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REVIEW

Association of mast-cell-related conditions with hypermobile syndromes: a review of the literature

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Abstract

Ehlers–Danlos syndrome (EDS) is a group of related connective tissue disorders consisting of 13 subtypes, each with its own unique phenotypic and genetic variation. The overlap of symptoms and multitude of EDS variations makes it difficult for patients to achieve a diagnosis early in the course of their disease. The most common form, hypermobile type EDS (hEDS) and its variant, hypermobile spectrum disorder (HSD), are correlated with rheumatologic and inflammatory conditions. Evidence is still needed to determine the pathophysiology of hEDS; however, the association among these conditions and their prevalence in hEDS/HSD may be explained through consideration of persistent chronic inflammation contributing to a disruption of the connective tissue. Aberrant mast cell activation has been shown to play a role in disruption of connective tissue integrity through activity of its mediators including histamine and tryptase which affects multiple organ systems resulting in mast cell activation disorders (MCAD). The overlap of findings associated with MCAD and the immune-mediated and rheumatologic conditions in patients with hEDS/HSD may provide an explanation for the relationship among these conditions and the presence of chronic inflammatory processes in these patients. It is clear that a multidisciplinary approach is required for the treatment of patients with EDS. However, it is also important for clinicians to consider the summarized symptoms and MCAD-associated characteristics in patients with multiple complaints as possible manifestations of connective tissue disorders, in order to potentially aid in establishing an early diagnosis of EDS.

Keywords Mast cell activation disorder · Mast cell · Joint hypermobility · Ehlers–danlos syndrome · Primary immunodeficiency disease · Allergy · Histamine · Tryptase · Immunology · Rheumatic disease · Musculoskeletal disease

Introduction

Ehlers–Danlos syndromes (EDS), a heterogenous group of connective tissue disorders (CTD), are characterized by joint hypermobility, skin hyperextensibility, and tissue fragility [1]. Of the 13 subtypes of EDS that have been described, hypermobile EDS (hEDS) is the most common, and as opposed to the twelve other EDS subtypes, hEDS lacks confirmatory laboratory/molecular tests [2]. hEDS and the hEDS variant, hypermobility spectrum disorder (HSD) are characteristically defined by the combination of the following three criteria:

1) Generalized joint hypermobility (Beighton score)
2) Combination of any two or more features including systemic manifestations, family history, or musculoskeletal complications and
3) The absence of exclusion criteria (Supplemental Tables 1,2,3) [1].

Common systemic features of hEDS include rheumatological manifestations, such as joint instability, arthralgia, myalgia, soft tissue injuries, and arthritis [3]. Additionally, recent studies have reported an increase in the prevalence of immune-mediated disorders such as rhinitis, asthma, urticaria, celiac disease, functional gastrointestinal disorders, as well as neuropathies in the hEDS/HSD population [4–16]. The relationship between immune-mediated disorders and hEDS/HSD is poorly understood. A potential link

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between hEDS/HSD and immune-mediated disorders may be explained by recurrent or chronic release of mast cell (MC)-derived factors. MCs have shown to contribute to barrier function and homeostasis within the connective tissue of multiple organ systems and are native to the epithelium of the gastrointestinal, urogenital and respiratory tracts, among others [17, 18]. While MCs are normally under tight regulation, aberrant immune activation of these cells results in mast cell activation disorders (MCAD) [17, 18]. Due to the intertwined relationship between MC and connective tissue, shared clinical features between MCAD and hEDS/HSD have been described in the literature [9, 19–21]. To that end, the objective of this review is to identify shared clinical features between EDS and MCAD- or MC-related conditions to establish a potential relationship. As both of these disorders are systemic conditions with multifactorial manifestations, understanding and recognizing the relationship between the two conditions may allow providers to identify and treat these cohorts of patients sooner.

Mast cells and mast cell activation disorders

MCs develop in the bone marrow and continue to mature at their site of residence in the connective tissue through the interaction of Kit tyrosine kinase receptor on MC surfaces with stem cell factor [18, 22]. While the exact mechanism of action of MC is out of the scope of this review, it is important to note that MC express a multitude of receptors such as high-affinity IgE and low-affinity IgG receptors, complement receptors, and toll-like receptors [17, 18, 22–24]. Upon the binding of these various receptors to their target, MCs release preformed granule mediators such as histamine, protease, as well as lipid mediators such as prostaglandins and leukotrienes [17, 18, 23, 24]. These mediators are able to carry out a variety of responses such as vasodilation, interactions with nerves, and facilitation of cellular chemotaxis [17, 23, 24].

While normally under tight molecular control, aberrant release of these preformed granules may result in MCAD. MCAD is characterized by recurrent episodes of the release of MC mediators which may occur in any organ system [18, 25]. Due to the various locations and receptors of MC, signs and symptoms of MCAD are diverse and may include irritable bowel symptoms; recurrent flushing, urticaria, and pruritus; cardiac arrhythmias and episodic hypotension; neuropsychiatric disorders; genitourinary conditions; rheumatological manifestations; and anaphylaxis [17, 26]. Mast cell activation syndrome (MCAS), a subtype of MCAD, should be considered in patients who experience recurrent or chronic episodes of MC activation in two or more organ systems, respond to treatment that combats MC-derived mediators or prevents MC degranulation, and have symptoms consistent with increased validated MC-derived mediators [27].

