general population.

In our cohort, lack of tissue integrity may cause structural abnormalities, decreased blood vessel wall strength, and/or altered motility or absorption, which may all contribute to development of GI disorders.
Ehlers-Danlos syndromes (EDS) are a heterogeneous group of hereditary disorders of connective tissue that are characterized by joint, skin, and vascular abnormalities.

Complete physicals and medical histories were obtained from 95 patients with hypermobile, classical, and vascular EDS enrolled in the National Institutes on Aging Protocol 2003-086, “Clinical and Molecular Manifestations of Hereditary Disorders of Connective Tissue.”

We found a high prevalence of food allergies in patients with EDS (14%) when compared with the general population (P<.0001). We also found a significantly higher incidence of gastrointestinal manifestations in our cohort when compared with the general population (P<.0001). The presence of food allergies also seems to correlate with gastrointestinal dysfunction in some patients. Of the patients who reported constipation, irritable bowel syndrome, gastroesophageal reflux disease, and/or chronic abdominal pain, many also reported having a food allergy (40%, 42%, 17%, and 20%, respectively).

Collagen abnormalities may cause mucosal lesions, altering tissue integrity and increasing the chance of larger proteins crossing the mucosal barrier and creating an immunogenic response. Multiple studies have correlated eosinophillic gastrointestinal disorders, allergic responses that fall in between IgE and TH2-type responses that are mediated by IL-5 and other eotaxins, with classic mast cell tissue degranulation, producing gastrointestinal disorders similar to those seen in our patients.

Understanding the mechanisms associated with food allergies in patients with EDS may aid in development of effective treatments.
Gastrointestinal Complications of Ehlers-Danlos Syndrome: Well-documented in Existing Literature

Research Article

Prevalence of Joint Hypermobility and Patterns of Articular Manifestations in Patients with Inflammatory Bowel Disease

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Conclusions

Joint hypermobility and the hypermobility syndrome are common in Crohn’s disease patients in the Greek Caucasian population while there is no difference on joint hypermobility in patients with ulcerative colitis compared to the healthy control group. It is two times more likely that the underlying IBD of a patient who exhibits joint hypermobility is CD rather than UC. The constellation of articular symptoms in CD patients does not always suggest an enteropathic spondylarthropathy but the coexistent joint hypermobility. The high incidence of this particular phenotype of JH on CD patients could support the hypothesis that collagen varieties may attribute to the pathogenesis of CD.
Gastrointestinal Complications of Ehlers-Danlos Syndrome: Well-documented in Existing Literature

Unexplained gastrointestinal symptoms and joint hypermobility: is connective tissue the missing link?

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CONCLUSIONS

The findings reported in this study suggest that a proportion of patients presenting to tertiary referral neurogastroenterology clinics with unexplained GI symptoms, diagnosed as having FGID, also have evidence of JHM, and a proportion of these are diagnosed with BJHS and GI dysmotility. Further research is required to ascertain the nature of the potential relationship between BJHS and unexplained GI symptoms.
Joint Hypermobility: A Common Association with Complex Functional Gastrointestinal Disorders.

Kovacic K¹, Chelimsky TC², Sood MR¹, Simpson P³, Nugent M³, Chelimsky G¹.

Abstract

OBJECTIVE: To evaluate the prevalence of joint hypermobility (JH) and comorbid conditions in children and young adults referred to a tertiary care neurogastroenterology and autonomic disorders clinic for functional gastrointestinal complaints.

STUDY DESIGN: This was a retrospective chart review of 66 new patients aged 5-24 years who fulfilled at least 1 pediatric Rome III criteria for a functional gastrointestinal disorder (FGID) and had a recorded Beighton score (n = 45) or fibromyalgia tender point score (n = 45) based on physician examination. Comorbid symptoms were collected and autonomic testing was performed for evaluation of postural tachycardia syndrome (POTS).

RESULTS: The median patient age was 15 years (range, 5-24 years), 48 (73%) were females, and 56% had JH, a significantly higher rate compared with population studies of healthy adolescents (P < .001; OR, 10.03; 95% CI, 5.26-19.13). POTS was diagnosed in 34% of patients and did not correlate significantly with hypermobility. Comorbid conditions were common, including sleep disturbances (77%), chronic fatigue (93%), dizziness (94%), migraines (94%), chronic nausea (93%), and fibromyalgia (24%).

CONCLUSION: JH and other comorbid symptoms, including fibromyalgia, occur commonly in children and young adults with complex FGIDs. POTS is prevalent in FGIDs but is not associated with hypermobility. We recommend screening patients with complex FGIDs for JH, fibromyalgia, and comorbid symptoms such as sleep disturbances, migraines, and autonomic dysfunction.
Joint Hypermobility Syndrome

Asma Fikree, BM BCh, MA, MRCP, Qasim Aziz, PhD, FRCP, Rodney Grahame, CBE, MD, FRCP, *

KEYWORDS

- Hypermobility • Hypermobility syndrome • Ehlers-Danlos syndrome • Dysautonomia
- Functional gastrointestinal disorder

KEY POINTS

- Joint hypermobility syndrome is a common, heritable disorder of connective tissue that is frequently overlooked.
- It is almost certainly identical to the Ehlers-Danlos Syndrome, hypermobility type.
- It is not a trivial articular problem occurring in healthy individuals; it is now recognized as a multisystemic disorder and a major source of chronic widespread pain, dysautonomias, and gastrointestinal dysmotility. It is a neglected area within rheumatology.
Gastrointestinal Complications of Ehlers-Danlos Syndrome: Under-appreciated by Clinicians

International Scholarly Research Network
ISRN Dermatology
Volume 2012, Article ID 751768, 22 pages
doi:10.5402/2012/751768

Review Article

Ehlers-Danlos Syndrome, Hypermobility Type: An Underdiagnosed Hereditary Connective Tissue Disorder with Mucocutaneous, Articular, and Systemic Manifestations

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Gastrointestinal Complications of Ehlers-Danlos Syndrome: Under-appreciated by Clinicians
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Gastrointestinal Complications of Ehlers-Danlos Syndrome: Under-appreciated by Clinicians
Ehlers-Danlos Syndrome is NOT “just” hypermobility.

