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The Relationship Between Hypermobile Ehlers-Danlos Syndrome (hEDS), Postural Orthostatic Tachycardia Syndrome (POTS), and Mast Cell Activation Syndrome (MCAS)

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Abstract
In recent years, an association between hypermobile Ehlers-Danlos syndrome (hEDS), mast cell activation syndrome (MCAS), and postural orthostatic tachycardia syndrome (POTS) has garnered attention and patients are increasingly presenting with this triad. However, a real relationship between these entities is unclear due to a lack of scientific validity. We conducted an extensive review of the literature using two different search strategies. A narrower strategy included 88 searches of various combinations of terms for each of the three conditions, yielding 19 unique papers. A broader search included 136 searches of various combinations of terms but included all forms of EDS and yielded 40 unique papers. Of these, only four and nine papers from the narrower and broader search strategies were original research articles. None of these papers resulted from a combination of the search terms for the three conditions. All three clinical entities are controversial in either existence or pathogenesis. MCAS is a poorly defined clinical entity, and many studies do not adhere to the proposed criteria when establishing the diagnosis. Patients previously diagnosed with EDS hypermobility type may not meet the new, stricter criteria for hEDS but may for a less severe hypermobility spectrum disorder (HSD). The pathophysiology of POTS is still unclear. An evidence-based, common pathophysiologic mechanism between any of the two, much less all three conditions, has yet to be described. Our review of the literature shows that current evidence is lacking on the existence of MCAS or hEDS as separate or significant clinical entities. Studies proposing a relationship between the three clinical entities are either biased or based on outdated criteria. The reason behind the purported association of these entities stems from an overlapping pool of vague, subjective symptoms, which is inadequate evidence to conclude that any such relationship exists.

Keywords Hypermobile Ehlers-Danlos syndrome · Mast cell activation syndrome · Mast cell disorder · Postural orthostatic tachycardia syndrome · Leaky gut · Fibromyalgia

Introduction

In the past several years, there have been increasing reports of patients having concurrent diagnoses of hypermobile Ehlers-Danlos syndrome (hEDS), mast cell activation syndrome (MCAS), and postural orthostatic tachycardia syndrome (POTS). Unlike other forms of Ehlers-Danlos syndrome, hypermobile Ehlers-Danlos syndrome has no known genetic mutation but is based solely on clinical criteria. Likewise, mast cell activation syndrome is not based on any objective test. Thus, EDS and MCAS are clinical diagnoses of exclusion, both with relatively new diagnostic criteria, and POTS is still a poorly understood disease. These disorders are all considered to be controversial in either existence or proposed pathophysiological mechanism.

In spite of the lack of evidence for the existence of these conditions, let alone their interrelationship, allergist/immunologists, geneticists, cardiologists, and other specialties have encountered an increasing number of patients who present with vague symptomatology and are convinced they are suffering from this triad. In the twenty-first century, medical information is not always disseminated in scientific or medical journals, but among internet sites of less-well repute. This study was undertaken to decipher if there is real evidence for

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these conditions and if there is indeed a relationship. Furthermore, despite the increasing number of patients who present with a diagnosis, valid or not, of all three conditions, it is difficult to come up with a plausible mechanistic reason as to why they would be related. A review of the literature is herewith examined to establish the strongest link among these three poorly defined conditions.

The introduction of the idea of mast cell activation syndrome has attracted the attention of many patients who have a vague constellation of symptoms with no discernable diagnosis. Symptoms vary from patient to patient and range from neurological symptoms, such as headache, to constitutional or psychological problems, including fatigue, foggy brain, loss of memory, and difficulty concentrating, to abdominal symptoms such as abdominal pain, bloating, and diarrhea and may involve skin related symptoms or signs such as pruritus, flushing, or urticaria. While we know that mediators released by mast cells can lead to some of these symptoms, this is only one of many reasons why an individual may present with any combination of these symptoms. Mast cell activation syndrome is an attractive diagnosis because there are no objective tests for it, and because we have limited knowledge of the pathophysiology behind the disease. It is difficult to prove, or disprove, but it provides an answer, albeit not necessarily a correct answer. For patients who have been suffering for years with these complaints searching for a reason for their ailments, mast cell activation syndrome is a welcome resolution. It is difficult to dispel the notion once it has been adopted by patients, even in the absence of any objective tests or data.

