The Suggested Relationships Between Common GI Symptoms and Joint Hypermobility, POTS, and MCAS

Eamonn M. M. Quigley, MD, FRCP, FRCPI, Oscar Noble, MD, and Usman Ansari, MD

Division of Gastroenterology and Hepatology, Lynda K. and David M. Underwood Center for Digestive Disorders, Houston Methodist Hospital and Weill Cornell Medical College, Houston, Texas

Corresponding author:
Dr Eamonn M. M. Quigley
Houston Methodist Gastroenterology Associates
6550 Fannin Street, SM 1201
Houston, TX 77030
Tel: (713) 441-0853
Fax: (713) 797-0622
E-mail: equigley@houstonmethodist.org

Abstract: An increasing number of reports suggest an association between a newly recognized disease cluster and significant and often disabling gastrointestinal (GI) symptoms. This cluster is composed of diagnoses of hypermobility spectrum disorders (HSDs) such as joint hypermobility and hypermobile variant Ehlers-Danlos syndrome (hEDS), postural orthostatic tachycardia syndrome (POTS), and mast cell activation syndrome (MCAS). The diagnosis of these entities remains a challenge, as the pathophysiology of each has not been completely elucidated and the diagnostic criteria continue to evolve. This article describes a cohort of young adult females who shared similar GI symptoms, with intractable nausea and vomiting being most prominent and gastroesophageal reflux disease and constipation also occurring. Most strikingly, these females also exhibited or reported a history of HSD, hEDS, POTS, and/or MCAS. The clinical course of their GI symptoms was remarkable for considerable challenges in management, and artificial nutritional support proved necessary for some. This article describes the clinical features and outcomes of their GI manifestations, examines how these manifestations might be linked to their systemic syndromes, and discusses whether a shared pathophysiology exists. Pending the definition of a common thread between these conditions, this article seeks to raise awareness of their clinical definitions and foster research that will hopefully improve outcomes for these patients.

Keywords
Disorders of gut-brain interaction, Ehlers-Danlos syndrome, joint hypermobility, mast cell activation syndrome, postural orthostatic tachycardia syndrome

Gastrointestinal (GI) symptoms such as abdominal pain, nausea, vomiting, and constipation are common in the general population and may originate from a wide variety of underlying causes, ranging from bowel obstruction to intestinal inflammation.[1,2] These symptoms also are seen in the context of endocrine, neurologic, or connective tissue disorders, illustrating the close relationship between the gut and the rest of the human body. These same symptoms may also occur in the absence of consistently identifiable pathology.[3] Formerly described as functional gastrointestinal disorders, these symptom clusters are now referred to as disorders of gut-brain interaction

Table 1. Patient Characteristics and Outcomes for Study Cohort

Age	**Years (range)**
Mean age	29 (19-49)
Mean age at symptom onset	21 (10-40)
Comorbidity	**n (%)**
POTS	19 (73)
Joint hypermobility syndrome	7 (27)
Superior mesenteric artery syndrome	3 (11)
MCAS	2 (8)
Mitochondrial disorder	2 (8)
Median arcuate ligament syndrome	1 (4)
Route of nutrition	**n (%)**
Regular diet or adjusted diet/ supplementation	13 (50)
PEG and/or J tube	6 (23)
Parenteral nutrition	7 (27)
Intervention	**n (%)**
Pyloric botulinum toxin	7 (27)
Gastric electrical stimulation	3 (11)
G-POEM	2 (8)
Gastric surgery	2 (8)

G-POEM, gastric peroral endoscopic myotomy; J, jejunostomy; MCAS, mast cell activation syndrome; PEG, percutaneous endoscopic gastrostomy; POTS, postural orthostatic tachycardia syndrome.

(DGBI), reflecting the commonly held belief that the symptoms originate from bidirectional interactions between the brain and the gut.[4] Of late, several systemic rheumatologic, immunologic, and cardiovascular disorders have been associated with GI symptoms and syndromes—such as gastroesophageal reflux, intractable nausea and vomiting, gastroparesis, and constipation—that formerly would have been described as DGBI. For example, GI symptoms have been widely reported in conjunction with hypermobility spectrum disorders (HSDs),[5] postural orthostatic tachycardia syndrome (POTS),[6] and mast cell activation syndrome (MCAS),[7] yet precisely why these symptoms are so prevalent in individuals affected by these conditions remains unclear. Over the past few years, we have encountered multiple individuals with striking and debilitating GI symptoms in conjunction with a variety of systemic disorders. This article reports on a cohort of such individuals and reviews the relationships between GI presentations and these systemic disorders to uncover whether any common pathophysiologic thread can be identified.