Irregular MC-mediated release may result from intrinsic defects including mutations in the c-kit gene or associated signaling pathways as well as multiplication of a MC specific protease subunit encoding alpha tryptase [17, 18]. Interestingly, factors external to the MC account for most MCAD [17]. In addition to the allergen-specific IgE driven diseases, there are immunologic and nonimmunologic syndromes that can drive MC activation. Recurrent or chronic release of MC-derived factors, including proinflammatory molecules, growth factors, and proteases, has been linked by several studies to heritable CTD like hEDS and HSD [9, 19, 21, 28]. The potential connection between hEDS/HSD and MC-related disorders may be explained by the presence of MC mediators, especially tryptase and histamine which have been found to promote proliferation of fibroblasts and production of collagen [28]. In 2014, it was found that familial hypertryptasemia may be associated with MCAS and was described in 9 families with an autosomal dominant inheritance pattern of elevated basal serum tryptase levels and MCAS. symptoms [22]. Furthermore, in 2016, the same group identified germline mutations in the gene that encodes alpha-tryptase, *TPSAB1* that led to increases in basal serum tryptase levels in 35 families presenting with MCAS-related complaints [29]. Of the total 96 patients identified with this mutation, 28% had joint hypermobility, a twofold increase when compared to incidence in the general population, thus indicating a possible correlation between hypermobile syndromes and MC-related disorders [29]. Another potential link may be explained in the reported triad of postural tachycardia syndrome (POTS), EDS, and MCAD, in which 46% of the population with the genetic mutation in *TPSAB1* exhibited orthostatic intolerance [29]. However, the connection among these three conditions has been debated in the literature [30].

MCAD-related disorders and hEDS/HSD

An association between EDS/HSD and MC-related disorders has been highlighted in the literature through prevalent findings of MC-related diseases in EDS/HSD patients (Fig. 1; Table 1) [9, 19–21]. A carefully obtained history in patients with the following described conditions and symptoms supporting MCAD- or MC-related etiology should be obtained in order to establish a potential EDS/HSD diagnosis.

Headaches

Headache has been shown to be prevalent in hEDS/HSD patients when compared to controls [20, 31–34]. In a study by Song et al., 67% of hEDS patients reported symptoms of