Ehlers-Danlos Syndrome affects the vital physiologic processes of digestion, nutrition, elimination, and gut-related immune function.
Gastrointestinal Complications of Ehlers-Danlos Syndrome: The Alimentary Canal

The Alimentary Canal

1. Mouth
   Mechanical and chemical processing (chewing reduces size of food; saliva digests carbohydrates)

2. Esophagus
   Transports food

3. Stomach
   Mechanical and chemical processing (digestion of proteins)

4. Small intestine
   Chemical processing and absorption (digestion of proteins, fats, carbohydrates; absorption of nutrients and water)

5. Large intestine
   Water absorption and feces formation
Gastrointestinal Complications of Ehlers-Danlos Syndrome: Layers of the Alimentary Canal

- **lumen**: *enteric microbiota*
- **mucosa**: serves as a barrier, allows absorption
  - epithelium: absorption, secretion
  - lamina propria: *connective tissue, lymphoid tissue, mast cells, eosinophils*
  - muscularis mucosae: smooth muscle
- **submucosa**: specialized structures
  - *dense irregular connective tissue*
  - *lymphoid tissue*
  - *nerves (submucosal plexus)*
  - *blood vessels*, glands
- **muscularis**: mixes, propels
  - *nerves (myenteric plexus)*
  - circular and longitudinal muscle
- **serosa / adventitia**: *connective tissue*
Gastrointestinal Complications of Ehlers-Danlos Syndrome: Layers of the Alimentary Canal
The alimentary canal encloses an environment considered to be external to the body.

• a very large surface area
  – about the area of a football field

• The mucosa of the gut is very analogous to skin.

• gut immune defenses
  – physical (e.g., intact mucosa, vomiting, diarrhea)
  – cellular (e.g., lymphoid cells, mast cells, eosinophils)
  – chemical (e.g., pH, antibodies)
Leukocytes in Alimentary Tissues

- **Gut-Associated Lymphoid Tissue (GALT)**
  - T lymphocytes, B lymphocytes, Natural Killer cells
    - lamina propria, submucosa
    - esophagus, stomach, small intestine, large intestine
    - tonsils, adenoids, appendix

- **myeloid cells**
  - e.g., mast cells, eosinophils
    - mucosa
Over 100 trillion organisms occupy the human gut.

- Over 1000 species identified so far.
  - bacteria
  - archea
  - fungi
  - protozoa

Our microbiota have 150 times more genes than us.

- 90% of the cells within our body are microbial.
- https://commonfund.nih.gov/hmp/

The colonic microbiome is the most biodense natural ecosystem known.

- $10^{10}$-$10^{12}$ cells/ml
- Bacteria make up ~60% of the dry mass of feces.
Bacterial Benefits

• ferment undigested carbohydrates
  – provide short chain fatty acids as energy

• enhance lipid metabolism
  – fat-soluble vitamin A, D, E, and K absorption

• assist in absorption of minerals
  – e.g., calcium, magnesium, iron

• synthesize nutrients
  – e.g., B vitamins, vitamin K, folate, biotin

• metabolize bile acids, sterols, and xenobiotics

• ferment non-digestible dietary residue and mucus

• support / regulate epithelial and lymphoid function

• affect the production of neurotransmitters by gut tissue
Gastrointestinal Complications of Ehlers-Danlos Syndrome: The Gut Microbiome

The gut flora as a forgotten organ

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A

Duodenum
$10^1 - 10^3 \text{ cfu/ml}$

Stomach
$10^4 - 10^5 \text{ cfu/ml}$

Colon
$10^{11} - 10^{12} \text{ cfu/ml}$

Jejunum/ileum
$10^8 - 10^9 \text{ cfu/ml}$

B

<table>
<thead>
<tr>
<th>Protective functions</th>
<th>Structural functions</th>
<th>Metabolic functions</th>
</tr>
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<tbody>
<tr>
<td>Pathogen displacement</td>
<td>Barrier fortification</td>
<td>Control IEC differentiation and proliferation</td>
</tr>
<tr>
<td>Nutrient competition</td>
<td>Induction of IgA</td>
<td>Ferment non-digestible dietary residue and endogenous epithelial-derived mucus</td>
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<tr>
<td>Receptor competition</td>
<td>Apical tightening of tight junctions</td>
<td>Ion absorption</td>
</tr>
<tr>
<td>Production of anti-microbial factors e.g., bacteriocins, lactic acids</td>
<td>Immune system development</td>
<td>Salvage of energy</td>
</tr>
<tr>
<td>Commensal bacteria</td>
<td>IgA</td>
<td>Vitamin K</td>
</tr>
</tbody>
</table>

Fig 1 | Functions of the intestinal flora. (A) Bacteria density increases in the jejunum/ileum from the stomach and duodenum, and in the large intestine, colon-residing bacteria achieve the highest cell densities recorded for any ecosystem. The most common anaerobic and aerobic genera are listed. (B) Commensal bacteria exert a miscellany of protective, structural and metabolic effects on the intestinal mucosa.
Gastrointestinal Complications of Ehlers-Danlos Syndrome: The Gut Microbiome and Immunomodulation

Probiotics, Prebiotics and Immunomodulation of Gut Mucosal Defences: Homeostasis and Immunopathology

Holly Hardy, Jennifer Harris, Eleanor Lyon, Jane Beal and Andrew D. Foey *

*Correspondence: andrew.foey@itn.org
Gastrointestinal Complications of Ehlers-Danlos Syndrome: Normobiosis vs. Dysbiosis

Normobiosis: A Balancing Act
- believed to prevent:
  - auto-immune disease
  - allergies
  - cancer
  - diabetes
  - obesity

Dysbiosis: Leads to Non-Specific Inflammation
- An inflamed mucosa is a less effective barrier.
- 2005 Nobel Prize in Physiology and Medicine
- Bacteriotherapy may restore normobiosis.
  - prebiotics and probiotics
  - fecal transplant
Gastrointestinal Complications of Ehlers-Danlos Syndrome:
Normobiosis vs. Dysbiosis

