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GASTROINTESTINAL MANIFESTATIONS OF EHLERS-DANLOS SYNDROME

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Introduction

Ehlers-Danlos Syndrome (EDS) consists of a heterogeneous group of non-inflammatory hereditary disorders of connective tissue whose principal clinical features are skin hyperextensibility, delayed wound healing, joint hypermobility (JHM), bleeding tendency and generalised connective tissue fragility. These clinical manifestations are present, to varying degrees, in each subtype of the condition. The most current nosology divides EDS into six major categories based on the phenotypic (individual anatomical characteristics) differences between them. Traditionally, EDS has been thought of as a rare disorder but its true incidence is unknown. The overall incidence of EDS has been estimated to be 1:5000 with the most common form of EDS, EDS-hypermobility type (EDS-HM), thought to have a population prevalence of 2.5%. Furthermore, many opinion leaders consider EDS-HM to be a clinical continuum with joint hypermobility syndrome (JHS). EDS is associated with a reduction in quality of life and multiple extra-articular comorbidities such as chronic fatigue and dysautonomia.

The gastrointestinal (GI) manifestations of EDS, and in particular EDS-HM/JHS, whilst often reported by patients have, until the recent past, received scant attention from the clinical and academic communities alike. This is likely to be a consequence of the increasing trend of sub-specialisation within medical practice, which often leads to a variety of disorders being managed in isolation within super-specialised clinics despite evidence that such disorders may actually represent a more generalised pathology. For instance, it is interesting to note that functional GI disorders (FGID), a highly prevalent but heterogeneous group of unexplained GI disorders, share a remarkable number of epidemiological and clinical features.

This information sheet consists of three parts. The first section concerns the role of connective tissue in maintaining the structural and functional integrity of the GI tract. The second section will examine how EDS may manifest in each region of the GI tract, with a particular focus on EDS-HM as this is the most prevalent type of EDS. Finally, a research strategy will be proposed to further investigate these putative links. For the purposes of this information sheet we shall consider EDS-HM and JHS to be one and the same and hereinafter only refer to EDS-HM.

The role of connective tissue in the gastrointestinal tract

The extracellular matrix (ECM) represents a complex structural entity that surrounds and supports cells and is often referred to as connective tissue. In humans, the ECM is composed of three major classes of molecules namely, structural proteins such as

collagen and elastin, specialised proteins such as fibrillin and fibronectin and proteoglycans such as the tenascins. In the human genome there are at least 30 different genes that combine in a variety of manners to create over 20 different types of collagen fibrils. Over 90% of the collagen within the body is type I collagen and is found in fibrous connective tissues such as ligaments, tendons and bone. Type II collagen is a component of hyaline cartilage with type III being found in highly cellular structures such as hepatic tissue and the vasculature. Types IV and V are integral to the basement membrane on which the epithelial membrane and the sensorimotor apparatus of the GI tract reside. Thus the ECM, and therefore collagen, plays a key role in the biomechanical properties of the GI tract. Thus far minimal attention in the literature has been placed on the assessment and study of the physical and physiological characteristics of the ECM in which the sensorimotor apparatus of GI tract is embedded.

Abnormalities within the collagen structure of the ECM that surround the GI tract are likely to alter the manner in which it deforms or stretches through influencing the functional integrity of the cellular mechanoreceptors contained therein. Many types of cells embedded within the muscularis mucosae of the GI tract have been purported to serve as mechanoreceptors such as intraganglionic laminar endings and interstitial cells of Cajal. It has been demonstrated that these types of cells may be activated by mechanical forces so it is not unreasonable to postulate that changes within the structures in which they are embedded, i.e. the ECM, are likely to influence their function. In this respect colonic desmosis may serve as a useful illustrative example. Colonic structural disorganisation is a condition characterised by an absence or a reduction of the ECM in the region of the myenteric plexus, between the circular and longitudinal muscle layers of the GI tract. It is associated with hypoperistalsis (reduced movement) or aperistalsis (no movement) segments within the colon and has been recognized as a primary cause of constipation.

Further evidence comes from the study of tenascin-X, coded for by the gene TNXB on chromosome 6, a large ECM glycoprotein that is present throughout the GI tract. Deficiency of tenascin-X has been implicated in the pathogenesis of Hirshsprung's disease, a disorder characterised by lack of neuronal cells in the colon that results in dysmotility and megacolon. It is fascinating to note that tenascin- X halpoinsufficiency has also been implicated in the connective tissue abnormalities that underpin the patho-physiology of a proportion of patients with EDS-HM. Acquired medical conditions that affect the composition of ECM in the GI tract, such as inflammatory bowel disease, radiation induced bowel injury and autoimmune disorders of the connective tissue are characterised by a reduction in compliance and ineffectual transit within the region of the affected GI tract, which ultimately contribute to the genesis of symptoms. These observations provide important evidence of the proof of concept that changes in the ECM per se can influence gut biomechanics and contribute to the development of symptoms. However, it must be stressed that whilst quantitative and qualitative differences are likely to be present in EDS, to date they have not yielded a diagnostic biomarker. Thus, the idea that similar differences may be observed in the GI tract in patients with EDS remains an exciting hypothesis but not as yet one substantiated by direct objective experimental evidence.