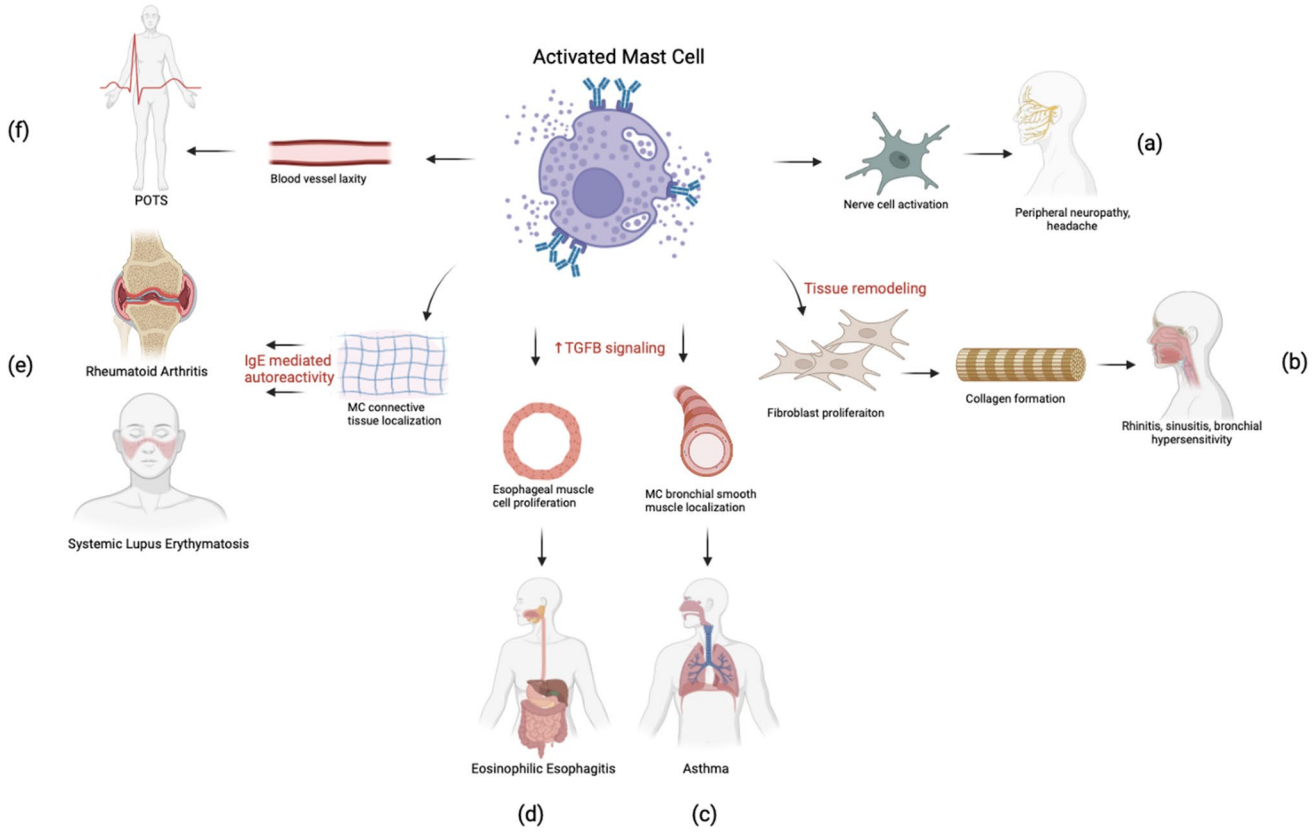

Fig. 1 Aberrant mast cell (MC) activation can produce inflammatory changes at the connective tissue level leading to dysfunction in multiple organ systems. In peripheral nerves, MC can localize to epineurium, perineurium, and endoneurium and release mediators which may activate nociceptors producing symptoms such as peripheral neuropathy and headache (**a**). MC-mediated upregulation of cytokines can lead to dysfunctional fibroblast proliferation in nasal and bronchial tissue leading to rhinitis and sinusitis (**b**). MC-induced TGFB upregulation and localization within bronchial smooth muscle cells can cause modification of matrix proteins of bronchial parenchyma contributing to tissue damage and Asthma (**c**). MC-induced TGFB upregulation in esophageal tissue can cause proliferation and smooth muscle contraction contributing to eosinophilic esophagitis symptoms (**d**). When MCs are localized to connective tissues, they can cause microenvironmental changes to the extracellular matrix, inducing IgE medicated autoreactivity and contributing to rheumatologic conditions such as rheumatoid arthritis and systemic lupus erythematosus (**e**). MC-induced changes may contribute to laxity within blood vessels, causing pooling of the blood in extremities, contributing to postural tachycardia syndrome (POTS) in which patients experience increase of heart rate with standing, a finding commonly associated with hEDS (**f**)

headache [20]. While the relationship between headaches and hEDS/HSD patients found in this study may be due to multifactorial etiologies associated with hEDS/HSD such as craniocervical junction instability, temporomandibular joint instability, and dysautonomia, MC-related diseases should be a consideration [20, 31–34]. Mediators of MC may activate the trigeminal pathway which, when prolonged, can cause intracranial headaches [35]. This may explain why Song et al. found that 95% of patients with both hEDS and MCAD also had headaches [20].

Peripheral neuropathy

Peripheral neuropathies have been associated with EDS/HSD [13–15]. In a study done in 2016, 95% of EDS patients reported neuropathic pain and 100% of patients showed a decrease in intraepidermal nerve fiber density [14]. In a later study, it was identified that of the 37 hEDS patients studied, 97% reported chronic pain, with neuropathic pain being the most common complaint [13]. Causes of peripheral neuropathy in hEDS/HSD have been explained by presence of ligament and capsular laxity resulting in abnormal pressure on peripheral nerves, or genetic factors involving deficiency of TNXB or collagen I, II, and V in the connective tissue of peripheral nerves [15, 36]. Nevertheless, MC-related disorders as an etiology of peripheral neuropathy in EDS patients cannot be ruled out. In peripheral nerves, MCs are located in the epineurium, perineurium, and endoneurium [37]. Chronic degranulation may result in nerve injury [37, 38]. Furthermore, MCs have been implicated in the activation of nociceptors in nerve endings [37, 38]. Future