The gut microbiota shapes intestinal immune responses during health and disease

June L. Round and Sarkis K. Mazmanian

Host genetics
Mutations in NOD2, IL23R, ATG16L and IGRM

Lifestyle
Diet
Stress

Early colonization
Birth in hospitals
Altered exposure to microbes

Medical practices
Vaccination use
Antibiotic hygiene

Dysbiosis

Disease
\( \uparrow T_{H1}, T_{H2} \) and \( T_{H17} \) cells

Health
\( \uparrow T_{Reg} \) cells
Autonomic Nervous System (ANS)

- Sympathetic Nervous System (SNS)
  - “Fight or Flight”

- Parasympathetic Nervous System (PNS)
  - “Rest and Digest”
### Gastrointestinal Complications of Ehlers-Danlos Syndrome: The Autonomic Nervous System

#### Parasympathetic Nerves

<table>
<thead>
<tr>
<th>Function</th>
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<tbody>
<tr>
<td>Constrict pupils</td>
</tr>
<tr>
<td>Stimulate saliva</td>
</tr>
<tr>
<td>Slow heartbeat</td>
</tr>
<tr>
<td>Constrict airways</td>
</tr>
<tr>
<td>Stimulate activity of stomach</td>
</tr>
<tr>
<td>Inhibit release of glucose; stimulate gallbladder</td>
</tr>
<tr>
<td>Stimulate activity of intestines</td>
</tr>
<tr>
<td>Contract bladder</td>
</tr>
<tr>
<td>Promote erection of genitals</td>
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#### Sympathetic Nerves

<table>
<thead>
<tr>
<th>Function</th>
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<tbody>
<tr>
<td>Dilate pupils</td>
</tr>
<tr>
<td>Inhibit salivation</td>
</tr>
<tr>
<td>Increase heartbeat</td>
</tr>
<tr>
<td>Relax airways</td>
</tr>
<tr>
<td>Inhibit activity of stomach</td>
</tr>
<tr>
<td>Stimulate release of glucose; inhibit gallbladder</td>
</tr>
<tr>
<td>Inhibit activity of intestines</td>
</tr>
<tr>
<td>Secrete epinephrine and norepinephrine</td>
</tr>
<tr>
<td>Relax bladder</td>
</tr>
<tr>
<td>Promote ejaculation and vaginal contraction</td>
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Figure 45-20 Biological Science, 2/e © 2005 Pearson Prentice Hall, Inc.
Gastrointestinal Complications of Ehlers-Danlos Syndrome: The Autonomic Nervous System

The major components and functions of the nervous system

**Central Nervous System**
- The central nervous system (CNS) consists of the brain and spinal cord and is responsible for integrating, processing, and coordinating sensory data and motor commands.

**Peripheral Nervous System**
- The peripheral nervous system (PNS) includes all the neural tissue outside the CNS.

1. **Receptors** are sensory structures that detect changes in the internal or external environment.

2. The sensory division of the PNS brings information to the CNS from receptors in peripheral tissues and organs.

3. Information processing includes the integration and distribution of information in the CNS.

4. The motor division of the PNS carries motor commands from the CNS to peripheral tissues and systems.

5. **Effectors** are target organs whose activities change in response to neural commands.

- Somatic sensory receptors provide position, touch, pressure, pain, and temperature sensations.
- Special sensory receptors provide sensations of smell, taste, vision, balance, and hearing.
- Visceral sensory receptors monitor internal organs.
- Skeletal muscle
- Cardiac muscle
- Glands
- Adipose tissue
- Somatic nervous system (SNS) controls skeletal muscle contractions.
- Autonomic nervous system (ANS) provides automatic regulation of smooth muscle, cardiac muscle, glands, and adipose tissue.
The functions of the alimentary canal are locally regulated by the Enteric Nervous System (ENS).
Gastrointestinal Complications of Ehlers-Danlos Syndrome: The Enteric Nervous System

The ENS is intrinsic to the alimentary canal, and it connects with the CNS via the SNS and PNS.
The Enteric Nervous System: “The Second Brain”

- can function autonomously
  - after spinal cord injury
  - with stored programs (e.g., vomiting)
- regulated by SNS and PNS
  - “Fight or Flight”
  - “Rest and Digest”
- Part of the “Brain-Gut Axis”

Think Twice: How the Gut's "Second Brain" Influences Mood and Well-Being

The emerging and surprising view of how the enteric nervous system in our bellies goes far beyond just processing the food we eat
Brain-gut axis as an example of the bio-psycho-social model

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“Schematic representation of the pattern of bidirectional brain–gut–microbe interactions. The brain can modulate various functions of the gut, as well as the perception of gut stimuli, via a set of parallel outflow systems that are referred to as the EMS, which include the sympathetic and parasympathetic branches of the ANS, the HPA axis, and endogenous pain-modulation systems. Activation of the EMS can occur via interoceptive and exteroceptive stressors. The enteric microbiota are likely to interact with gut-based effector systems and with visceral afferent pathways, which establish a bidirectional brain–gut–enteric microbiota axis. Abbreviations: ANS, autonomic nervous system; CNS, central nervous system; EMS, emotional motor system; GI, gastrointestinal; HPA, hypothalamus–pituitary–adrenal.”
Common Forms of Autonomic Dysfunction (Dysautonomia)

- Postural Orthostatic Tachycardia Syndrome (POTS)
  - tachycardia (very fast heart rate)
- Neurocardiogenic Syncope (NCS)
  - syncope (fainting or nearly fainting)
- Neurally Mediated Hypotension (NMH)
  - hypotension (low blood pressure)
- Orthostatic Intolerance (OI)
  - poor tolerance of:
    - upright positions
    - rapidly changing positions
Diet
- nutrient-dense vs. nutrient-poor
- affects the health of the gut microbiome
  - in turn, affects gut-related immune function

Exercise
- Some conditions can be caused by inactivity.
  - e.g., gall bladder disease, diverticulitis, constipation
- Activity may prevent inflammatory bowel disease.