The Patient Cohort

We describe a cohort of 26 patients with intractable nausea and vomiting evaluated at Houston Methodist Hospital over the past 5 years (Table 1). All were young adult females. In all cases, endoscopic, imaging, and routine laboratory studies had failed to reveal any abnormalities that might explain their symptoms.

Table 1 lists the rates of additional comorbidities, along with nutritional strategies and the rates of use of various interventions. Most notable were the high prevalences of POTS and joint hypermobility. Twelve patients (46%) had an overlap between 2 or more of the listed comorbidities. As judged by nutritional status, half of all patients had a poor outcome in that they required ongoing supplemental nutrition via either the enteral route or total parenteral nutrition. Six patients (23%) were dependent on total parenteral nutrition. Oral intake and tube feeding via percutaneous endoscopic gastrostomy and/or jejunostomy tube were unsuccessful in these patients, who notably could not tolerate any peroral or intraluminal fluid or nutrient no matter how small the size of the oral bolus or how low the rate of intraluminal infusion. Many patients required additional interventions, but symptoms persisted. Symptoms did not resolve in any patients.

Delayed gastric emptying was documented on scintigraphy in 13 patients (50%) and was normal in 6 patients (23%). The results were not available in the remaining patients, largely owing to an inability to complete a gastric emptying study. Twenty patients (77%) had gastroesophageal reflux disease and/or constipation. Psychiatric comorbidities were common, with anxiety in 12 patients (46%), depression in 6 patients (23%), attention deficit hyperactivity disorder in 4 patients (15%), and an eating disorder in 1 patient (4%).

This population shared not only remarkably similar demographic characteristics, but also a common clinical presentation and an unexpectedly high rate of association with disorders such as POTS and joint hypermobility syndrome. This population also exhibited a high prevalence of psychiatric comorbidities and had poor functional outcomes. Although delayed gastric emptying is frequently documented in such individuals, the pathogenesis of their intractable symptoms remains unclear. The following section explores the possible relevance of systemic disorders to this population cluster.

Definitions and Diagnostic Criteria

Before exploring the relevance of these disorders to GI symptomatology, it is critical to review their definitions.

Table 2. Diagnostic Criteria for hEDS

Criteria 1	Positive Beighton score
Criteria 2	The presence of 2 or more features (A-C): **Feature A:** Systemic manifestations of a more generalized connective tissue disorder (5 must be present): 1. Unusually soft or velvety skin 2. Mild skin hyperextensibility 3. Unexplained striae distensae or rubrae at the back, groins, thighs, breasts, and/or abdomen in adolescents, men, or prepubertal females without a history of significant gain or loss of body fat or weight 4. Bilateral piezogenic papules of the heel 5. Recurrent or multiple abdominal hernia(s) 6. Atrophic scarring involving ≥2 sites and without the formation of truly papyraceous and/or hemosideric scars, as seen in classical EDS 7. Pelvic floor, rectal, and/or uterine prolapse in children, men, or nulliparous women without a history of morbid obesity or other known predisposing medical condition 8. Dental crowding and high or narrow palate 9. Arachnodactyly, as defined in ≥1 of the following: (i) positive wrist sign (Walker sign) on both sides, (ii) positive thumb sign (Steinberg sign) on both sides 10. Arm span-to-height ratio ≥1.05 11. Mild or greater MVP based on strict echocardiographic criteria 12. Aortic root dilatation with Z-score >2 **Feature B:** Positive family history: ≥1 first-degree relative independently meeting the current criteria for hEDS **Feature C:** Musculoskeletal complications (must have ≥1): 1. Musculoskeletal pain in ≥2 limbs, recurring daily for ≥3 months 2. Chronic, widespread pain for ≥3 months 3. Recurrent joint dislocations or frank joint instability in the absence of trauma
Criteria 3	All of the following should be met: 1. Absence of unusual skin fragility, which should prompt consideration of other types of EDS 2. Exclusion of other heritable and acquired CTDs, including autoimmune rheumatologic conditions. In patients with an acquired CTD (eg, lupus, RA), additional diagnosis of hEDS requires meeting both Features A and B of Criteria 2. Feature C of Criteria 2 (chronic pain and/or instability) cannot be counted toward a diagnosis of hEDS in this situation. 3. Exclusion of alternative diagnoses that may also include joint hypermobility by means of hypotonia and/or connective tissue laxity. Alternative diagnoses and diagnostic categories include, but are not limited to, neuromuscular disorders (eg, Bethlem myopathy), other hereditary disorders of the connective tissue (eg, other types of EDS, Loeys-Dietz syndrome, Marfan syndrome), and skeletal dysplasias (eg, osteogenesis imperfecta). Exclusion of these considerations may be based upon history, physical examination, and/or molecular genetic testing, as indicated.