Table 1 MCAD-related disorders in hEDS/HSD patients

Disorder	First author	Study type	Participants	Findings
Mast cell activation disorder	Szalewski (2019)	Retrospective case series	> 2 million patient charts at a university hospital	Significant increase in prevalence of idiopathic urticaria in EDS patients compared to random co-occurrence in the general population
	Song (2020)	Retrospective case series	98 EDS patients at a physical medicine and rehabilitation clinic	24% EDS patients had MCAS diagnosis
	Cheung (2015)	Retrospective case series	15 patients with diagnosis of POTS and EDS	66% of patients with POTS and EDS had symptoms suggestive of a mast cell disorder
	Luzgina (2011)	Prospective case–control	12 patients with phenotypical signs of connective tissue disorders and 16 patients without these signs	Patients with signs of connective tissue disorder had a higher density of chymase positive mast cells in their undamaged skin
Headaches	Malhotra (2020)	Retrospective case series	140 patients with hypermobility disorders	66% of patients with hypermobility disorders reported headache or neck pain; of those, migraine (83%) was the most common headache type
	Rombaut (2010)	Retrospective case series	72 hEDS patients compared to 69 patients with fibromyalgia and 65 patients with rheumatoid arthritis	32% hEDS patients reported headache, 76% FM reported headache, 1.6% RA patients reported headache
	Maeland (2011)	Questionnaire	250 EDS patients	48% EDS patients reported headache
	Puledda (2015)	Prospective case–control study	33 HSD/hEDS patients with migraines matched with 66 migraine controls	HSD/hEDS patients had significantly more frequent headache symptoms and earlier age of onset compared to controls with migraines
Peripheral neuropathies	Cazzato (2016)	Prospective case series	20 adults with HSD/hEDS	19 out of 20 patients reported neuropathic pain. All 20 patients had a decrease in intraepidermal nerve density
	Voermans (2009)	Prospective case series	40 EDS patients	85% had mild-to-moderate muscle weakness, 60% had reduction in vibration sense, 13% had axonal polyneuropathy
	Benistan (2019)	Prospective case series	37 hEDS patients	97% reported severe chronic pain with the most common type of pain being neuropathic
Urticaria	Szalewski (2019)	Retrospective case series	> 2 million patient charts at a university hospital	Significant increase in prevalence of idiopathic urticaria in EDS patients compared to random co-occurrence in the general population
	Greiwe (2018)	Case report	EDS patient	Pt. with EDS, MCAS, POTS presents with inducible urticaria
	Sachinvala (2018)	Case report	EDS patient	EDS patient with history of adrenergic urticaria successfully treated with omalizumab

Table 1 (continued)

Disorder	First author	Study type	Participants	Findings
Sinusitis	Ayres (1985)	Retrospective case series	20 EDS patients	25% EDS patients had recurrent sinusitis
	Zhang (2019)	Case Report	hEDS patient	hEDS patient with severe sinusitis
	Fouda (2000)	Prospective case–control	30 HSD patients with sinusitis and 10 controls with sinusitis	Tissue biopsies from middle meatus of patients with HSD showed increased density and abundant amount of collagen fibrils compared to controls on histology
Asthma	Morgan (2007)	Retrospective case series	126 HSD patients, 162 EDS patients, 221 healthy controls	Significant increased prevalence of asthmatic symptoms and atopy in HSD/EDS patients compared to controls
	Al-Rawi (2012)	Prospective case–control	100 patients with asthma and 100 controls	Joint hypermobility was found in 70.1% of patients with asthma and 29.9% of controls
Gastrointestinal disorders: Eosinophilic esophagitis	Traif (1992)	Case report	EDS patient	EDS patient with eosinophilic gastroenteritis
	Abonia (2013)	Retrospective case series	42 patients with eosinophilic esophagitis with a connective tissue disorder	Eightfold risk of eosinophilic esophagitis in patients with connective tissue disorder when compared to the general population
Gastrointestinal disorders: Celiac disease	Danese (2011)	Prospective case series	31 hEDS patients	16% of hEDS patients diagnosed with celiac disease
	Fikree (2015)	Prospective case–control	13 patients with primary diagnosis of celiac disease	30.8% prevalence of hEDS found in patients with celiac disease
Gastrointestinal disorders: Inflammatory bowel disease	Vounotrypidis (2009)	Prospective case–control	83 patients with irritable bowel disease and 67 healthy controls	Prevalence of hEDS found to be 12.2% in Crohn's disease and 3.6% in ulcerative colitis
	Fikree (2015)	Prospective case control	25 patients with Crohn's disease and 38 patients with ulcerative colitis	32% prevalence of HSD/EDS found in patients with Crohn's Disease and 21% prevalence found in ulcerative colitis
	Castori (2010)	Prospective case series	21 hEDS patients	Symptoms of IBD presented as abdominal pain in 61.9% of patients and constipation/diarrhea in 33.3% of patients

Table 1 (continued)

Disorder	First author	Study type	Participants	Findings
Urogynecologic conditions	Castori (2012)	Case series	82 post-puberal women with joint hypermobility	Dysmenorrhea (82.9%), menorrhagia (53.7%), irregular menses (46.3%), and vulvodynia (31.7%)
	Sorokin (1994)	Questionnaire	68 women with EDS	Recurrent anovulation (41.3%), recurrent vaginal infection (53%), abnormal cytologic smears (19%), irregular menses (28%), endometriosis (15.8%), vaginal dryness (25%)
	Hurst (2014)	Questionnaire	775 reproductive age women with EDS	44.1% infertility, 32.8% intermenstrual bleeding,; 32.9% heavy menstrual bleeding, 92.5% dysmenorrhea and 77% dyspareunia
	Hugon-Rodin (2016)	Questionnaire	386 women with hEDS	76% menorrhagia, 72% dysmenorrhea, 43% dyspareunia
Rheumatologic conditions	Ozlece (2015)	Case report	EDS patient	MS diagnosis was established in a patient with past history of EDS
	Vilsaar (2008)	Case series	4 MS patients	EDS diagnosis in 4 MS patients
	Sachinvala (2018)	Case study	EDS patient	MS diagnosis in patient with EDS
	Rodgers (2017)	Retrospective Case series	379 hEDS patients	97 patients (25.5%) found to have at least one rheumatologic condition
	Branch (1978)	Case report	EDS patient	EDS patient with systemic lupus erythematosus and myasthenia gravis
	Asherson (2006)	Case report	EDS patient	EDS patient with systemic lupus erythematous
	Wallman (2014)	Retrospective case series	109 patients suffering from autonomic dysfunction with at least one POTS symptom	18% of patients with POTS diagnosis met criteria for EDS
	Shaw (2019)	Questionnaire	4385 patients with POTS	25% of participants had diagnosis of EDS with 9% having a diagnosis of MCAS