Medications
- prescription vs. non-prescription
  - “pharmaceutical” vs. “nutraceutical”
  - supplements, herbs, teas, etc.
- intended effects vs. side effects
EDS is a disorder affecting the production, maintenance, or repair of connective tissues.

- The alimentary canal is rich in connective tissue.

Gut-related immunity is part of alimentary health.

- Dysregulation of gut-related immunity is prevalent in EDS.

Normobiosis is necessary for healthy alimentary function.

- Dysbiosis is prevalent in EDS.

The autonomic nervous system affects whether the alimentary canal is “on” (“Rest and Digest”) or “off” (“Fight or Flight”).

- Autonomic Dysfunction is prevalent in EDS.

Persons with EDS can either support or thwart alimentary functions through diet, exercise, and medicine or supplement use.

- Persons with EDS often have a sub-optimal diet, find it difficult to exercise, and are on numerous medications or supplements.
Connective tissue abnormalities in EDS may affect gastrointestinal physiology by causing:

- structural issues affecting the alimentary canal.
  - microscopic (may be inflammatory or non-inflammatory)
    - tissue biopsy
  - macroscopic
    - imaging
    - direct inspection (e.g., endoscopy, colonoscopy, surgery)
    - may vary with time

- gastrointestinal dysmotility.

- Functional Gastrointestinal Disorders (FGIDs).
  - FGIDs are those without a known underlying structural, biochemical, metabolic, or autoimmune cause.
Gastrointestinal Complications of Ehlers-Danlos Syndrome: Structural Issues

The Teeth

- dentin dysplasia
- root dilaceration
- hypodontia
- ectopic eruption
- delayed eruption
- transmigration
- fracture after minor stress
- recurrent caries (i.e., tooth decay)
- premature loss
- difficulty with hemostasis after tooth extraction
- difficulty achieving dental anesthesia
The Oropharynx

- Mucosa, Gingiva, and Alveolar Bone
  - xerostomia
  - fragility
  - breakdown
  - odontogenic keratocysts

- Tongue
  - hypermobility (Gorlin’s Sign)

- Temporomandibular Joint (TMJ)
  - dysfunction
  - dislocation
The Esophagus

- dilation (e.g., megaesophagus)
- diverticula (e.g., giant epiphrenic diverticula)
- Gastroesophageal Reflux Disease (GERD)
  - reduced lower esophageal sphincter tone
  - esophageal reflux
  - laryngopharyngeal reflux ("Silent Reflux")
    - may cause excessive phlegm, cough, postnasal drip
    - may mimic bronchitis, asthma, sinusitis, etc.

- hiatal hernia (very common)
- rupture or perforation
- arterial rupture
The Stomach

• GERD
• gastritis
• peptic ulceration
  – complications may be particularly severe in VEDS
    ▪ hematemesis
    ▪ melena
    ▪ very rarely: erosion of the aorta by a duodenal ulcer
• diverticula: nidus for perforation
  – comorbid gall bladder and small intestinal diverticula
• hiatal hernia (very common)
The Stomach (cont’d)

- diaphragmatic eventration
- gastric malrotation
- volvulus
- gastric infarction
- visceroptosis
The Small Intestine

- dilation
  - e.g., megaduodenum, dilation of entire small bowel
  - has been linked to bacterial overgrowth, malabsorption
- diverticula: nidus for perforation
- hernia
- visceroptosis
The Small Intestine (cont’d)

- **perforation**
  - with or without diverticula
  - more common in VEDS
  - symptoms
    - pain
    - emesis
    - hematemesis
    - peritonitis
  - may be more prone to abscess formation
    - inability to wall off infectious processes
  - may require partial small bowel resection and anastomosis

- **intramural hematomas**
  - more common in VEDS
  - may be heralded by hematemesis
  - focal necrosis increases risk of perforation
Special Alimentary Structures

- Liver, Gall Bladder, Pancreas
  - may rupture

- Appendix
  - Appendicitis is likely less common in EDS than in the general population.
The Large Intestine

- dilation
  - megacolon
  - dolichocolon
- diverticula: nidus for perforation
- hernia
- visceroptosis
Recurring and Generalized Visceroptosis in Ehlers–Danlos Syndrome Hypermobility Type

Chiara Dordoni,1 Marco Ritelli,1 Marina Venturini,2 Nicola Chiarelli,1 Lidia Pezzani,1 Annalisa Vascellaro,2 Piergiacomo Calzavara-Pinton,2 and Marina Colombi1

1 Division of Biology and Genetics, Department of Biomedical Sciences and Biotechnology, Medical Faculty, University of Brescia, Brescia, Italy
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Visceroptosis of the Bowel in the Hypermobility type of Ehlers-Danlos Syndrome: Presentation of a Rare Manifestation and Review of the Literature

Eyal Reinstein1,*, Mark Pimentel2, Mitchel Pariani1, Stephen Nemec1, Thomas Sokol3, and David L Rimoin1,†
The Large Intestine (cont’d)

- spontaneous perforation(s)
  - with or without diverticula
  - more common in VEDS
  - may have history of constipation, pain
    - diverticula
    - intramural hematoma
    - tear in seromuscular coat
  - likelihood increases with age
  - more frequent in women
  - most common in sigmoid colon
  - may be multifocal
  - tend to recur
    - Colostomy is often recommended.
      ✓ Risk of colostomy stenosis is significant.
    - Colectomy with ileostomy is often needed.
      ✓ Ileoproctostomy can be considered.
  - Perforation may be considered “inevitable”.
    - Prophylactic colectomy may be advised.
The Rectum

• traumatic perforation
  – more common in VEDS
  – most likely to occur in rectum
    ▪ Avoid enemas.
    ▪ Avoid manual disimpaction.
    ▪ Avoid colonoscopy.

