ARTICLE

Gastrointestinal Involvement in the Ehlers–Danlos Syndromes

ASMA FIKREE, GISELA CHELIMSKY, HEIDI COLLINS, KATCHA KOVACIC, AND QASIM AZIZ*

Current evidence suggests that an association exists between non-inflammatory hereditary disorders of connective tissue such as the Ehlers–Danlos syndromes (EDS) and gastrointestinal (GI) symptoms. Patients with EDS can present with both structural problems such as hiatus hernias, visceroptosis, rectoceles, and rectal prolapse as well as functional problems such as disordered gut motility. It has recently been demonstrated that patients with hypermobile EDS (hEDS) present with GI symptoms related to the fore and hind-gut and these patients frequently meet the criteria for functional gastrointestinal disorders such as functional dyspepsia and irritable bowel syndrome. Presence of GI symptoms in EDS patients influences their quality of life. Specific evidence based management guidelines for the management of GI symptoms in EDS patients do not exist and these patients are often treated symptomatically. There is, however, recognition that certain precautions need to be taken for those patients undergoing surgical treatment. Future studies are required to identify the mechanisms that lead to GI symptoms in patients with EDS and more specific treatment guidelines are required.

KEY WORDS: Ehlers–Danlos syndrome; gut motility; abdominal pain; constipation; diarrhea

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INTRODUCTION

The current information on the gastrointestinal manifestations of Ehlers–Danlos syndrome (EDS) are summarized in this review. Information about management principles based on current evidence is provided together with suggestions for future research in the field.

METHODS

The gastrointestinal (GI) group had a number of telephone conferences to discuss the content of the literature review. It was agreed that a comprehensive literature search should be conducted and each member should provide a list of references relevant to specific areas.

The search terms used were "Ehlers–Danlos and gastrointestinal," "Ehlers–Danlos and GI," "Joint-hypermobility and joint hypermobility syndrome (JHS) and gastrointestinal," "Ehlers–Danlos hypermobility (EDS-HT)," "Ehlers–Danlos and perforation," "Ehlers–Danlos vascular," "Ehlers–Danlos type IV and gastrointestinal."

Management and Care Guidelines

There are currently no well validated national or international management and care guidelines for the management of EDS-related GI symptoms. GI symptoms are normally managed on empirical grounds using best practice models and evidence.

There are anecdotal reports of global improvement of hypermobile type of Ehlers–Danlos syndrome (hEDS) related symptoms following patient-led "trial and error" diet-based interventions, as well as through the use of enteral nutrition via nasogastric feeding, percutaneous endoscopic gastrostomy/jejunostomy feeding, and total parenteral nutrition. In 2005, a novel and theoretical approach to symptom management in

Dr. Asma Fikree is a consultant gastroenterologist at the Royal London Hospital, London, UK. Her Ph.D. was on gut manifestations of hypermobile EDS.

Dr. Gisela Chelimsky is a pediatric gastroenterologist in Milwaukee, Wisconsin, and is affiliated to Children's Hospital of Wisconsin and the Medical College of Wisconsin.

Dr. Heidi Collins is a physical medicine and rehabilitation specialist. She is chair of the EDNF Professional Advisory Network and works at Beacon Medical Group, Memorial Hospital, South Bend, IN.

Dr. Kovacic is assistant professor and a Pediatric Gastroenterologist. She is part of the nationally recognized GI motility program at the Children's Hospital of Wisconsin, Center for Pediatric Neurogastroenterology, Motility and Autonomic Disorders.

Prof. Qasim Aziz is a professor of neurogastroenterology at Barts and The London School of Medicine and Dentistry, and specialists in disorders of gut function.

