CLINICAL VIGNETTE

Recurrent Constipation, Diarrhea and Bloating in a Patient with Ehlers Danlos Syndrome

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A 35-year-old male requested evaluation for bouts of significant bloating, abdominal pain, and recurrent constipation alternating with diarrhea. Prior evaluations were non-diagnostic, including normal blood counts, colonoscopy, and biopsy of small bowel mucosa. He reported arthralgias in multiple joints that were refractory to over-the-counter non-steroidal treatment. He had undergone bilateral hernia repairs at a young age and reported that his joints "pop" occasionally, requiring him to manually reduce the joint into position. A complete family history revealed that his 14-year-old daughter was diagnosed with hypermobile Ehlers-Danlos Syndrome (hEDS). The patient's mother also had hEDS with associated co-morbidities of a stroke at 36, dental crowding, and joint disorders. One sibling was diagnosed as "double-jointed" and had episodes of supraventricular tachycardia. Another sibling had club feet and flat feet. Our patient was concerned that he carried the gene.

Physical exam was notable for significant hyperextension of joints, including both thumbs, both knees, and his left 5th digit. He was able to perform a reverse namaste pose (joining his hands behind his back in a prayer gesture), suggesting hypermobility of the spine. The finding of hypermobility in 5 out of 9 joints produced in an elevated Beighton score. This scoring system for hypermobility assigns one point for each of the following joints: thumbs, elbows, knees, knuckles of the 5th finger, and the spine.[1] A score of 4 or more in the appropriate clinical context (family history, frequent dislocations, etc.) is suggestive of hypermobility.

Our patient was referred for genetic testing because of the elevated Beighton score, clinical history, recurrent inguinal hernias, and significant family history. Genetic testing was indicative of classical Ehlers-Danlos Syndrome (cEDS).

Discussion

The Ehlers-Danlos Syndromes (EDS) are a group of heritable connective tissue disorders commonly characterized by tissue fragility, hypermobility, and hyperextensibility.[2] The pathophysiology of most EDS subtypes involves heritable mutations in collagen synthesis and/or processing. Sporadic cases have been identified associated with spontaneous mutations.

The condition is largely diagnosed clinically and includes several subtypes. Identifying the type of EDS is essential to guide management and counseling. There are 13 subtypes described in the 2017 classification system. Affected proteins can involve all areas of the body, including the musculoskeletal system, gastrointestinal tract, cardiovascular system, teeth and gums, and cornea. The most common form is cEDS, affecting 1 in 10–20,000 individuals. cEDS involves an autosomal dominant inheritance pattern with associated mutated genes of COL5A1 and/or COL1A1, which code for type V and type I collagen.[2] In contrast, the molecular basis of hEDS is unknown. Diagnosis is largely based on clinical presentation. This type is considered the least severe type of EDS, although significant complications, primarily musculoskeletal, can occur.[2]

Major clinical criteria include atrophic scarring, skin hyperextensibility, and generalized joint hypermobility. Minor clinical criteria include epicanthic folds, skin fragility, soft "doughy" skin, easy bruising, recurrent hernias, joint hypermobility, molluscoid pseudotumor, subcutaneous spheroids, or a family history of a first-degree relative affected by the condition.

Further evaluation is guided by presenting symptomatology. Patients with EDS, especially those with hEDS, are often misdiagnosed with conditions such as fibromyalgia, chronic fatigue syndrome, or depression. While these conditions may exist concomitantly, careful attention and a high index of suspicion should be applied, as misdiagnosis may prevent a patient with EDS from receiving appropriate treatment, counseling, and genetic referrals.

Our patient presented with primarily gastrointestinal (GI) symptoms along with hypermobility. The prevalence of GI symptom such as abdominal pain, postprandial fullness, constipation, and diarrhea are significantly higher in individuals with hypermobile type hEDS.[3]

Despite the increased presence of symptoms, the underlying pathophysiology is unclear. Connective tissue abnormalities and autonomic dysfunction have been implicated as an etiology. In addition, most studies suggest a significant functional (ie not structural) component to GI symptoms as well.

As such, a multidisciplinary, biopsychosocial model of care is required for these patients. There are no current well-validated

guidelines for the management of EDS-related digestive symptoms. Management is based on best practices directed at improving symptoms without excessive restrictions that could lead to nutritional compromise or have a negative physical or psychological impact. Table 1 presents disorders of gut–brain interaction (DGBI) in the differential of patients presenting with nutritional compromise.[4]

Table 1 Summary of the main foregut gut–brain disorders, key features, management options and optimal nutrition approach