CTD, connective tissue disorder; hEDS, hypermobile variant Ehlers-Danlos syndrome; MVP, mitral valve prolapse; RA, rheumatoid arthritis.

Adapted from Malfait et al.[8]

Hypermobile Variant Ehlers-Danlos Syndrome/ Hypermobility Spectrum Disorder

An international symposium on Ehlers-Danlos concluded that joint hypermobility and hypermobile variant Ehlers-Danlos syndrome (hEDS) should be merged into a single phenotypic continuum, HSD.[8-10] HSD refers to a group of conditions related to joint hypermobility, which is defined as the ability to extend the range of motion of a single joint or multiple joints beyond their physiologic axes. Within this spectrum, some phenotypes are asymptomatic whereas others are symptomatic, some are localized to 1 joint whereas others involve multiple joints in the body, and some present with specific systemic manifestations.[8-10]

Table 3. Diagnostic Criteria for Postural Orthostatic Tachycardia Syndrome

Orthostatic intolerance lasting ≥6 months with the presence of the following 3 characteristics:
• Increase in heart rate ≥30 bpm within 5 to 10 minutes of quiet standing or upright tilt (or ≥40 bpm in individuals 12-19 years)
• Absence of orthostatic hypotension (>20 mm/Hg drop in SBP or >10 mm/Hg in DBP)
• Frequent symptoms that occur on standing, such as lightheadedness, palpitations, tremulousness, generalized weakness, blurred vision, exercise intolerance, and fatigue

bpm, beats per minute; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Adapted from Vernino et al.[13]

Table 4. Diagnostic Criteria for Mast Cell Activation Syndrome

Criteria 1 (clinical criteria)	Episodic acute onset of symptoms with involvement of ≥2 of the 4 organ systems listed below: • Cardiovascular: tachycardia, lightheadedness, hypotension, syncope • Cutaneous: urticaria, angioedema, flushing, pruritus • Digestive: abdominal cramps, diarrhea, vomiting • Upper and/or lower respiratory: nasal congestion, sneezing, shortness of breath, wheezing, inspiratory stridor, hypoxia
Criteria 2 (laboratory criteria)	Event-related increase in serum tryptase above the individual's sBT, must be evaluated within 4 hours of the event Calculate using the following formula: sBT + 20% of sBT = (120% of sBT) + 2 ng/mL
Criteria 3 (medication response criteria)	Symptomatologic improvement when using drugs that target mast cells, mast cell mediator production, and/or mast cell mediator effects • Drugs: antihistamines, leukotriene modifiers, cyclooxygenase inhibitors, mast cell–stabilizing agents

sBT, serum baseline tryptase.

Adapted from Gülen et al.[17]

The different variants along the phenotypic continuum of the HSDs can be differentiated based on: (1) the Beighton score, which is used to assess generalized joint hypermobility[8]; and (2) the presence of musculoskeletal involvement, such as trauma, chronic pain, disturbed proprioception, and/or the presence of minor musculoskeletal physical traits such as pes planus.[8,9] It is important to note the age-related differences in the threshold for diagnosis of hypermobility; this reflects the normal reduction in joint mobility with age. A failure to recognize this may lead to an overdiagnosis of HSD in adolescents and young adults.[10]

EDS encompasses 13 subtypes.[8] Among these, the only subtype that does not have a known genetic or defined pathophysiology is type 3, the hypermobile variant,[11] which is also known as hEDS. This is the variant most linked to the presence of GI symptoms. This absence of a genetic marker is a major limitation when it comes to the definitive diagnosis of hEDS, whose diagnosis therefore rests entirely on clinical grounds. Criteria for the clinical diagnosis of hEDS are provided in Table 2.