*Correspondence to: Professor Qasim Aziz, The Wingate Institute of Neurogastroenterology, 26 Ashfield Street, London E1 2AJ.
E-mail: q.aziz@qmul.ac.uk
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EDS was described by Mantle et al. [2005]. The authors suggested that attention to nutrient intake, by use of supplements, may impact on symptom severity in EDS. Tinkle [2009] has also reported his experience with similar selected nutraceuticals in hEDS. In a 2015 review of gastrointestinal and nutritional issues in hEDS, Castori et al. [2015] suggested that there is a theoretical basis which suggests that lifestyle and nutrients may be beneficial in hEDS. Consequently, it is reasonable to postulate that these features may be managed or improved by nutritional supplementation and lifestyle modifications. In the author's own clinical practice, low FODMAP (Fructose, Oligosaccharides, Disaccharides, Monoamines, and Polyols) diet is frequently used to good effect for abdominal bloating, pain, and diarrhea, these features often overlap with irritable bowel syndrome (IBS) where the efficacy of this diet is now well established. Given that approximately 37% of patients with a diagnosis of IBS meet the criteria of hEDS [Fikree et al., 2015], it is not surprising that efficacy of this diet is being seen. However, further controlled studies are required to determine efficacy of the diet based interventions in patients with GI symptoms associated with hEDS.

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Surgical management of patients with vascular EDS who develop acute GI complications such as bleeding or perforation has been described in the literature. These approaches range from refrain from intervention with conservative non-surgical management of intestinal perforation [Casey et al., 2014] to more conventional surgical management with resections of appropriate segments of the gut. It has been suggested that during surgery, all organs must be treated gently due to tissue fragility [Omori et al., 2011]. A systematic review of GI surgery and related complications in EDS [Burcharth and Rosenberg, 2012] suggests that surgery in patients with EDS is associated with a high risk of complications, which is why preoperative indications should be carefully considered. Furthermore, optimal therapy for these patients includes the awareness that EDS is a systemic disease involving fragility, bleeding, and spontaneous perforations from almost all organ systems. The authors suggested that a nonsurgical approach can be the best choice for these patients, depending on the condition.

Desmopressin has been used in a preliminary study of hEDS associated bleeding symptoms such as easy bruising, epistaxis, menorrhagia, and gum bleeding [Mast et al., 2009]. In these patients, desmopressin was given intranasally or intravenously and led to significantly reduced bleeding time. In the same study, desmopressin was also given to patient's pre-surgery (non-GI surgery) and none of these patients suffered from any post-surgical bleeding complications, in contrast, 30% of the patients who did not receive desmopressin developed post-operative bleeding complications. This suggests that desmopressin may have a role in the management of GI peri-surgical bleeding complications in EDS patients but further studies are required to test this hypothesis.

Recently, Fikree et al. [2015] have demonstrated that a significant proportion of patients with Functional Gastrointestinal Disorders (FGID) meet the criteria for hEDS. Patients with this overlap have a different phenotype with more chronic pain, somatization, autonomic symptoms and anxiety, and poorer pain-related quality of life compared to those without the overlap. Thus, it is likely that management of FGID patients with and without EDS overlap may differ. For instance, those with overlap may require earlier identification and holistic multidisciplinary management involving for instance rheumatologists, autonomic neurologists, and pain specialists.

Chronic musculoskeletal and visceral pain is common in patients with EDS. It is, therefore, likely that opioids will be considered in the management of these patients, which can significantly influence GI function and lead to deterioration in symptoms. Hence, avoidance of opioids should be a consideration in those with GI involvement.

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Recognition that anatomical abnormalities such as diverticulosis, rectoceles, and prolapse can occur in patients with EDS may help to plan investigation and treatment in patients with GI symptoms. For instance, constipation is common in patients with hEDS [Fikree et al., 2014], and recognition that symptoms may at least partly be due to rectal evacuatory dysfunction due to the anatomic abnormalities such as rectocele and or prolapse may help to guide the management toward nurse led therapy aimed at improving defecatory dynamics or in some severe cased

surgical correction of the anatomic abnormality.

GI Connective Tissue Abnormalities in Disease

Localized abnormalities in connective tissue have been described in association with GI pathology. In diverticular disease, there is increased elastin deposition in the taenia of the colon, and structural changes in the collagen of the smooth muscle [Whiteway and Morson, 1985]. Patients with hiatus hernias have fragmentation and distortion of elastin in their gastro-hepatic and phreno-esophageal ligaments [Curci et al., 2008]. Children with megacolon have atrophy of collagen in the tendinous connective tissue membrane of the myenteric plexus and muscularis propria, referred to as "atrophic desmosis" [Meier-Ruge, 1998]. Evidence also exists for the association between GI pathology and both inflammatory and non-inflammatory connective tissue disorders [Braun and Sieper, 1999]. A rationale, therefore, exists for an influence of connective tissue disorders on gut structure and function. Evidence now exists of involvement of the entire GI tract in EDS.