• rectocele

• prolapse
  – often in infancy
  – less likely with increasing age

• hemorrhoids
Gastroparesis (Delayed Gastric Emptying)

- About 4% of the US population has gastroparesis.
- About a third of all cases are idiopathic.
- For the rest, an underlying cause is identifiable.
  - commonly recognized causes include:
    - autonomic neuropathy (e.g., Diabetes Mellitus)
    - vagus nerve damage (e.g., after abdominal surgery)
    - connective tissue abnormalities
      - heritable (e.g., EDS)
      - acquired (e.g., Scleroderma)
    - Parkinson’s Disease
    - mitochondrial disorders
  - additional recognized causes include:
    - Anorexia Nervosa and Bulimia Nervosa
    - smoking
Gastrointestinal Dysmotility is well-documented in EDS.

• esophageal dysmotility
  – includes ineffective esophageal motility, nonspecific esophageal motility disorder

• gastric dysmotility
  – includes gastroparesis (delayed gastric emptying)

• small bowel dysmotility
  – includes pseudoobstruction

• colonic dysmotility
  – includes delayed colonic transit, constipation, Chronic Intestinal Pseudoobstruction (Ogilvie Syndrome), diarrhea, Irritable Bowel Syndrome

• rectal evacuatory dysfunction
Gastrointestinal Complications of Ehlers-Danlos Syndrome: Dysmotility

Chronic Intestinal Pseudo-obstruction: Assessment and Management

FRANCES L. CONNOR* and CARLO DI LORENZO†
*Division of Pediatric Gastroenterology, and the Division of Hepatology and Nutrition, Royal Children’s Hospital, Herston, Australia; and
†Columbus Children’s Hospital, Columbus, Ohio

Neurogastroenterol Motil (2007) 19, 440-452
doi: 10.1111/j.1365-2982.2007.00602.x

REVIEW ARTICLE

Chronic intestinal pseudo-obstruction: manifestations, natural history and management

V. STANGHELLINI, E. F. COGLIANDO, R. DE GIORGIO, G. BARBARA, B. SALVIOLI & E. CORINALDES
Department of Internal Medicine and Gastroenterology, University of Bologna, Bologna, Italy

Table 1 Main causes of secondary chronic idiopathic pseudo-obstruction and relative gut tissue that is predominantly involved

<table>
<thead>
<tr>
<th>Affected control mechanism of GI function</th>
<th>Underlying disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrinsic autonomic nervous system</td>
<td>Stroke, encephalitis, calcification of basal ganglia, orthostatic hypotension and diabetes</td>
</tr>
<tr>
<td>Enteric nervous system</td>
<td>Paraneoplastic, viral infections, iatrogenic (anthraquinones), diabetes, Hirschsprung, Chagas and Von Recklinghausen</td>
</tr>
<tr>
<td>Enteric smooth muscle layer</td>
<td>Myotonic dystrophy and progressive systemic sclerosis</td>
</tr>
<tr>
<td>Mixed enteric neuro-myoopathy</td>
<td>Scleroderma, dermatomyositis, amyloidosis, Ehlers-Danlos, jejunal diverticulosis and radiation enteritis</td>
</tr>
<tr>
<td>Undetermined</td>
<td>Hypothyroidism, hypoparathyroidism, phaeochromocytoma and iatrogenic (clonidine, phenothiazines, antidepressants, antiparkinsonians, antineoplastic, bronchodilators)</td>
</tr>
</tbody>
</table>
Gastrointestinal Complications of Ehlers-Danlos Syndrome: Dysmotility – Faces of the Disorder
Functional Gastrointestinal Disorders (FGIDs)

• Rome III Criteria

• Documented in EDS
  – Functional Esophageal Disorders
    ▪ e.g., Functional Dysphagia, Globus
  – Functional Abdominal Pain Syndrome
  – Irritable Bowel Syndrome
  – Functional Diarrhea
  – Functional Constipation
    ▪ e.g., chronic (slow transit) constipation
  – Functional Fecal Incontinence
  – Functional Defecation Disorders
EDS patients are recognized to suffer numerous nutritional deficiencies and related conditions.

- Nutritional deficiencies in EDS occur despite:
  - meeting recommended dietary intake goals.
  - diligent oral supplementation.

Formal research is lacking regarding the specific pathophysiology of how EDS affects nutritional status.
The most likely culprit causing EDS-related malnutrition is **malabsorption** due to:

- intrinsic connective tissue abnormalities.
- inflammation (e.g., in the setting of dysbiosis).
- dysautonomia (e.g., “Rest and Digest” is “off”).
Acknowledged / Suspected Nutritional Deficiencies in EDS

- minerals: e.g., magnesium, potassium, calcium, iron
- vitamins: e.g., Vitamin C, Vitamin D, vitamin K

Associated conditions include:

- osteopenia, osteoporosis, and osteomalacia.
- anemia.
- skin and small blood vessel fragility.
- myriad musculoskeletal and neurologic symptoms.

Some deficiencies are only apparent clinically.

- For example, magnesium deficiency is NOT always accompanied by hypomagnesemia!
Gastrointestinal Complications of Ehlers-Danlos Syndrome: Nutritional Deficiencies

Repletion of deficiencies should not be expected to bring immediate results, as the conditions they cause may require weeks, months or even years to improve.

Repletion of deficiencies may not fully reverse developmental or chronic conditions.