Postural Orthostatic Tachycardia Syndrome

According to the American College of Cardiology, POTS is a form of orthostatic intolerance lasting for at least 6 months that is most prevalent among young people, especially premenopausal women.[12] The diagnostic criteria are listed in Table 3.

Although a unifying etiology for POTS has not been elucidated, 3 principal hypotheses have been proposed to explain its pathophysiology[13,14]:

The Autoimmune Hypothesis The autoimmune hypothesis is supported by the identification of autoantibodies against the angiotensin II type 1 receptor, cardiac membrane receptors, cholinergic receptors, and especially adrenergic receptors in up to one-half of all patients with POTS.[14] The observation that patients often report the onset of symptoms after an acute, potentially viral illness led to the suggestion that cross-reactivity with viral antigens might be responsible. The very recent description of the onset of POTS following COVID-19 infections has provided further support for this hypothesis.[15]

The Sympathetic Hyperactivity Hypothesis Evidence to support the sympathetic hyperactivity hypothesis includes the demonstration of increased plasma catecholamine levels (particularly norepinephrine) and, very rarely, a point mutation in the *SLC6A2* gene that leads to almost complete loss of function of the norepinephrine transporter.

The Neuropathic Dysautonomia Hypothesis The neuropathic dysautonomia hypothesis is supported by the presence of sympathetic denervation in a small segment of the population with POTS. The etiopathogenesis

Table 5. MCAS Phenotypes

Primary phenotype: (mono)clonal MCAS	Fulfills MCAS diagnostic criteria (Table 4) + the presence of (mono)clonal populations of MCs with the presence of activating mutations in *KIT* (usually *KIT* D816V) and/or aberrant expression of CD25
Secondary phenotype: nonclonal MCAS[a]	Fulfills MCAS diagnostic criteria (Table 4) + the presence of allergy, hypersensitivity, and/or other reactive condition; these conditions can be IgE-dependent or -independent: • IgE-dependent secondary MCAS triggers: food, drugs, hymenoptera venom, inhalant allergens • IgE-independent secondary MCAS triggers: endogenous peptides, drugs that interact with MRGPRX2 (vancomycin or narcotics), physical stimuli, stress, toxins, venoms, complement activation (C3a, C5a, cytokine receptors, MRGPRX2, viral receptors, toll-like receptors)
Idiopathic phenotype	Fulfills MCAS diagnostic criteria (Table 4) + no evidence of (mono)clonality + no evidence of allergy, hypersensitivity, and/or other reactive condition

IgE, immunoglobulin E; MC, mast cell; MCAS, mast cell activation syndrome.

[a]MCs can be elevated in specific tissue sections from reactive expansion.

Adapted from Gülen et al.[17]

of POTS in a given individual likely reflects variable contributions from and/or interactions between these mechanisms.[16]

Mast Cell Activation Syndrome

MCAS refers to a group of disorders that present with episodic multisystem symptoms as a result of the inappropriate activation of mast cells (MCs) and the release of related mediators. The diagnosis is often based on the updated Vienna consensus criteria (Table 4),[17,18] although more inclusive criteria, which do not require an elevation in tryptase, have also been proposed.[19] Which of these criteria is employed greatly affects the prevalence of MCAS in any given population.[19]

MCAS is further classified into 1 of 3 clinical phenotypes (Table 5), with the mechanism of MC activation varying by phenotype. It is important to note, however, that symptoms overlap, as the different triggers for MC activation have common effectors and mediators. The most severe forms of MCAS feature mixed phenotypes with the individual exhibiting findings that are consistent with more than 1 variant of MCAS, such as both primary and secondary MCAS.[20]