EDS AND ABNORMAL GI TRACT

EDS and Abnormal GI Anatomy

In a study of EDS patients, only 11 out of 143 (7.7%) who underwent endoscopic assessment had a hiatus hernia [Nelson et al., 2015]. A study in patients with lower urinary tract dysfunction demonstrated that patients with hEDS were significantly more likely to have symptoms of rectal evacuatory dysfunction and evidence of rectal morphological anomalies, for example, rectal prolapses, compared to those without hEDS [Manning et al., 2003]. In a case series of EDS patients at the Mayo clinic, all 4 patients who underwent an MR proctogram had an anterior rectocele [Nelson et al., 2015]. In the same study, 12 (11%) out of 110 who underwent colonoscopy had diverticulosis or diverticulitis.

Case reports of patients with hEDS describe further anatomical abnormalities in small numbers of patients. Diverticular disease has been described in association with EDS [Lindor and Bristow, 2005]. Visceroptosis of the bowel has been described in two patients with hEDS [Reinstein et al., 2012]. This refers to the downward displacement of abdominal organs below their natural position. It is rare and its aetiology is unknown. It can cause kinking of thin walled structures such as blood vessels and nerves and thereby cause symptoms, which can be severe. In the case described, the patient presented with a 4 year history of abdominal distension and bloating that interfered with her eating and activities of daily living.

EDS and Abnormal GI Physiology

Results of gastrointestinal physiological studies were reported in a retrospective observational study from the Mayo clinic in EDS patients of whom the vast majority had hEDS (71.7%) [Nelson et al., 2015]. About 13 out of 46 (28%) patients who underwent colonic transit studies had abnormal results; nine with slow transit and four with fast transit. A total of 60% of these patients with abnormal colonic transit had hEDS In the same study, 17 out of 76 (22%) patients had abnormal gastric emptying half being fast and half being slow Abnormal oesophageal manometry was present in 5 out of 11 (31%) patients. About 7 out of 16 patients (44%) had pathological acid reflux on reflux testing.

Association Between hEDS and GI Symptoms

The association between hEDS and GI symptoms was first described 12 years ago by Hakim and Grahame [2004]. They found that hEDS patients attending a hypermobility clinic had significantly more GI symptoms compared to age and sex matched controls (37% vs. 11%). The most common GI symptoms were nausea, abdominal pain, constipation, and diarrhea. It was felt that dysautonomia was one mechanism by which this may occur [Gazit et al., 2003; Hakim and Grahame, 2004], and since then it has been shown that Postural Tachycardia Syndrome (PoTS) is associated with GI symptoms such as nausea, reflux, bloating, constipation, and diarrhea [Mathias et al., 2011]. Thus, it would appear that hEDS, autonomic symptoms, and GI symptoms are indeed linked, though the exact mechanism for the association is unknown.

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As that landmark study, other studies in various hospital settings and countries, have confirmed that GI symptoms are common in patients with an existing diagnosis of hEDS. In a study of 21 hEDS patients attending a genetics clinic in Italy, 87% of patients were found to have GI symptoms, most commonly dyspepsia (67%), gastro-oesophageal reflux (57%), recurrent abdominal pain (62%), alternating constipation and diarrhea (33%), and abdominal hernias (5%) [Castori et al., 2010]. Furthermore, the same author demonstrated that the incidence of GI symptoms increased with age, and that older hEDS patients were more likely to have GI symptoms than their younger counterparts.