Ehlers-Danlos Syndrome, with a Focus on Hypermobile EDS

History

Ehlers-Danlos syndrome (EDS) is a cluster of inherited connective tissue disorders that shares a variety of common features, most notably hyperextensibility of the skin, hypermobility of the joints and fragility of the tissue. Multiple individuals with features associated with EDS have been described throughout history. The earliest account was in 400 BC, when Hippocrates described nomad warriors who were unable to use their weapons due to hyperlaxity of their shoulder and elbow joints [1]. Tschernogobow first described a disease characterized by skin fragility and hypermotility of joints in 1892. The syndrome was named in 1936 after two dermatologists who further characterized the disease, Edvard Lauritz Ehlers and Henri-Alexandre Danlos. As time progressed, more individuals were chronicled with similar features. In 1949, after reviewing multiple pedigrees of this syndrome, Johnson and Falls suggested that EDS was an autosomal dominant trait. In 1955, Jansen posited that EDS was the result of a genetic defect of collagen [2].

Classification

The classification of EDS began in the late 1960s and is still being refined today. The first attempt to classify this syndrome in 1988 proposed nine subtypes of EDS [2]. The next classification, established in 1998, was the Villefranche Nosology, which included six major subtypes and has been used extensively over the past two decades for the diagnosis of EDS. This classification considered clinical symptoms, known genetic defect, mode of inheritance, and a set of major and minor criteria. The subtypes were given Roman numerals and a descriptor that represented the key feature of the subtype [3].

The most recent and current classification, established in 2017 by the International EDS Consortium, is based on the Villefranche Nosology and recognizes 13 subtypes of EDS. This classification retains the same subtypes and descriptors as the Villefranche Nosology, but now includes new subtypes that have been recognized over the past two decades. Major and minor diagnostic criteria are included in the new classification, but a definitive diagnosis of an EDS subtype can only be obtained with molecular confirmation of a defect in the respective gene (with the exception of the hypermobile type). The new 2017 classification is depicted in Table 1. In addition to the clinical classification, another type of classification was proposed in the same consensus paper, which is based on the pathogenetic mechanisms of each subtype. This classification separates the subtypes into six groups (lettered A through F), each of which are believed to share a common pathogenic pathway based on which genes are affected. An additional "unresolved" group includes hypermobile EDS, for which there has not been a genetic defect identified. Table 1 includes information regarding the pathogenetic grouping of each subtype of EDS. A 2017 paper by Malfait et al. contains complete classification information of the remaining EDS subtypes [4].

Epidemiology

The prevalence of Ehlers-Danlos syndrome (all types) has been estimated to be at a minimum of 1 in 5000 individuals [5]. The prevalence of the different subtypes of EDS is based on the Villefranche Nosology, as this is the only data that has been reported thus far. According to this classification, hypermobility type EDS (Type III) is purported to be the most common, and believed to comprise up to 80–90% of all EDS patients [6]. This is followed by the classical type (Types I and II) and the vascular type (Type IV). The remaining types in the Villefranche Nosology, kyphoscoliosis, arthrochalasia and dermatosparaxis type, are considered to be much rarer than the first three mentioned [3, 7].

EDS has been known to affect both males and females equally. However, hypermobile type EDS seems to preferentially affect females. In a cohort of 38 patients with hypermobile EDS, 34 females and four males were affected.