Prevalence of Gastrointestinal Symptoms by Syndrome

Hypermobile Variant Ehlers-Danlos Syndrome/ Hypermobility Spectrum Disorder

GI symptoms appear to be common in hEDS/HSD.[21-23] Lam and colleagues compared questionnaire responses from 603 individuals who fulfilled hEDS/HSD criteria and 603 matched controls.[5] The population had a mean age of 39 years and was predominantly female (96%) and White (90%). Although 98% of patients with hEDS/HSD fulfilled at least 1 of the symptom-based criteria for the definition of a DGBI, only 47% of the controls did so. Furthermore, 84% of those with hEDS/HSD had a DGBI involving 2 or more organ regions (eg, esophagus, stomach, or bowel) compared with just 15% of controls. Conversely, hEDS/HSD is more common than would be expected by chance among those with a DGBI.[24]

Interestingly, hEDS/HSD has been associated with an increased prevalence of immune-mediated GI disorders such as celiac disease,[25] inflammatory bowel disease,[24,26,27] and eosinophilic esophagitis.[28] Interestingly, MCs have also been implicated in the pathophysiology of eosinophilic esophagitis.[29]

Vascular compression syndromes, which have also been associated with hEDS, include superior mesenteric artery syndrome, median arcuate ligament syndrome, nutcracker syndrome, and May-Thurner syndrome. Four of the patients in our cohort reported 1 of these syndromes, but the true prevalence of these disorders in hEDS, as well as their pathophysiology in this context, remains to be defined.[30-33] Visceroptosis has also been reported in association with hEDS.[34]

Postural Orthostatic Tachycardia Syndrome

GI symptoms are common in POTS.[6,35,36] Mehr and colleagues reviewed 6 studies including 352 patients. The pooled data revealed a prevalence of nausea and abdominal pain of up to 69%; 4 of the 6 studies included results of gastric emptying studies and described rapid gastric emptying in 43% and delayed gastric emptying in 20%.[6] Here again, the issue of overlap between these entities becomes relevant with GI symptoms in hEDS/HSD being more frequent among those who also had POTS[37,38]

and instances of co-occurrence of MCAS[39] and eosinophilic disorders[40] also reported in association with POTS.

Mast Cell Activation Syndrome

GI symptoms appear to be highly prevalent in MCAS.[7] Weinstock and colleagues suggested that GI symptomatology related to MCAS is frequently misdiagnosed as a functional GI disorder.[7] Among 20 patients with refractory irritable bowel syndrome (IBS), 19 had symptoms compatible with MC activation and of the 12 who were tested for MC mediators, 11 had positive results.[7] Hamilton and colleagues also reported a high frequency of specific GI symptoms among MCAS patients, ranging from a prevalence of 57% for nausea and vomiting to 14% for constipation.[41]

Potential Mechanisms of Gastrointestinal Symptomatology by Syndrome

Hypermobile Variant Ehlers-Danlos Syndrome/ Hypermobility Spectrum Disorder

It has been suggested that alterations in the composition of connective tissue, specifically in its extracellular matrix, are responsible for the hyperlaxity of the musculoskeletal system in patients with hEDS/HSD.[42] Similar mechanisms may explain the development of symptoms originating from other organ systems, such as the GI tract, where components of the gut wall may be compromised. Although no consistent and specific collagen defects or associated mutations have been found in hEDS/HSD, it has been reported that up to 5% to 10% of patients have an autosomal recessive mutation in the *TNXB* gene that encodes for tenascin X, an extracellular glycoprotein responsible for the organization and maintenance of its extracellular matrix.[43] The extracellular matrix plays a fundamental role in the development and differentiation of neuronal subtypes that innervate the smooth muscle of the intestine, suggesting the existence of fundamental interactions between the extracellular matrix and neurodevelopment within the enteric nervous system.[44-48] These interactions are thought to be of fundamental importance in the pathogenesis of Hirschsprung disease.[49] Furthermore, tenascin X has been implicated in the pathogenesis of slow transit constipation.[50] In genetically engineered animal models of EDS (which feature joint hypermobility related to mutations in type V collagen–encoding genes), hypersensitivity to mechanical but not thermal stimuli was evident in the paws and abdominal area[51,52] and led to the hypothesis that a generalized hypersensitivity to mechanical stimuli was present. In one of these studies, hypersensitization of myelinated A fibers and activation of the spinal dorsal horn were also evident.[52] Although not studied, one could imagine how similar changes in the mechanoelastic properties in the GI tract, together with altered mechanosensory afferent responses, could lead to visceral pain. Sensitization, which refers to a reduction in the threshold for perception of sensation arising from the visceral organs, may then occur because of the afore-described augmented afferent signaling.[53] Indeed, visceral hypersensitivity has been widely accepted as a potential mechanism for the development of DGBI[54] and could represent a pathophysiologic mechanism shared by DGBI, hEDS, and HSD.[55] In addition, studies of fibroblasts in the skin in EDS suggest that chronic inflammation may also be involved.[56] Interestingly, and as noted in our own cohort, psychiatric diagnoses have been strongly associated with pain[57] and constipation[58] in EDS. In a study that compared anorectal manometry findings and balloon expulsion tests in patients with either hEDS or HSD vs others being evaluated for problems with rectal evacuation, no significant differences were evident between the various patient groups.[58] In contrast, rectal hyposensitivity has been associated with EDS and proposed to be a major factor in the development of constipation.[59]