In a prospective cross-sectional study of over 600 new patients in

secondary care GI clinics, Fikree et al. [2014] looked at three groups of patients including those with established hEDS from rheumatology clinics (hEDS-Rh), those with hEDS albeit previously undiagnosed (hEDS) and those without hEDS (non-hEDS). They demonstrated that approximately one-third of unselected patients attending GI clinics have previously undiagnosed hEDS based on validated clinical criteria; however, the GI symptom profile in these patients is less severe than that observed in patients with established hEDS referred from rheumatology clinics. In the newly diagnosed hEDS patients, there was a significant association with gastro-oesophageal reflux and dyspeptic symptoms but not with alternating bowel habit, chronic abdominal pain, dysphagia, globus, and bloating; however, these symptoms were more common in the hEDS-Rh group. Autonomic dysfunction, chronic pain, and analgesic use, but not psychopathology, showed increasing trends across the three groups, being highest in patients with hEDS-Rh. Thus, they concluded that hEDS is common in GI clinics, with increased burden of upper GI and extra intestinal symptoms.

Studies from a Genetics Department in Belgium not only confirm that GI symptoms such as constipation, diarrhea, bloating, and swallowing problems are present in hEDS, but that these GI symptoms are associated with clusters of other extra-articular symptoms, in particular cognitive problems, insomnia, postural dizziness, and syncope [Rombaut et al., 2011]. This group also recognized that there was large heterogeneity in presentation and not all patients had the same cluster of symptoms. Consequently, they performed a cluster analysis and identified that two main clusters. In both clusters, musculoskeletal symptoms were most prominent; however, the pattern of extra-articular symptoms differed. GI symptoms were particularly prominent in the cluster, which also had high levels of fatigue, cutaneous changes, orthostatic, immune, urogynecological, visual, and respiratory problems [De Wandele et al., 2013].

hEDS and Organic GI Disorders

Only two published studies exist which demonstrate a possible association between hypermobility and organic disorders, and these were done in patients with inflammatory bowel disease (IBD) and celiac disease. The first was performed in a Greek Hospital setting [Vounotrypidis et al., 2009] which described that the prevalence of hEDS in Crohn's disease (12.2%) was higher than that in UC (3.6%) but this difference was not statistically significant. Fikree et al. [2015] also demonstrated a relatively high prevalence of JHS in Crohn's disease and ulcerative colitis patients (32% and 21%, respectively). No other studies have further examined this association between EDS and IBD.

One small study demonstrated a high prevalence of celiac disease in hEDS patients [Danese et al., 2011]. Thirty-one patients attending a genetics clinic with an established hEDS diagnosis were screened for celiac disease using IgA/G endomysial antibodies and/or anti-tissue transglutaminase, of which six (19%) tested positive. Duodenal biopsies from five had features consistent with celiac disease. The prevalence of celiac disease (16%) in the hEDS group was, therefore, significantly higher than the estimated population prevalence (1%) [Danese et al., 2011]. However, there are a number of limitations to this study. First, the population prevalence of celiac disease was estimated rather than calculated. Second, the basis on which hEDS patients were selected for testing for celiac disease is not described and, therefore, there may be a degree of selection bias. Nevertheless, these results were broadly corroborated in another study with a small sample size, where hEDS was diagnosed in four out of 13 (30%) patients attending GI clinics with a new diagnosis of celiac disease [Fikree et al., 2015].

hEDS and Functional GI Disorders

Direct evidence for an association between FGID and generalized joint hypermobility initially came from a retrospective observational study in tertiary gastroenterology setting [Zarate et al., 2009]. A subgroup of these patients were assessed further by a rheumatologist, and found to have hEDS. Patients with hEDS tended to have motility problems in their gut on physiological testing, for example, small bowel dysmotility, delayed gastric emptying and delayed colonic transit. This study suggested that in a tertiary neurogastroenterology setting, hEDS was associated with GI dysmotility.

In studies demonstrating the presence of GI Symptoms in hEDS, GI symptoms were often attributable to FGID subtypes such as IBS, rectal evacuatory dysfunction, and functional constipation [Manning et al., 2003; Castori et al., 2010; Zeitoun et al., 2013], all of which are ROME III categories of FGID. In another paper, two-thirds of patients with hEDS who reported having appendectomies for abdominal pain did not have a positive outcome of surgery, suggesting that the pain was more likely to be secondary to a functional cause rather than appendicitis [Rombaut et al., 2011].