Gastrointestinal manifestations of EDS

Gastrointestinal manifestations are common amongst patients with EDS. It has been estimated that between 37.0%-85.7% of patients, with EDS, complain of GI related symptoms. A recent study reported that in patients with EDS-HM the most common GI

symptoms were dyspepsia/nausea/vomiting (66.7%), abdominal pain (61.9%), gastrooesophageal reflux (57.1%), and altered bowel habit (33.3%). Performing our own review of the literature, in combination with our own clinical experience, EDS may manifest in any segment of the GI tract from the mouth to the anus. We will now review each of these, which we shall separate anatomically in a head to toe direction. An additional section will focus upon abdominal pain and FGID in EDS. The main focus of this review will be the description of specific diagnoses that are related to EDS, rather than their management due to the relative paucity of evidence for the latter in EDS. It must be stressed that not all patients with EDS will suffer such complications and indeed many of the more serious complications such as viscus perforation are confined to classical and vascular EDS and remain relatively uncommon.

Oral

Oral and dental manifestations may occur in any type of EDS but are most severe in patients with the type of periodontitis, formerly known as type VIII. Patients suffer premature loss of teeth and alveolar bone. This premature loss of teeth is compounded by the observation that teeth are prone to fracture after relatively minor trauma.[37] The mucosa of the buccal cavity may be easily stretched in EDS, and the tongue may display hypermobility (this is the basis of Gorlin's sign, the ability to touch one's tongue to the tip of one's nose). Gingival fragility may also present with bleeding after minor trauma such as tooth brushing or mastication. Mastication may also precipitate dislocation or subluxation of the temporo-mandibular joint.

Oesophagus

Structural and functional defects are observed in patients with EDS. For instance, the most commonly reported oesophageal abnormality related to EDS is hiatus hernia. In a recent preliminary study from our unit, 33.3% of patients with EDS-HM had high resolution oesophageal manometric evidence of hiatus hernia. A hiatus hernia is defined as the proximal displacement of the proximal part of the stomach through the diaphragmatic hiatus. A hiatal hernia may interfere with the efficiency of the anatomical reflux barriers of the lower oesophageal sphincter and the crural diaphragm. The failure of these mechanisms, due to the development of a hiatus hernia, has been postulated to be due ligamentous laxity of the phrenooesphageal ligaments, which may result in reflux of gastric contents into the oesophagus thereby leading to symptoms of reflux and heartburn. Many studies have demonstrated the close relationship between hiatus hernia, greater oesophageal acid exposure and consequentially increased severity of symptoms and oesophagitis. It is therefore not surprising that the most common oesophageal symptom in EDS is reflux with 55% of patients with EDS-HM who attended our clinic reporting it. In an important study, Al-Rawi et al. assessed the prevalence of JHM in 50 patients with a confirmed hiatus hernia vs. 50 age, sex, parity and body mass index matched controls without hiatus hernia. The prevalence of JHM was 22% in the hiatus hernia+ vs. 6% in the group without hiatus hernia ($p<0.001$). This evidence suggests that the presence of hiatus hernia may be an important pathophysiological factor in explaining reflux symptoms suffered by patients with EDS.

Although extremely rare, the serious complication of spontaneous oesophageal rupture has been reported. There is no evidence to suggest that EDS confers an increased risk of oesophageal rupture due to protracted vomiting (Boerhaave's syndrome).

Stomach

The incidence of peptic ulcer disease in EDS is not dissimilar to that of the general population. There is no evidence linking an increased incidence of upper

gastrointestinal bleeding in EDS, although intuitively one may expect this sequelae of peptic ulceration to be more severe in patients with EDS-vascular type. Previously held concerns regarding the safety of endoscopy, as a diagnostic tool, have been largely unfounded.

Amongst the most prevalent symptoms 'emanating' from the stomach is nausea and vomiting, which in our series we observed in 34% and 29% of patients respectively. Our investigative strategy in such patients is to perform a gastric emptying study, where we have previously demonstrated abnormalities in over 75%. The most frequent abnormality is a delay in gastric emptying, which is our opinion is may be due to the sluggish GI tract biodynamics conferred by abnormalities of the ECM that characterises EDS.