These hypotheses need to be formally tested in relation to the GI manifestations of EDS but could certainly explain the marked hypersensitivity to food intake and luminal nutrient infusion noted among some in our patient cohort.

Postural Orthostatic Tachycardia Syndrome

Although several factors may contribute to the pathogenesis of GI symptoms in POTS, numerous theories can be invoked to explain the high prevalence and heterogeneity of GI symptoms in POTS. These theories include the effects of dysautonomia itself, the effects of dysautonomia on GI motility,[60,61] and the consequences of hypovolemia, as well as overlap with disorders such as median arcuate ligament syndrome, MCAS, or hEDS/HSD.[35,36]

POTS-related GI symptoms can be divided into those that are persistent and those that are orthostatic (ie, related to posture). These symptoms are not all reproducible by positional changes, which suggests that factors such as psychologic stress, visceral hypersensitivity, and behavioral amplification may also contribute.[36,61]

Gastrointestinal Dysmotility It has been proposed that dysmotility is a significant driver of GI symptoms in POTS. Among 35 children and young adults with orthostatic insufficiency and GI symptoms, 31 experienced nausea, vomiting, and abdominal pain during the tilt table test. Baseline antroduodenal manometry was abnormal in 14% of patients, but 68% of those who had normal baseline manometry demonstrated abnormal motor patterns during the tilt table test. Abnormal

manometric findings included neurogenic intestinal dysmotility, gastric or duodenal regurgitation of food, antral hypomotility, and visceral hyperalgesia, with some patients exhibiting more than 1 abnormal finding during the tilt table test.[62] Others have also reported a high prevalence of small bowel dysmotility[63] and visceral sensitization in POTS.[64]

Abnormal motor function of the stomach has also been reported. In one study of 163 patients with POTS, scintigraphy demonstrated that 34% had normal gastric emptying, 48% had rapid gastric emptying, and 18% had delayed gastric emptying.[65] The researchers also found that delayed gastric emptying had the greatest effect on symptoms, as 60% of patients who had delayed gastric emptying reported vomiting, compared with 35% who had a normal gastric emptying rate and 24% of those who had accelerated emptying.

Interestingly, and supportive of the autoimmune hypothesis, the presence of autoantibodies to muscarinic acetylcholine receptors has been associated with the prevalence and severity of GI symptoms in POTS.[66]

Hypovolemia Symptoms such as nausea, dizziness, abdominal pain, and flushing were shown to improve in all 16 POTS patients following the administration of fludrocortisone in one study.[67] Symptom improvement was most evident among those whose symptoms were reproducible on tilt table testing.

Abnormal Gastric Electrical Activity Electrogastrography has also been utilized to evaluate gastric motor function in POTS.[68,69] In one study, patients with POTS demonstrated higher pre- and postprandial gastric electrical rhythm variability than control patients, and this variability was more pronounced in those who had GI symptoms than those who did not.[68] Another study compared electrogastrography before and during tilt table testing in 25 children with POTS and 24 controls.[69] Although baseline activity was similar between the 2 patient populations, significant differences between POTS and control groups become evident on tilt table testing, with the patients with POTS exhibiting gastric arrhythmias that included tachygastria in the fundus and bradygastria in the antrum.[69]

Although these findings suggest that abnormal gastric myoelectrical activity could explain impaired fundic accommodation and decreased gastric emptying, there is still much to learn about the relationships between gastric electrical signals, motility, and function and the symptoms of POTS.