Summary of studies demonstrating MCAD-related disorders seen in hEDS/HSD patients. Findings divided into: headache, peripheral neuropathies, urticaria, sinusitis, asthma, eosinophilic esophagitis, celiac disease, inflammatory bowel disease, urogynecologic conditions, rheumatologic conditions. Studies were obtained from literature review

studies establishing this association between MC-related disorders, peripheral neuropathies, and hEDS/HSD are warranted.

Urticaria/flushing/angioedema

Urticaria is a finding prevalent in patients with EDS when compared to the general population [9, 10]. In addition to basophils, MCs are one of the most commonly implicated inflammatory cells involved in urticaria [39]. Elevated levels of proinflammatory cytokines such as IL-33 promote the adhesion, maturation, and degranulation of MCs in chronic urticaria [40]. While previous studies by Greiwe and Szalewski et al. have established a connection between EDS and urticaria, the direct cause of this association has not been well established and it is therefore not unreasonable that this relationship could be explained by MC-related disorders.

Rhinitis/Sinusitis

EDS/HSD has been associated with rhinitis and/or sinusitis [4–6]. A previous study found an anatomic variation with increased density and quantity of collagen fibrils in EDS patients with sinusitis as compared to control patients with sinusitis [5]. MCs play a role in upregulation of chemokines/cytokines in fibroblasts and epithelial cells as well as expression of matrix metalloproteinases, which interact with extracellular matrix proteins and thus may play a role in the nasal and bronchial hyperresponsiveness and tissue remodeling found in EDS patients with sinusitis [41].

Asthma

Localization of MCs within the bronchial smooth muscle bundles in patients with asthma indicates an important role of MCs in the pathophysiology of this disease [42]. Unsurprisingly, studies have pointed to a relationship between asthma and hEDS/HSD. In one study, a questionnaire and clinical assessment was performed on 509 subjects (221 healthy controls, 126 HSD, 162 EDS). Asthma was significantly more prevalent among patients with EDS/HSD when compared to the control group (HSD: OR 2.7, 95% CI 1.4–4.1, $p = 0.002$; EDS: OR 3.1, 95% CI 1.8–5.2, $p < 0.001$) [7]. A smaller study followed 200 patients to determine prevalence of joint hypermobility in patients with asthma (100 asthma patients, 100 matched healthy controls). It was found that joint hypermobility was present in 70.1% of patients with asthma compared to only 29.9% in healthy controls [8]. Morgan et al. suggest that modifications of the matrix proteins in the lung parenchyma as a result of hEDS/HSD may alter the biomechanics, repair and remodeling responses following tissue damage leading to the development of asthma [7]. In patients with MC-related disorders, chronic tissue damage could be exacerbated by the aberrant release of MCs, increasing the likelihood of development of asthma. Though not a well-established connection, the relationship between asthma, MC-related disorders, and hEDS/HSD is plausible.

Gastrointestinal disorders

Several studies have demonstrated hEDS/HSD patients with eosinophilic esophagitis (EoE) [43, 44]. In a study by Abonia et al., the rate of EoE present in a hospital-based cohort of patients with CTD, including hEDS/HSD, was analyzed. It was found that there is an eightfold increase of risk of EoE in patients with CTD, and these patients may be at an increased risk for diffuse extraesophageal gastrointestinal diseases when compared to EoE patients without CTD [43]. While previously studies have focused on the role of eosinophils in the pathogenesis of EoE, recent studies have suggested that MCs have a role in the clinical manifestation of the disease [45]. Animal and cellular studies have shown that MCs can cause esophageal muscle cells to proliferate into a more contractile phenotype and that the mediators released by MCs can activate smooth muscle contraction, thus causing esophageal abnormalities [45]. Furthermore, Abonia et al. noted that TGFB signaling is often enhanced in patients with connective tissue diseases and that elevated TGFB levels in esophageal tissue of EoE patients are localized in both eosinophils and MC, thus explaining this relationship [43].