Small bowel

Whilst not as common as in the colon, perforation of the small bowel in EDS is well documented. The small bowel is particularly prone to perforation on account of the relative thin nature of the GI tract in this region. The most frequent findings at laparotomy are small bowel diverticular disease and intrajejunal intramural haematomas. Small bowel perforation always requires surgery, with some anecdotal evidence to suggest that primary end-to-end anastomosis is the treatment of choice.

Abdominal bloating is another common symptom, particularly in patients with EDS-HM. The mechanisms that underlie bloating are not fully understood, but it is thought that dysmotility of the small bowel may play a crucial pathophysiological role. We have demonstrated in patients with EDS-HM that 57% may have manometric evidence of dysmotility within the small bowel, which may account for the relatively high prevalence of this symptom. If we couple this dysmotility with the aforementioned diverticular disease, patients with EDS are likely to be more prone to the development of small bowel bacterial overgrowth. In our experience in patients with EDS, the most common manifestations of small bowel bacterial overgrowth are diarrhoea, pain, bloating and halitosis.

Colon

Spontaneous colonic perforation is a well-recognised GI complication of EDS and is particularly associated with the vascular type. Spontaneous colonic perforation may occur at any age, but its incidence diminishes after the 5th decade. Clinical presentation is most frequently characterised by acute onset abdominal pain and peritonitism often in the context of a protracted history of constipation. Spontaneous perforations are most common in the sigmoid colon, where they may or may not be associated with diverticular disease. Rectal perforation is rare but often associated with the use of enemas. The key to the success of surgical treatment is the recognition of the underlying disorder of connective tissue, especially in terms of the increase in risk of peri -and post-operative complications. Again, definitive evidence is scant, but it is generally recommended that primary side-to-side anastomosis (joining) reduces the risk of anastomotic failure. A key ethical question concerns whether the surgeon should perform a colectomy with end-ileostomy at the index perforation/event, as the risk of re-perforation is high. Further research and debate is needed to address this issue although clearly patient choice is paramount.

Chronic constipation in adults is a common and debilitating problem that may present to a wide variety of specialist and non- specialist physicians. The Rome III multinational consensus on FGID has sought to define constipation. Whilst the Rome III definition is comprehensive, it is rather unwieldy for day-to-day use. More helpfully,

McCallum and colleagues define constipation as "…any patient experiencing consistent difficulty with defaecation". Constipation is common in the general population with prevalence being estimated to be in the order of 12-19%, with increasing age and female gender being risk factors.

The causes of constipation are often multi-factorial but are generally cited as being due to dietary, metabolic, neurological, painful anorectal disorders or as side effect of prescribed medications.

Constipation is a common in patients with EDS, particularly in the paediatric population with JHS. De Kort et al. questioned the parents of 89 children, aged 5 - 12 years, with a diagnosis of EDS- HM and compared them with a group of 116 healthy controls of the same age. They found that the parents of 19% of boys with EDS-HM reported constipation in comparison to 4% of the parents of controls ($p = 0.02$). Reilley et al., sought to further expand these observations and studied patients, aged 7-17 years, who had been diagnosed with slow transit constipation (STC), a form of chronic constipation associated with the delayed colonic passage (transit) of stool. In a group of 39 patients who had been diagnosed with STC, 15 (38%) had generalised JHM compared with 8 (20%) out of 41 healthy controls ($p= 0.06$). In a post hoc analysis by gender, 10 (38%) of 26 STC males had JHM vs. 1(4%) out of 23 controls. The authors conclude that generalised JHM is particularly higher in male children with STC. Recent preliminary data have suggested that there may be differences in the anatomy of the colon in patients with EDS with up to 14% having demonstrable a dolichocolon. Taken together these results provide further weight to the assertion that EDS may manifest with sluggish GI tract biodynamics due to underlying connective tissue abnormalities.

Rectum and anus

Faecal incontinence is defined as the involuntary passage of faecal material through the anal canal. It is an under reported symptom which often has a devastating impact on quality of life. FI has a community prevalence of 4.2 men and 1.7 women per 1,000 between the ages of 15-64 years. Risk factors for the development of FI include female gender, increasing age, poor general health and prostate disease. Jha et al., in a case control study, questioned 30 female patients with EDS-HM and found that the prevalence of urinary and FI to be significantly higher than in 30 healthy controls (60% vs. 30%; $p=0.037$, 23 vs. 0%; $p=0.01$ respectively). In a follow up study by the same group, validated questionnaires evaluating symptoms of urinary and FI, were sent to members of the Hypermobility Syndrome Association with a physician confirmed diagnosis of EDS-HM. Based on the questionnaire results, 14.9% of responders had FI with the elderly and those with an elevated body mass index being most at risk. The results of this study must be interpreted with a note of caution as there may have been an element of self-selection bias on the part of the responders, in that those members who took part in the research may possibly have more severe symptoms than a more representative population of patients with EDS. Nevertheless, these findings are interesting and provide a valuable insight into prevalence of these disorders in EDS-HM.