While National Guidelines are established for nutritional standards, without specific research, how these guidelines may need to be modified specifically for persons with EDS is presently unclear.
A novel therapeutic strategy for Ehlers–Danlos syndrome based on nutritional supplements

D. Mantle, R.M. Wilkins, V. Preedy

Medical Hypotheses (2005) 64, 279–283

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Nutritional supplement</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint injury/ arthritis</td>
<td>Glucosamine</td>
<td>1500 mg/day</td>
</tr>
<tr>
<td>Scoliosis/</td>
<td>Vitamin C</td>
<td>750 mg/day</td>
</tr>
<tr>
<td>Osteoporosis/</td>
<td>MSM/silica</td>
<td>1500 mg/3 mg/day</td>
</tr>
<tr>
<td>Bone fracture</td>
<td>Calcium/vitamin K</td>
<td>500 mg/35 µg/day</td>
</tr>
<tr>
<td>Muscle weakness/</td>
<td>Magnesium</td>
<td>200 mg/day</td>
</tr>
<tr>
<td>Fibromyalgia/</td>
<td>Carnitine</td>
<td>250 mg/day</td>
</tr>
<tr>
<td>Sciatica</td>
<td>Coenzyme Q₁₀</td>
<td>100 mg/day</td>
</tr>
<tr>
<td>Fragile skin/</td>
<td>Vitamin C</td>
<td>As above</td>
</tr>
<tr>
<td>Bruising/</td>
<td>MSM plus silica</td>
<td>As above</td>
</tr>
<tr>
<td>Poor healing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding/</td>
<td>Vitamin C</td>
<td>As above</td>
</tr>
<tr>
<td>Varicose veins/</td>
<td>Pycnogenol</td>
<td>80 mg/day</td>
</tr>
<tr>
<td>Raynauds syndrome/</td>
<td>Coenzyme Q₁₀</td>
<td>As above</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Periodontitis</td>
<td>Coenzyme Q₁₀</td>
<td>As above</td>
</tr>
<tr>
<td>Inflammation/ pain</td>
<td>ɣ-linolenic acid</td>
<td>240 mg/day</td>
</tr>
<tr>
<td>Exhaustion/ depression</td>
<td>Coenzyme Q₁₀</td>
<td>As above</td>
</tr>
</tbody>
</table>
Not all forms of EDS are proven to be due to mutations in genes encoding collagen.

- faulty collagen vs. faulty gene products regulating or interacting with collagen

**Collagen Assembly**

- triple helix of coiled protein chains made of amino acids
  - a high proportion of **glycine, proline, and lysine**
- requires **vitamin C** for hydroxylation of procollagen molecules
  - without hydroxylation, procollagen is degraded
- ultrastructure: molecules are arranged together (e.g., fibrils, laminae)

**Collagen Digestion**

- catabolized first into smaller peptide chains
- ultimately catabolized into amino acids
  - assembled into new peptide chains or catabolized via Krebs Cycle

**Bottom Line:**

- No established research or clinical experience has proven that collagen supplementation is helpful for persons with EDS!
- Theoretically, a diet adequate in glycine, proline, lysine, and vitamin C (or supplementation) would support collagen biosynthesis.
Are persons with EDS more prone to:

- food allergies or other forms of hypersensitivity?
- inflammatory or autoimmune disorders of the alimentary canal? (e.g., gluten sensitivity, Celiac Disease, Crohn’s Disease, ulcerative colitis, microcytic colitis, eosinophilic esophagitis)
- Mast Cell Activation Disorders?

Available medical knowledge as well as ample patient experience indicates a connection between EDS and dysregulation of gut-related immune function.

- Formal research is lacking regarding the specific pathophysiology of how EDS affects gut-related immunity.
The most likely culprits causing dysregulation of gut-related immune function in EDS are:

- intrinsic connective tissue abnormalities.
- dysbiosis.
- dysautonomia.
High prevalence of Food Allergies in Patients with Ehlers-Danlos Syndromes.

H. Zhang¹, B.F. Griswold¹, L. Sloper¹, M. Lavallee³, C.A. Francomano², N.B. McDonnell², A. Gustafson¹
1) LCI, NIA/NIH, Baltimore, MD; 2) GBMC, Baltimore, MD; 3) IUSM, South Bend, IN.

“...Collagen abnormalities may cause mucosal lesions, altering tissue integrity and increasing the chance of larger proteins crossing the mucosal barrier and creating an immunogenic response. Multiple studies have correlated eosinophilic gastrointestinal disorders, allergic responses that fall in between IgE and TH2-type responses that are mediated by IL-5 and other eotaxins, with classic mast cell tissue degranulation, producing gastrointestinal disorders similar to those seen in our patients. Understanding the mechanisms associated with food allergies in patients with EDS may aid in development of effective treatments.”
AMERICAN ACADEMY OF ALLERGY, ASTHMA & IMMUNOLOGY

2012 AAAAI Annual Meeting
Orlando, FL
March 2–March 6, 2012

J ALLERGY CLIN IMMUNOL
FEBRUARY 2012

Gastrointestinal food allergies in children with Ehlers Danlos type 3 syndrome


CONCLUSION: We describe a group of children with food induced GI allergies that also have EDS III. They commonly have multiple food allergies, eosinophilic colitis and require both enteral and parenteral nutritional support.
High prevalence of eosinophilic esophagitis in patients with inherited connective tissue disorders
Gastrointestinal Complications of Ehlers-Danlos Syndrome: Dysregulation of Gut-Related Immune Function

Joint Hypermobility Syndrome

Asma Fikree, BM BCh, MA, MRCP\textsuperscript{a}, Qasim Aziz, PhD, FRCP\textsuperscript{a}, Rodney Grahame, CBE, MD, FRCP\textsuperscript{b,*}

KEYWORDS
- Hypermobility
- Hypermobility syndrome
- Ehlers-Danlos syndrome
- Dysautonomia
- Functional gastrointestinal disorder

KEY POINTS
- Joint hypermobility syndrome is a common, heritable disorder of connective tissue that is frequently overlooked.
- It is almost certainly identical to the Ehlers-Danlos Syndrome, hypermobility type.
- It is not a trivial articular problem occurring in healthy individuals; it is now recognized as a multisystemic disorder and a major source of chronic widespread pain, dysautonomias, and gastrointestinal dysmotility. It is a neglected area within rheumatology.


Gluten is a prolamin protein composed of gliadin and glutenin found in wheat and other grains (e.g. rye, barley) common in the Western diet.

Some persons respond to gluten exposure with gluten-sensitive enteropathy.

- Celiac Disease
- Gluten Sensitivity (Gluten Intolerance)
Celiac Disease (Coeliac Disease, Sprue):

- is an autoimmune disorder.
  - anti-transglutaminase antibody positivity
  - HLA-DQ2, HLA-DQ8 positivity
  - Autoimmune comorbidities are common.
- involves “leaky” intestinal mucosa due to a combination of the innate inflammatory response and a maladaptive immune response.
- causes multiple GI complaints (e.g., diarrhea, abdominal pain, bloating, mouth ulcers, lactose intolerance).