Recent studies have also shown key involvement of the innate immune system in the pathogenesis of celiac disease, evidenced by the increase in number of MC during the progression of this condition [11]. Celiac disease is an autoimmune disease involving the activation of ingested gluten by the enzyme tissue transglutaminase and its subsequent recognition by CD4 + T cells as a pathogen in the small intestine at the level of the epithelium [12]. Frossi et al. showed that activation of the innate immune system happens first before the induction of the gluten-specific T cell response. In addition to gluten exposure, genetic factors such as HLA-DQ2 and DQ8 haplotypes and environmental factors also play a role in the development of celiac disease [12]. A combination of these factors contributes to epithelial insult and leads to subsequent clinical manifestations such as diarrhea, anemia, and abdominal pain among others. Danese et al. found over a tenfold increase in prevalence of celiac disease in patients with hEDS/HSD. Another small study found that hEDS was likely to be diagnosed in 30% of patients who presented to a GI clinic with a new diagnosis of celiac disease [46]. Patients with celiac disease have been

shown to have increased antibody titers against collagen types I, III, V, and VI, potentially explaining this interrelationship between hEDS/HSD and celiac disease [47].

Elevated numbers of MC have been observed in patients with inflammatory bowel disease (IBD) as well [48]. Ulcerative colitis and Crohn's disease have also been implicated in the literature to affect patients with EDS. One study analyzing patients from a hospital in Greece found that the prevalence of hEDS in Crohn's disease was 12.2% and the prevalence of hEDS in ulcerative colitis was 3.6% [49]. Fikree also described a high prevalence of patients with EDS/HSD with Crohn disease and ulcerative colitis (32% and 21%, respectively) [46]. While the association of IBD and MC-related conditions is important to consider, another potential explanation between the association of hEDS/HSD and IBD may be due to the close proximity of connective tissue components to the muscularis propria and myenteric plexus in the GI tract, and thus, aberrant connective tissue dysfunction may be a possible cause for gastrointestinal diseases [50]. Other stem cell studies have shown that collagen is necessary for enteric neural progenitor cells to differentiate into neurons and glia cells, thus supporting the notion that the connective tissue is involved in the development of the enteric nervous system [51].

Urogynecologic conditions

Patients with hEDS have been identified via a questionnaire as having menstrual disturbances such as menorrhagia (32.9–76%) [52–55]. This may be due to increased MC activation due to the release of heparin which will contribute to increased prevalence of not only menorrhagia, but also dyspareunia and vaginitis [56]. It has been previously reported that diphenhydramine administered as a vaginal douche successfully reduced dysfunctional uterine bleeding in patients with MCAS not responsive to oral antihistamine treatment [57]. While these authors do not recommend this form of treatment, it does provide insight into the potential MC etiology of menorrhagia.

An additional survey of 1225 women with EDS found that 44.1% self-reported infertility [54]. Infertility could potentially be the result of anovulation, pelvic pain, and vaginal dryness. Pelvic pain such as interstitial cystitis and vulvodynia in particular may be associated with MCAS. In a study that looked at vulvar biopsies in patients with vulvodynia, > 60 MC/mm^2 (range, 40–120 MC) were found in subepithelial distribution surrounding the vestibular glands [57]. Majority were in a degranulated or activated state, which can lead to nociceptive and neuropathic pain over time [57].

Rheumatologic conditions

Kolkhir et al. discovered similarities between the pathogenesis of systemic lupus erythematosus (SLE) and chronic spontaneous urticaria, which both involve IgE-mediated autoreactivity brought on by MC [58]. Key involvement of MCs in multiple sclerosis (MS) and rheumatoid arthritis (RA) also has been demonstrated in separate studies [59, 60]. Multiple studies have found an association between MS and EDS [61–63]. In a study done in 2008, it was found that the prevalence of EDS was up to 11 times more frequent in patients with MS than in the general population [63]. Potential hypothesis elucidating the association of the two conditions implicates abnormalities of extracellular matrix proteins such as collagen in the venular walls of glial cells within the blood brain barrier [63]. These abnormalities or microenvironmental changes within the extracellular matrix may result in activation of metalloproteinases that can cause altered migration of immune cells in the central nervous system, thus resulting in MS [63]. Lastly, SLE and RA have been described in separate cases in the literature as being comorbid conditions to patients with EDS [64–66]. A retrospective analysis of patients with hEDS showed an association between hEDS and various rheumatologic conditions [65]. Patients with hEDS who had associated joint pain, joint laxity and arthralgia who received comprehensive rheumatologic evaluation were likely to be diagnosed with at least one rheumatologic condition [65]. Although the findings of this analysis suggest an association between rheumatologic conditions such as psoriasis, ankylosing spondylitis, and rheumatoid arthritis and hEDS, the mechanism underlying the association between one genetic disorder leading to increased risk of multiple rheumatologic conditions with varying etiologies is not yet established [65].