Constipation can be a manifestation of obstructed defaecation (OD). Different pathophysiologies may underlie OD, and tests of anorectal function, such as proctography, play an important role in the identification of the underlying cause whether it is mechanical or functional as well as aiding in the direction of further management. Rectal prolapse or intussusception is a recognised mechanical risk for OD and it has been established in previous studies that there is an association between rectal and genital prolapse and EDS-HM. Our group has performed a prospective study

designed to evaluate the link between OD and JHM. The prevalence of JHM was 30% in patients presenting to our tertiary centre for physiological investigation OD, significantly higher than the general population. Proctography demonstrated an obstructing mechanical cause in a 71% of patients with JHM vs. 34% without (p=0.001). These findings provide further evidence that the defaectory difficulties that these patients encounter may be secondary to laxity of the ECM within the gut.

Abdominal pain and functional gastrointestinal disorders in EDS

The fact that FGID and EDS-HM share a number of epidemiological and clinical features is remarkable. Within modern gastroenterological practice, there is a failure to make an objective diagnosis in a substantial proportion of patients despite considerable technological advances in modalities such as cross sectional imaging and GI endoscopy. In such patients with unexplained GI symptoms, in whom abdominal pain is often a feature, the diagnosis of a FGID is frequently made. These are a heterogeneous group of disorders that account for 2-5% of consultations in primary care and more than 40% of all new referrals to gastroenterological outpatient clinics. We have prospectively evaluated the incidence of EDS-HM in a cohort of 115 patients who attended our tertiary referral neurogastroenterology clinic; 63% of the patients presenting to the clinic had GI symptoms without a known underlying structural, metabolic or autoimmune disorder or in the absence of a unifying diagnosis at the time of referral. Many of these had been incorrectly labelled in secondary care as having irritable bowel syndrome (IBS). Of these patients, 58% had evidence of JHM and in 61% of these a diagnosis of EDS-HM was made.

FGID have a considerable socioeconomic impact in terms of absenteeism, presenteeism and increased healthcare utilisation, with costs being in the order of $34 billion in the seven largest western economies. Whilst many hypotheses have been proposed to explain the origin of symptoms in FGID, it is not surprising that no single factor has achieved primacy due to the marked heterogeneity of these disorders. Thus considering the aforementioned comments regarding medical specialisation, it is not unreasonable to surmise that a proportion of patients with FGID, currently investigated, diagnosed and managed in isolation by gastroenterologists, could be in fact be suffering from the same multifaceted generalised disorder such as EDS.

IBS is the most prevalent example of a FGID, characterised by recurrent abdominal pain and disordered defaecation. IBS has a multitude of extra-gastrointestinal manifestations and is co-morbid with a number of disorders including fibromyalgia (FM), the latter often associated with EDS-HM. Common to all of these syndromes is chronic unexplained pain with emerging evidence suggesting this is a sequelae of aberrancies of sensorimotor physiology which may occur at multiple levels, including genetic, the stress responsive systems as well as the peripheral and central nervous systems amongst others. If we couple the fact that pain is prominent in EDS and the hypothesis that there may be abnormalities in the ECM of the GI tract that could lead to disordered sensorimotor function, an intriguing possibility is that patients with EDS may present with a disorder with a clinical phenotype similar to that that is current termed and understood as IBS.

Future research strategies

Thus far, the proposal of the pathophysiological association between FGID and EDS, based on connective tissue aberrancies within the GI tract remains unproven. Our group is currently undertaking a series of prospective studies to further evaluate the putative associations between GI tract symptoms and EDS. Establishment of a positive association between FGID and EDS would lend further support to the hypothesis that the two disorders may share a similar underlying aetiology, based on abnormal connective tissue.

Conclusions

Hitherto, the GI manifestations of EDS have received little attention despite the observation that they represent a considerable symptom burden in sufferers. EDS may manifest at any level of the GI tract from the mouth to the anus. Central to its successful and efficacious treatment is physician education in the recognition of the disorder and its multisystem complications, especially with respect to the GI tract. For too long, the GI manifestation of EDS has been the realm of the case report, retrospective uncontrolled study and clinical anecdote. Further work is now urgently needed to objectively establish the epidemiology of the GI manifestations of EDS, as well as identifying molecular and genetic abnormalities that underlie the pathophysiology of this group of disorders of connective tissue.

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