Foregut gut–brain disorder diagnosis	Key features	Diagnostic basis and tests	Management options	Optimal nutrition approach
Oesophageal dysmotility	Difficulty swallowing	Abnormalities on high resolution manometry	Dietary adjustment and eating behavioural modification.	Oral nutritional supplements if needed. NG feeding if malnourished.
Rumination syndrome	High pressure gastric contractions precede regurgitation/vomiting	Typical history. Concurrent impedance/manometry with meal provocation	Diaphragmatic breathing, baclofen, Nissens fundoplication (selected patients)	Optimised effortful oral feeding, short term bridging NJ to therapies only if malnourished
Cyclical vomiting syndrome and cannabis hyperemesis syndrome	Bouts of hyperemesis with intervals of normality. History of migraines. Relief from hot baths.	Clinical history is typical. Exclusion of other structural or central neural causes	May respond to tricyclics and migraine prophylaxis. Abstinence from cannabis.	Short bouts may need parenteral fluids/electrolytes. NJ likely to be unstable and unnecessary.
Chronic nausea and vomiting	Low-grade background constant nausea and vomiting	Clinical history and exclusion of other structural or central neural causes	Prokinetics, antiemetics, gut–brain neuromodulators	Optimised effortful oral feeding, avoid NJ unless malnourished.
Functional dyspepsia and gastroparesis	Overlapping spectrum of varying degrees of sensorimotor impairment of gastroduodenal function	Clinical history and solid meal gastric emptying test off medication affecting gastric emptying (but not based on gastric emptying study alone)	Pain management (avoid opioids), psychosocial support, buspirone, gut-brain neuromodulators including mirtazapine, pro-kinetics.	If malnourished with predominantly gastric muscle failure (gastroparesis), then trial of NJ with view to longer term post-pyloric feeding tube.
CIPO and enteric (small bowel) dysmotility (ED)	Non-mechanically obstructed dilated small bowel (CIPO) or significantly abnormal small bowel manometry or transit (ED)	CIPO—dilated small bowel radiologically. ED—small bowel manometry or abnormal transit. Full thickness biopsy if undergoing venting surgery.	Prokinetics, small intestinal bacterial overgrowth therapy, non-opioid analgesia with gut–brain neuromodulators	CIPO more likely to need parenteral nutrition than ED which should be manageable with optimised effortful oral or enteral feed.
Centrally mediated abdominal pain and narcotic bowel syndrome (NBS)	Chronic continuous abdominal pain with neuropathic features. Escalating opioid doses in NBS.	Clinical history and exclusion of other causes.	Non-opioid analgesics (eg, duloxetine). Opioid stabilisation and reduction. Mu-opioid antagonists.	Avoid enteral tube and parenteral feeding.
Somatoform disorder/ central sensitivity syndrome	Overlapping multiple functional symptom syndromes	Psychiatric evaluation	Clinical psychology/ liaison psychiatry. Central neuromodulators	Avoid iatrogenesis due to escalating invasive approaches.
Avoidant restrictive food intake disorder	Restrictive and avoidant behaviours not body image driven, but anxiety, fear, food related symptom and fixed (eg, health) beliefs	Psychiatric evaluation.	Clinical psychology and liaison psychiatry input	If severely malnourished may need short-term bridging enteral tube feeding to therapies but need not be post-pyloric.

CIPO, chronic intestinal pseudo-obstruction; ED, enteric dysmotility; NBS, narcotic bowel syndrome; NG, nasogastric; NJ, nasojejunal.

Since our patient reported significant constipation alternating with bouts of diarrhea, we ensured he had an effective bowel regimen. He was also prescribed a diet low in poorly absorbed, fermentable, short-chain carbohydrates, otherwise known as a low FODMAP diet (fructose, oligosaccharides, disaccharides, monoamines, and polyols). Such diets have been helpful in managing GI symptoms in patients with hypermobility syndromes.[5] We educated our patient regarding a low FODMAP diet and instructed him to keep a food diary. Dieticians experienced in GI disorders are essential to the success of the

diet as several factors need to be addressed including the type and severity of symptoms, baseline FODMAP intake, overall nutritional content, and daily meal pattern.

The low FODMAP diet is administered in three phases: restriction of all dietary FODMAPs, followed by rechallenge, and then reintroduction of specific FODMAPs according to the tolerance of patients. Strict adherence has been shown to improve symptoms, stool output, quality of life, and the overall well-being of patients. If a strict low-FODMAP diet is felt necessary, it should be used for an initial period of 4 to 6 weeks as the diet may negatively impact the intestinal microbiome. Our patient's abdominal symptoms appeared better controlled after intervention.

In addition to diet modification, aerobic activities favoring the legs are recommended, as the increased muscle tone provides better vascular resistance to orthostatic changes. Pool-based exercises show advantages for patients with EDS because there is low joint stress, all movements are resistance-based, and the water pressure helps maintain peripheral vascular resistance.[6] Water exercises can be swimming with or without a kick board, water aerobics or simple water- walking. If pool therapy is not available or contraindicated, then seated-aerobic exercises or low-joint-impact exercises are preferred. Typical examples would be recumbent cycling, rowing machines, and, if upright activity is tolerated, elliptical or adaptive motion trainers. The goal of the exercise program is to downregulate the sympathetic nervous response by overloading it during exercise. The body of evidence on exercise and rehabilitation interventions for people with EDS supports benefit for various physical and psychological outcomes.

Our patient followed a daily 30-minute exercise routine for five weeks. To prevent negative impact on the joints, the physiatrist suggested a recumbent cycle, rowing machine, or water-based exercise.

We counseled against the use of opiates, which are frequently prescribed to patients with EDS to alleviate joint pain. We also referred the patient's family for genetic counseling given the strong heritable component to the disease.

Conclusion

Our patient benefited from a well-coordinated multidisciplinary approach to his EDS. Communication across several specialties, which may be affiliated with different medical centers, and primary care is essential to avoid fragmentation of care.[7]

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