Mast Cell Activation Syndrome It has been estimated that up to 9% of patients with POTS have concomitant MCAS.[70] POTS-related GI symptoms in these individuals could be triggered by the activation of MCs and the release of their mediators, providing an opportunity for treatment with drugs that target MCs and an opportunity for prevention with avoidance of triggers of MC degranulation, such as certain foods. POTS and MCAS have been reported in association with migraine.[71]

Hypermobile Variant Ehlers-Danlos Syndrome The co-occurrence of POTS, MCAS, and hEDS in the same individual has been well documented.[72] In one study, approximately 25% of patients with POTS had a concomitant diagnosis of hEDS.[70] In another study, 23% of children with POTS had EDS and 39% had HSD.[73] Conversely, a study evaluating orthostatic symptoms in 48 patients with hEDS revealed that all had 5 or more orthostatic symptoms compared with only 10% of controls.[74] The co-occurrence of POTS has also been identified as a potent predictor of GI dysmotility in EDS.[23] As described previously, patients with hEDS have a high prevalence of GI symptoms; thus, GI symptoms in POTS might be explained by this overlap when it occurs. These findings suggest a significant overlap, not only in terms of GI symptoms but also in relation to orthostatic symptoms, which has led some to propose the co-existence of POTS and hEDS as a distinct subtype of POTS.[75] Evidence in support of this proposal includes observations that, in comparison to hEDS in isolation, those with hEDS and POTS are younger, exhibit more frequent GI symptoms, appear to feature the involvement of more organs of the GI tract, and exhibit an increased prevalence of non-GI manifestations such as fatigue, fibromyalgia, and depression.[76]

Mast Cell Activation Syndrome

MCs are closely associated with epithelia and connective tissues in multiple organ systems, including the GI tract, as they are distributed throughout all vascularized tissues. They contribute to homeostasis by performing multiple functions such as host defense, tissue repair, wound healing, and angiogenesis.[77,78] MCs display an array of receptors that recognize molecules produced by a plethora of stimuli such as allergens, tissue injury, inflammation, or infection, either directly through toll-like receptors or indirectly via immunoglobulin receptors.[77,78] Upon co-engagement of receptors that recognize alarmins and pathogens, MCs release bioactive mediators that result in innate and adaptive immune responses, blood flow regulation, and tissue repair.[7,77,78] The proposed mechanisms underlying the development of MC-related symptoms may include an increased number of CD-117–positive MCs in the GI tract, and small intestinal bacterial overgrowth (SIBO).[7]

Increased Number of CD-117+ Mast Cells in the Gastrointestinal Tract The suggested upper limit of normal for MCs per high-power field (HPF), identified using CD-117, in GI tract biopsies is 20. This definition is derived from a study by Jakate and colleagues wherein the researchers found that the mean number of MCs/HPF in normal healthy GI tissues was 13, with a standard deviation of 3.5.[79] Similarly, Weinstock and colleagues demonstrated that in most patients with MCAS, more than 20 MCs/HPF was commonly identified in the duodenum and ileum, with lower levels found in the stomach and colon, and the lowest number of all in the esophagus.[7]

A role for MCs in the pathogenesis of GI symptoms is supported by evidence of increased MC density, more MC degranulation, and a higher concentration of MC mediators in GI tissues among patients with IBS[80,81] and the clinical association of MC disorders with IBS-type symptoms.[82] Several lines of evidence obtained from studies in patients with IBS indicate an important role for MC mediators, released from degranulating MCs, in the mediation of visceral hypersensitivity and pain in IBS.[83-88] These observations are of considerable relevance to pain in MCAS.