Malnutrition due to malabsorption Celiac Disease may be severe.

- weight loss, fatigue, anemia, coagulopathy, osteopenia and osteoporosis, neuropathy, psychiatric manifestations
Gluten Sensitivity (Gluten Intolerance):

- IS NOT an autoimmune disorder.
  - may or may not be accompanied by anti-gliadin antibodies
- is due to an innate inflammatory response to gluten.
  - part of the normal physiology of oxidative stress
- is similar to Celiac Disease.
  - may be accompanied by extreme pain and fatigue
- is usually less severe than Celiac Disease.
- is a diagnosis of exclusion.
  - rule out Celiac Disease
  - rule out true wheat allergy
Review

Celiac Disease, Inflammation and Oxidative Damage: A Nutrigenetic Approach

Gianna Ferretti ¹, Tiziana Bacchetti ², Simona Masciangelo ³ and Letizia Saturni ³*  

Nutrients 2012, 4, 243-257; doi:10.3390/nu4040243

Abstract: Celiac disease (CD), a common heritable chronic inflammatory condition of the small intestine caused by permanent intolerance to gluten/gliadin (prolamins), is characterized by a complex interplay between genetic and environmental factors. Developments in proteomics have provided an important contribution to the understanding of the biochemical and immunological aspects of the disease and the mechanisms involved in toxicity of prolamins. It has been demonstrated that some gliadin peptides resistant to complete proteolytic digestion may directly affect intestinal cell structure and functions by modulating gene expression and oxidative stress. In recent years, the creation of the two research fields Nutrigenomics and Nutrigenetics, has enabled the elucidation of some interactions between diet, nutrients and genes. Various dietary components including long chain ω-3 fatty acids, plant flavonoids, and carotenoids have been demonstrated to modulate oxidative stress, gene expression and production of inflammatory mediators. Therefore their adoption could preserve intestinal barrier integrity, play a protective role against toxicity of gliadin peptides and have a role in nutritional therapy of celiac disease.
Figure 1. Intestinal epithelial damage in celiac disease: role of “toxic” and “immunogenic” peptides.
A Potential “Nutrigenetic” Approach

• *In vitro* nutrition research demonstrates protective effects of certain nutrients against gluten cytotoxicity.
  – phytonutrients (lycopene, quercitine, vitamin C, tyrosol)
  – DHA

• *In vivo* nutrition research is needed to determine whether additional specific nutrients bolster antioxidant defenses against gluten cytotoxicity.
  – long chain unsaturated fatty acids
  – antioxidant vitamins
  – plant polyphenols
  – carotenoids
Gastrointestinal Complications of Ehlers-Danlos Syndrome: Special Topic – A Few Words on Mast Cell Activation

Hyperadrenergic Postural Tachycardia Syndrome in Mast Cell Activation Disorders
Cyndya Shibao, Carmen Arzubiaga, L. Jackson Roberts II, Satish Raj, Bonnie Black, Paul Harris and Italo Biaggioni

Hypertension. 2005;45:385-390; originally published online February 14, 2005;
doi: 10.1161/01.HYP.0000158259.68614.40
Mast cell activation is a NORMAL protective immune system response triggered by a pathogen.
- e.g., insect venom

Mast Cell Activation Disorders (MCADs) include:
- overreaction to a valid trigger.
- activation without any trigger.

Signs of Mast Cell Activation (“degranulation”)
- skin: flushing, rash, itching, dermatographism
- pulmonary: wheezing, shortness of breath
- upper respiratory: congestion, throat swelling
- cardiac: tachycardia, (near-)syncope
- neurologic: poor memory, headache
- GI: abdominal pain, diarrhea
Gastrointestinal Complications of Ehlers-Danlos Syndrome:
Special Topic – A Few Words on Mast Cell Activation

Previous management of suspected disorders of mast cell activation DID NOT recommend a trial of ant mediator treatment when mast cell mediators are not elevated in serum when symptomatic.

Image:
http://ainotes.wikispaces.com/Mast+Cell+Disorders
(Original article not cited; Author: “Akdis”)

Flowchart:
- Adult patient with unexplained and recurrent anaphylaxis (or symptoms consistent with anaphylaxis)
- Perform careful skin exam for urticaria pigmentosa (UP)
  - UP not present
    - Measure baseline total tryptase
      - >20 ng/mL
        - Presyncope, syncope, or documented hypotension
          - Bone marrow biopsy
            - Criteria for systemic mastocytosis met
              - Diagnosis: Systemic mastocytosis
            - Criteria for systemic mastocytosis NOT met
              - Clonal markers present on mast cells: c kit D816V or CD25 (by histochem or flow)
                - Diagnosis: Monoclonal mast cell activation syndrome
              - No clonal markers present on mast cells
                - Diagnosis: Mast cell activation disorder
      - <20 ng/mL
        - Measure mast cell mediators when symptomatic: Serum tryptase OR In 24-hour urine: N-methylhistamine - PGD2 - PGF2
          - Elevated
            - Trial of antimediator treatment
              - Response
                - Reconsider other diagnoses that could mimic anaphylaxis
              - No response
                - Diagnosis: Mast cell activation disorder
          - Normal
            - Reconsider other diagnoses that could mimic anaphylaxis
With the recognition of nc-MCAS, the most recent thinking now mandates a trial of medications to block mast cell mediators REGARDLESS of whether mast cell mediators are elevated in serum when symptomatic.
Available medical knowledge as well as ample patient experience indicates a connection between EDS and dysregulation of gut-related immune function, including Mast Cell Activation Disorders.