Fikree et al. [2015] further studied the association between hEDS and FGID and the impact of this association on comorbidities and quality of life (QOL). In a prospective case-control study in secondary care GI clinics over 2 years, hEDS was assessed prior to consultation in consecutive new patients. It was demonstrated that hEDS prevalence was higher in FGID compared to organic GI disorders (39.0% vs. 27.5%, ORadj: 1.51, CI: 1.07–2.12, $P = 0.02$), and particularly associated with functional gastroduodenal disorders (44.1%, ORadj: 2.08, CI: 1.25–3.46, $P = 0.005$), specifically postprandial distress syndrome (51%, ORadj: 1.99, CI: 1.06–3.76, $P = 0.03$). FGID patients with hEDS had increased chronic pain, fibromyalgia, somatization scores, urinary autonomic scores, and worse pain-related QOL scores. The authors concluded that hEDS is significantly associated with FGID, and this subgroup of patients have increased comorbidity and decreased QOL.

hEDS and GI Symptoms in Children

Data on gastrointestinal manifestations in children with hEDS is limited.

However, several studies link constipation with childhood generalized joint hypermobility (GJH) as determined by the Beighton score. These studies found constipation rates ranging from 11% to 38% in hypermobile children. Constipation was more common in hypermobile boys [de Kort et al., 2003; Adib et al., 2005; Reilly et al., 2008].

A variety of gastrointestinal symptoms and functional GI disorders have also been linked to joint hypermobility in children. Pacey et al. [2015] reported gastrointestinal symptoms in 54% of children with GJH. Kovacic et al. [2014] found a 56% prevalence of GJH in adolescents diagnosed with complex functional GI disorders. In these patients, fibromyalgia appeared associated with GJH. A large population study in India found a high prevalence of GJH and a possible link of this condition with moderate-severe malnutrition [Hasija et al., 2008].

GI Symptoms in Other Subtypes of EDS

GI symptoms have been described in EDS I, II, and IV subtypes as well as in patients with Tenascin X deficiency.

In classic EDS (cEDS), diverticular disease has been described [Kitsiou-Tzeli et al., 2010]. Although spontaneous acute pancreatitis has been described in cEDS, it is not clear if this is a true association or an incidental finding [Sarra-Carbonell and Jimenez, 1989].

Various GI manifestation of the vascular type of EDS (vEDS) has been described. Most of these relate to organ perforation and or bleeding [Pepin et al., 2000; Baichi et al., 2005; Diz et al., 2009; Omori et al., 2011; Anderson and Sweetser, 2014; Yoneda et al., 2014]. Familial cases of sigmoid perforation have also been described [Surgey et al., 2011]. There also appears to be increased risk of colonic perforation during colonoscopy [Rana et al., 2011]. Occult and overt small bowel perforation can also occur [Aldridge, 1967; Leake et al., 2010]. Even esophageal perforation has been described [Habein, 1977]. Furthermore, congenital diaphragmatic hernia (CDH) has been reported in two siblings with a suspected diagnosis of vEDS with consanguineous parents [Lin et al., 2006]. The index case was a 3-year-old girl who had surgery for CDH at 5 months of age, with recurrence 6 months later followed by further surgery. Recurrence at 3 years of age prompted further investigations. Two-dimensional echocardiography revealed an atrial septal defect, dilatation of the pulmonary arteries, and suspected abnormally tortuous aorta. Subsequent contrast-enhanced magnetic resonance angiography revealed marked tortuousity of the aorta and the innominate, left common carotid, left subclavian, and bilateral vertebral arteries, that was suggestive of EDS. Further detailed evaluation of the patient revealed hyper elastic skin and mild hypermobility of the knee joints. A chromosome study did not demonstrate an obvious abnormality but diagnosis of vEDS was made on clinical grounds. Subsequently, her 1-year-old brother was also diagnosed with CDH.

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vEDS complicated by eventration of the diaphragm and colonic and jujenal perforation has been described [Iwama et al., 1989]. Post-operative celiac artery thrombosis [Debnath et al., 2007] and other complications [Freeman et al., 1996] can also occur in vEDS. In addition, spontaneous rupture of the liver [Gelbmann et al., 1997; Mistry et al., 2000; Ng and Muiesan, 2005] and spleen [Privitera et al., 2009] as well as post-operative bleeding into the liver capsule [Blaker et al., 2007] has been reported in these patients.