Postural tachycardia syndrome

POTS is defined as a multifactorial syndrome in which patients experience a recurrent increase in heart rate on standing without orthostatic hypotension [67]. It has been reported that hEDS is the most common disorder associated with POTS [68]. In one study done on the POTS population, it was found that 18% met the criteria for EDS [69]. Patients with hEDS may have vascular laxity which could lead to the pooling of blood in the lower extremities thus leading to POTS, which could be a potential explanation for this relationship [67]. Another potential explanation, however, could be the relationship between MC-related disorders, EDS, and POTS [28, 67]. Shibao et al. described a group of patients with POTS who also experienced MC-related symptoms such as flushing, shortness of breath, headache, lightheadedness, excessive diuresis, and gastrointestinal symptoms [70]. When comparing this group to patients with those without

MC-related symptoms and POTS as well as normal controls, it was found that this subgroup of patients had higher levels of urine methylhistamine [70]. Cheung et al. found that in a questionnaire given to patients with a diagnosis of both POTS and EDS, 66% participants reported MC symptoms [19]. In another questionnaire study, of the 4835 patients who were diagnosed with POTS, 25% were found to have a diagnosis of EDS and 9% were found to have been diagnosed with MCAS [71]. Because all three disorders are based on clinical diagnosis rather than quantitative studies, further work needs to be done to determine to what extent the association among this triad of conditions exists [30].

COVID-19

Recent studies highlighted overlapping symptoms between patients with previous COVID-19 and patients with EDS- or MC-related disorders. Similar to EDS- and MC-related disorders, COVID-19 is a multisystem disorder associated with extrapulmonary manifestations including thrombosis, arrhythmias, gastrointestinal symptoms, dermatologic, and neurologic complications [72]. Carfi et al. explored persistent symptoms in 87.4% of 143 patients after acute COVID-19 infection, in which the most commonly reported symptoms were fatigue, dyspnea, joint pain, and chest pain [73]. These symptoms have been commonly reported in patients with EDS/MC-related disorders due to the many associated conditions and complications as noted above. It is unclear at the moment whether COVID-19 symptoms are worsened by coexisting EDS, and risk of complications from COVID-19 differ based on the patient's presenting risk factors and other medical conditions not related to EDS. Theoharides published a study in 2020, exploring the role of MC in COVID-19 infection and found that MC may serve as hosts for SARS-CoV-2 by expressing angiotensin converting enzyme 2, an important receptor for SARS-CoV-2 [74]. Following stimulation of MC by SARS-CoV-2, MCs are able to rapidly secrete preformed granules as well as cytokines and chemokines 6–24 h later. MC-derived vasoactive mediators are then able to infiltrate multiple organs, including crossing the blood brain barrier leading to "COVID Brain Fog."[72] Interestingly, pharmacotherapy used in MC-related disorder patients has been found to be effective in mitigating the severity of the viral illness and preventing increase in post-COVID-19 chronic illnesses, bringing to light the importance of MC-targeted treatment in management of COVID-19 patients and maintenance of antihistamine therapy in MC-related disorder patients with COVID-19 infection [75–77]. Valent et al. also recommended that patients with mastocytosis receive vaccination for SARS-CoV-2 as a majority has been found to tolerate the vaccine well with the exception of few reports of adverse reactions [75]. Although there have been no published studies indicating whether EDS patients can undergo COVID-19 vaccination, those with a known history of anaphylaxis or severe reactions to vaccines should discuss risks and benefits of receiving the vaccine with their primary care doctor.

Treatment

There is no cure for MC-related disorders; therefore, MCAD and related conditions should be treated based on symptoms (Table 2). Therapy should always include targeted therapy at controlling MC mediator production and release such as antihistamines, omalizumab, or leukotriene antagonists [28]. In general, the comorbidity of hEDS/HSD is not known to affect the approach to treatment of MC-related conditions; however, corticosteroids should be avoided [28]. Patients should reduce exposure to any triggers as patients may have physical sensitivities (temperature, ultraviolet radiation, etc.), antigenic sensitivities (pollen, mold, etc.), and food intolerances [28]. Desensitization therapy can also be considered. An in-depth review of treatment modalities is beyond the scope of this review.

Discussion

The purpose of this review was to demonstrate the critical role that MC play in EDS by highlighting close associations of EDS with various MC-associated conditions and other immunologic disorders. Over the years, it has been purported that EDS has affected approximately 255 million

Table 2 MCAD treatments

Allergens	1. Avoidant measures (diet, environment) 2. Medications: histamine blockade 3. Desensitization (immunotherapy) 4. Traditional Chinese herbal therapy 5. Omalizumab 6. Anti-interleukin monoclonal antibodies
Autoimmune disorders	1. Anti-inflammatory agents 2. Immune globulin supplement 3. Traditional Chinese herbal therapy
Primary immune deficiency	1. Prophylactic antibodies 2. Immune globulin supplement
Connective tissue disorders	1. Physical therapy 2. Surgery 3. Vagal stimulation 4. Acupuncture 5. Oxygen therapy

There is no specific treatment regimen for MCAD disorders. Rather, treatment is supportive treatment of symptoms. Table adapted from Seneviratne et al

people worldwide [2]. Given the association of EDS with many different disorders as noted above, this finding reinforces the need for physicians from different specialties to closely communicate with each other to manage a patient with EDS. hEDS is the most common subtype that is found to be associated with these disorders, most likely due to a higher number of individuals diagnosed with this subtype compared to others. A recent abstract studied the prevalence of MCAS in hEDS patients and showed that nearly 1 in 3 patients with MCAS had comorbid diagnosis of hEDS in a sample size of 37,665 patients diagnosed with either MCAS or hEDS or both [76]. However, despite this close relationship, both hEDS and MCAS have no specific genetic marker yet discovered. Therefore, it is important for clinicians to diagnose and manage these conditions independently as a direct causation has not been found between hEDS and MCAS and unnecessary diagnostic testing and procedures can potentially harm patients with either disorder.