Small Intestinal Bacterial Overgrowth SIBO was reported in 30.9% of 139 patients with MCAS compared with only 10% of 30 controls,[89] and could have contributed to such symptoms as diarrhea and bloating. In interpreting these data, one needs to be mindful of the limitations of currently utilized tests for the diagnosis of SIBO.[90] Nevertheless, one can hypothesize that SIBO, in MCAS, could occur secondary to altered motility resulting from the local effects of MC mediators on perineural tissues, direct damage to glial cells, or an abnormal immune response. One can also visualize how SIBO and/or an abnormal small intestinal microbiome could promote MC activation, which results in lymphocyte activation. T lymphocytes, in turn, secrete more inflammatory mediators that further activate MCs, increase intestinal permeability, and thereby initiate a vicious cycle of inflammation and increased permeability.[7]

The Suggested Relationships and Common Links Between These Syndromes

Visceral hypersensitivity, psychologic stress, and somatic amplification are common denominators among those with DGBI such as IBS and chronic constipation.[91] Indeed, many of the GI symptoms reported by patients with HSD, hEDS, POTS, or MCAS are like those that characterize DGBI,[24,37] as are more systemic manifestations such as fatigue, fibromyalgia, and sleep disturbance.[76,92] Whereas the investigation of the underlying pathophysiology of GI symptoms in HSD, hEDS, POTS, and MCAS is still in its infancy, the available data—as reviewed previously—reveal potential contributions from visceral hypersensitivity and comorbid psychopathology in these disorders as well.

One clear message from the available literature is that HSD/hEDS, POTS, and MCAS frequently coexist,[39,58,71-75,93,94] and have been referred to as a "new disease cluster."[93] In perhaps the largest study to date, based on a population of 37,665 patients diagnosed with MCAS, hEDS, or both, almost 1 in 3 patients with MCAS had a comorbid diagnosis of hEDS.[95]

It is also plausible to suggest that basic disease mechanisms, such as altered physiochemical properties of the gut, dysautonomia, and MC degranulation, may contribute to symptom expression and, indeed, interact to amplify symptom severity. For example, Kohno and colleagues found that MC mediators such as histamine, prostaglandin D2, n-methylhistamine, and prostaglandin 11-B-PGF2-alpha were elevated in plasma and/or urine among POTS patients with atypical symptoms such as allergic manifestations, GI symptoms, and skin rashes in comparison with those POTS patients whose symptoms were confined to those regarded as typical of the disorder.[39] Indeed, Monaco and colleagues went so far as to propose that the MC might be the common thread that runs among hEDS/HSD, MCAS, and POTS by citing evidence that MC mediators such as tryptase and histamine promote proliferation of fibroblasts and the production of collagen.[95] This hypothesis is supported by the description of germline mutations in *TPSAB1* (the gene that encodes for alpha-tryptase) in 35 families with MCAS in one study.[96] Of 96 individuals with the mutation, 28% presented clinical findings compatible with HSD, a 2-fold increase in prevalence compared with the general population. In addition, 46% exhibited orthostatic intolerance. The most prevalent GI symptoms in this cohort were those regarded as typical of gastroesophageal reflux (present in 65%) and IBS (present in 49%). These rates represent a 3- to 5-fold increase over what would be expected in the general population.[96]

The limitations of the current literature need to be emphasized, as these disorders are defined by criteria that continue to be updated[9,16,19] and are not always in agreement. How diligently these criteria have been applied in research studies or clinical practice is unknown and will, of course, influence the prevalence of each individual disorder, as well as their overlap. The effect of comorbid psychopathology, an important confounding factor in DGBI, must also be remembered.

Conclusion

Our case series illustrates the clinical challenges presented by a group of patients who share many phenotypic features: young age, female sex, prominence of nausea and vomiting, frequent psychologic comorbidities, poor nutritional prognosis, and an apparent overlap with a group of disorders that are relatively new to the gastroenterology literature: hEDS/HSD, POTS, and MCAS.[41,97] Although these diagnoses are not always based on currently available criteria, one cannot escape the conclusion that GI symptoms are common in these disorders. Plausible hypotheses have been advanced for the pathogenesis of these symptoms and for their amplification among those in whom more than one of these disorders coexist. It is evident that there is an urgent need for consensus on the clinical definition of these syndromes among patients with GI symptoms; only then can their true prevalence be defined and their natural history documented. Although data are limited, there are clues to, at the very least, spur investigation of the pathophysiology of GI ills in these populations. Future prospective studies are needed employing accepted diagnostic criteria, a detailed evaluation of psychologic and nutritional status, and the use of available and validated methodologies to accurately assess effects on GI function and morphology.

Disclosures

The authors have no relevant conflicts of interest to disclose.

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