In a review of surgical complications of vEDS by Freeman et al. [1996], 44 gastrointestinal and 45 vascular complications of vEDS have been reported in the literature between January 1975 and July 1995. This included 41 colon perforations, two paraesophageal hernias, 22 spontaneous haemorrhages, 17 aneurysms, and 5 arterial dissections. A total of 27 colonic perforations were treated with resection and diversion, 11 with total abdominal colectomy (TAC), and 3 with primary colon repair. Re-perforation occurred in 15 resection/diversion patients versus none treated with TAC ($P < 0.05$). Seven patients (23.3%) died from their gastrointestinal complications. Twelve (30%) patients died from vascular complications of vEDS, seven of whom had been treated with arterial reconstruction ($P < 0.05$). This review supports treating colon perforations in vEDS patients with TAC and end ileostomy to avoid a re-perforation or an anastomotic leak. Stillman et al. [1991] have described spontaneous colonic perforation, a complication traditionally treated by primary closure of the perforated segment and creation of an end colostomy, while attempts at bowel re-anastomosis often result in repeated colon perforations. They present a patient with vEDS with colonic perforation proximal to an end colostomy, and describe the surgical strategy to prevent recurrences of this and other postoperative complications associated with the syndrome.

GI symptoms have been described in patients with Tenascin X (TNX) deficiency including abdominal pain [Lindor and Bristow, 2005] episodes of spontaneous and secondary ileus and perforations (sigmoid and duodenum), with post-operative incisional hernia and incarceration. Chronic constipation and rectal prolapse, pan colonic diverticulosis with diverticulitis, uterine prolapse, and moderate sized hiatus hernia [Lindor and Bristow, 2005] have also been described. Increased incidence of GI problems in family members of TNX deficiency patients have been described including chronic constipation since childhood, and rectal prolapse. Spontaneous perforation of colonic diverticulum,

multiple intra-abdominal abscesses, duodenal and sigmoid diverticulae have also been reported in TNX deficient patients. Gastric ulceration [Hendriks et al., 2012] and GI bleeding [Schalkwijk et al., 2001] has also been described in a male patient with homozygous for TNX deficiency.

FUTURE DIRECTIONS

It is clear from the above literature review that GI symptoms can occur in all EDS subtypes. GI perforations and bleeding complications are less likely in hEDS and most likely in vEDS than in the other subtypes. There is a high prevalence of hEDS in patients presenting with the features of FGID especially functional dyspepsia. hEDS patients with GI symptoms also often have a combination of musculoskeletal, autonomic, and urinary tract symptoms.

There remain several knowledge gaps and future work will be needed to address these on an epidemiological, physiological, cellular, molecular, and genetic level. The aetiology of GI symptoms in individuals with EDS will need to be determined and this will require investigation of biomechanical, autonomic, and sensorimotor function of the upper GI tract. The understanding of which EDS individuals will develop GI symptoms and how they progress over time, what other factors such as poor nutrition, traumatic life events, viral infections, and so on, precipitate the worsening of GI and extra-intestinal symptoms in these patients will require longitudinal studies. Improving our understanding of the above-mentioned factors will enable better treatment strategies to be devised.

Identification of the nature of the connective tissue defect in EDS and its relation to the functioning of the GI tract is undeniably an important question now and will require genetic studies in humans and validation studies in animal models. The mechanism of the link between EDS and PoTS also needs further study. Furthermore, signaling between the extracellular matrix (component of connective tissue) and intracellular structures is now recognized as being critical to normal cellular function, and there has been increasing research into various signaling components (e.g., growth factors) which might provide treatable targets in the future. Genetic studies such as exome sequencing on families of patients with hEDS, and in patients who have had deep phenotypic profiling perform are some of the methods that may pave the way of identification of the molecular abnormalities that underlie this hitherto difficult to understand disorders.

CONCLUSION

Current literature suggests an association between all subtypes of EDS and GI symptoms. This association is common and has hitherto been underestimated. The group observed that evidence for GI symptoms to be included as a major EDS diagnostic criteria is compelling. However, a causative relationship between abnormalities in connective tissue and GI symptoms has not yet been established. Similarly, specific evidence based guidelines for the management of EDS patients with GI symptoms are not yet available.

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