MCs are associated closely with the epithelium, contributing to its homeostasis by responding to and repairing tissue injury [74, 78–80]. MCs display an array of receptors which recognize molecules derived from tissue injury or inflammation through direct Toll-like receptors and indirect immunoglobulin receptors. Upon co-engagement of receptors that recognize alarmins and pathogens, MCs release mediators that result in innate and adaptive immune responses, regulate blood flow, and coordinate tissue repair [78]. Due to the disrupted collagen in patients with hEDS, where these MC reside, MCs act aberrantly, thus resulting in the syndrome of symptoms and disorders discussed in this review.

Relatedly, both EDS and MCAS have been redefined several times due to their wide range of systemic manifestations and subsequent need to categorize the condition into different subtypes based on specific clinical features. The 2017 EDS classification provided stricter criteria for EDS diagnosis and also illuminated the difference between hEDS and HSD. Kohn and Chang in 2020 stated that the classification of MCAD is still being refined today; however, in the article, they simplified the definitions of different types of MCAS, and proposed that primary MCAS due to mastocytosis is to be called mastocytosis, which in part would support the idea that concurrent MCAS in patients with hEDS is related simply to mastocytosis [30]. Defining specific criteria for these conditions have alleviated some of the concerns in misdiagnosing either condition as both rely on the symptoms for diagnosis.

Above, we note studies that showed that a significant percentage of individuals with a genetic mutation in *TPSAB1* had MCAS, EDS, or POTS, or a combination of the three. Weiler et al. emphasized that these types of findings do not mean that one condition is a cause of another and that clinicians should be wary about diagnosing and treating the three conditions as a group [18]. Kohn and Chang also emphasized that overlapping or shared symptoms cannot be the basis of establishing an association between hEDS and MCAD and that there must be a common pathologic mechanism that exists to define such a relationship [30]. As shown above, the symptoms experienced by patients with hEDS, MCAD, or both are nonspecific and not unique to any particular condition or EDS subtype. This idea that an association between two conditions cannot be created based on shared symptoms alone is also reflected when exploring the relationship between hEDS and any MC-related disorders noted above. Therefore, more studies need to be done with patients that are diagnosed with EDS and MCAD using the most recent criteria published. It is clear from our review, however, that MCs are a crucial component of the pathogenesis of EDS as there is increasing prevalence of MC-related disorders in EDS patients. As hEDS is the only EDS subtype without a genetic etiology, our findings highlight the need to discover the genetic marker of hEDS so that the exact mechanisms of how MCs are involved in hEDS/HSD can be further elucidated.

Limitations

There are several limitations in this review. First, most of the studies that we mentioned had small sample sizes, as we made an effort to focus on studies that included patients diagnosed with the most recent EDS criteria. As more individuals are being diagnosed with EDS using this criteria, our hope is that there will be many studies published soon with larger sample sizes. In addition, the patient population explored in these studies were mostly women; therefore, the findings noted in our review may not be entirely attributable to male EDS patients. Lastly, as noted above, the associations made between EDS- and MC-related conditions are based on studies that do not establish a direct causation and focus on overlapping symptoms. As genetic etiology is currently unknown for the most common type of EDS, hEDS, there is no paper that provides sufficient evidence for the relationship of hEDS with its associated conditions. Most of the studies also focused on hEDS only, which is a limitation in itself as the findings may not apply to other EDS subtypes.

Conclusion

This study demonstrates an association between the features of MCAD- or MC-related conditions and hEDS/HSD based on the current literature. While no current evidence exists that directly links the two conditions, this paper demonstrates that these multifactorial conditions have many overlapping features that should be further explored. Recognizing the shared clinical features of these conditions should

allow for earlier diagnosis and treatment of patients with hEDS/HSD and MC-related conditions.

Abbreviations EDS: Ehlers–Danlos Syndrome; HSD: Hypermobile spectrum disorder; hEDS: Hypermobile Ehlers–Danlos syndrome; MC: Mast cells; MCAD: Mast cell activation disorder; MCAS: Mast cell activation syndrome; IgE: Immunoglobulin E; POTS: Postural tachycardia syndrome; EoE: Eosinophilic esophagitis; CTD: Connective tissue disorders; IBD: Inflammatory bowel disease; SLE: Systemic lupus erythematosus; MS: Multiple sclerosis; RA: Rheumatoid arthritis

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Declarations

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