Formal research is lacking regarding the specific pathophysiology of how EDS affects Mast Cell Activation.
Gastrointestinal Symptoms Associated with Orthostatic Intolerance

Sean D. Sullivan, Joseph Hanauer, Peter C. Rowe, Diana F. Barron, Anil Darbari, and Maria Oliva-Hemker

Departments of Pediatric Gastroenterology and Nutrition and Pediatrics, The Johns Hopkins University School of Medicine, The Johns Hopkins University, Baltimore, Maryland

**Conclusion:** Pediatric patients with chronic upper gastrointestinal symptoms may have underlying orthostatic intolerance. In patients with upper gastrointestinal symptoms and orthostatic intolerance, treatment of orthostatic intolerance may result in resolution of gastrointestinal symptoms. *JPEN* 40:425–428, 2005. **Key Words:** Orthostatic intolerance—Postural tachycardia syndrome—Neurally mediated hypotension—Tilt table test. © 2005 Lippincott Williams & Wilkins

**FIG. 1.** Most common presenting gastrointestinal and systemic symptoms in patients diagnosed with orthostatic intolerance.
Postural tachycardia syndrome—current experience and concepts

Christopher J. Mathias, David A. Low, Valeria Iodice, Andrew P. Owens, Mojca Kirbis and Rodney Grahame

Abstract | Postural tachycardia syndrome (PoTS) is a poorly understood but important cause of orthostatic intolerance resulting from cardiovascular autonomic dysfunction. PoTS is distinct from the syndromes of autonomic failure usually associated with orthostatic hypotension, such as pure autonomic failure and multiple system atrophy. Individuals affected by PoTS are mainly young (aged between 15 years and 40 years) and predominantly female. The symptoms—palpitations, dizziness and occasionally syncope—mainly occur when the patient is standing upright, and are often relieved by sitting or lying flat. Common stimuli in daily life, such as modest exertion, food ingestion and heat, are now recognized to be capable of exacerbating the symptoms. Onset of the syndrome can be linked to infection, trauma, surgery or stress. PoTS can be associated with various other disorders; in particular, joint hypermobility syndrome (also known as Ehlers-Danlos syndrome hypermobility type, formerly termed Ehlers-Danlos syndrome type III). This Review describes the characteristics and neuroepidemiology of PoTS, and outlines possible pathophysiological mechanisms of this syndrome, as well as current and investigational treatments.

Clinical Recommendations
Until specific research is available regarding the pathophysiology and effective diagnosis and treatment of gastrointestinal issues secondary to EDS, each recognized issue should each be addressed according to current standards in the hopes of improving the nutritional and immune status and thereby the overall health of affected EDS patients:

- structural / anatomic issues, dysmotility, or FGIDs
- dysbiosis
- malabsorption
- gut-related immune dysregulation
- dysautonomia
Recognize **structural disorders, gastrointestinal dysmotility, and FGIDs** affecting digestion and address according to established clinical standards.

Consider clearly and weigh carefully the **recognized risks** of rupture, abscess, stenosis, recurring perforation, hemorrhage, poor wound healing, etc., when considering surgery or invasive procedures (e.g. proctoscopy, flexible sigmoidoscopy, colonoscopy, manual disimpaction, and enemas), especially in CEDS and VEDS.
To address **dysbiosis**, consider:

- using **prebiotics**.
  - e.g., inulin, FOS, XOS, GOS, lactulose, chicory root, jerusalem artichoke, dandelion greens, garlic, leeks, onion, asparagus, bananas.

- using **probiotics**.
  - e.g. *kefir*, yogurt, miso, tempeh, kimchi, sauerkraut

- increasing intake of antioxidants and fiber.
  - fresh or raw greens and vegetables
  - ancient grains
    - buckwheat, amaranth, chia, millet, quinoa, sorghum, taro
  - beans, peas, chickpeas, lentils, nuts and almonds
  - certain fruits

- supplementing vitamin D and omega FAs.

- In some cases, use of broad-spectrum antibiotics (e.g., Rifaximin) in combination with multi-strain probiotics (e.g., VSL#3) is warranted.

In the future, will profound or refractory dysbiosis in EDS be an accepted / approved clinical indication for fecal transplant?
To avoid **dysbiosis**, also consider:

- avoiding refined carbohydrates.
- limiting daily intake of fructose <25g/day.
- eliminating sugar alcohols (e.g. xylitol, sorbitol).
- eliminating artificial sweeteners (e.g., aspartame).
- minimizing intake of saturated fats.
- avoiding fried, grilled, and toasted food.
- reducing intake of cured meat.
- limiting alcohol consumption.
- eliminating or minimizing casein, gluten, and zein.
- eliminating polypharmacy where possible.
Determine and correct nutrient deficiencies caused by malabsorption.

• **Consider specialized testing** to identify deficits of micronutrients or deficits of nutrients not always accurately assessed with routine laboratory testing (e.g., magnesium).

Pursue **parenteral repletion** of nutrients for persons with EDS refractory to increased dietary intake or oral supplementation of deficient nutrients.
Determine when patients will benefit from specialized diets.

It is reasonable to advise persons with EDS who manifest symptoms concerning for gluten enteropathy to avoid gluten intake.

It is reasonable to consider other exclusion diets, depending upon individual circumstances. For example:

- Dairy-free or Lactose-free
- Low Fructose
- Low Histamine or “Anti-Inflammatory”
- No Nightshade Vegetables
- Low FODMAP
It is reasonable to **offer a trial of mast cell mediator blocking agents** to those persons with EDS who have symptoms concerning for nc-MCAS, regardless of whether they have **elevated mediator levels on serum testing when symptomatic**. Blocking agents include:

- quercetin
  - dietary intake vs. over-the-counter supplement
- type I and type II histamine blockers
- cromolyn sodium and ketotifen
- cysteinyi leukotriene receptor 1 blockers
- 5-lipoxygenase inhibitor
- aspirin
- omalizumab
- systemic or topical steroids
Strive to gain control over any dysautonomia so that a state of “Rest and Digest” is not continually suppressed by a state of “Fight or Flight.”
Gastrointestinal Complications of Ehlers-Danlos Syndrome: Sometimes Between a Rock and a Hard Place
Gastrointestinal Complications of Ehlers-Danlos Syndrome

THE END