Table 1 2017 Clinical classification of the Ehlers-Danlos syndromes, with pathogenetic regrouping. Adapted from Malfait et al. [4]

2017 Clinical subtype and abbreviation	IP	Gene(s) implicated	Protein(s) implicated	Regrouping according to pathogenetic mechanisms
Classical EDS (cEDS)	AD	Major: COL5A1 Rare: COL1A1	Type V collagen Type I collagen	Group A: defects in collagen primary structure and processing
Classical-like EDS (clEDS)	AR	TNXB	Tenascin XB	Group C: defects in structure and function of myomatrix, the interface between muscle and ECM
Cardiac-valvular (cvEDS)	AR	COL1A2	Type I collagen	Group A: defects in collagen primary structure and processing
Vascular EDS (vEDS)	AD	Major: COL3A1 Rare: COL1A1	Type III collagen Type I collagen	Group A: defects in collagen primary structure and processing
Hypermobile EDS (hEDS)	AD	Unknown	Unknown	Unresolved
Arthrochalasia EDS (aEDS)	AD	COL1A1 COL1A2	Type I collagen	Group A: defects in collagen primary structure and processing
Dermatosparaxis EDS (eEDS)	AR	ADAMTS2	ADAMTS-2	Group A: defects in collagen primary structure and processing
Kyphoscoliotic EDS (kEDS)	AR	PLOD1 FKBP14	LH1 FKBP22	Group B: defects in collagen folding and cross-linking
Brittle cornea syndrome (BCS)	AR	ZNF469 PRDM5	ZNF469 PRDM5	Group F: disorders of intracellular processes
Spondylodysplastic EDS (spEDS)	AR	B4GALT7 B3GALT6 SLC39A13	β4GalT7 β3GalT6 ZIP13	Group D: defects in glycosaminoglycan biosynthesis Group F: disorders of intracellular processes
Musculocontractural EDS (mcEDS)	AR	CHST14 DSE	D4ST1 DSE	Group D: defects in glycosaminoglycan biosynthesis
Myopathic EDS (mEDS)	AR or AD	COL12A1	Type XII collagen	Group C: defects in structure and function of myomatrix, the interface between muscle and ECM
Periodontal EDS (pEDS)	AD	C1R C1S	C1r C1s	Group E: defects in complement pathway

IP inheritance pattern, *AD* autosomal dominant, *AR* autosomal recessive, *NMD* non-sense-mediated mRNA decay

13 family members were physically examined as well, and nine females and four males were found to be affected by hEDS. The total percentages were 84% females and 16% males, representing a ratio in favor of females [8].

Pathogenesis and Mechanisms

The pathogenesis and mechanisms behind most of the EDS subtypes have been characterized and are fairly well understood. The 2017 guidelines for classification and diagnosis of EDS includes an entire new regrouping of the subtypes based on implicated genes, affected proteins and pathways that lead to each subtype. However, a gene implicated in hypermobile EDS has still not been identified.

Hypermobile EDS (hEDS) is known to be inherited in an autosomal dominant fashion [9]. There have been a few cases and studies that have pointed to certain genes as being responsible for hEDS, yet the evidence has not been substantiated. For example, mutations in the gene coding for tenascin X (TNXB), which normally functions as an extracellular matrix protein, have been suggested to play a role in the genetics of hEDS. In a small number of cases, there seemed to be a haploinsufficiency of tenascin X (TNXB), but it was only found to be partially penetrant in females, and not at all in males [10]. Following this, a missense variant of TNXB was shown to be associated with an hEDS phenotype in 10 patients from seven families [11]. However, the deficiencies in TNXB do not account for a sizeable proportion of patients affected by hEDS [6]. Among these studies are also case reports of multiple other gene mutations that are linked to hEDS, for example, the COL3A1 [12] and LZTS1 [13] genes. However, these reports have not been substantiated by subsequent data or studies.

Therefore, due to the lack of a known genetic defect in patients with hEDS, we can only speculate on the mechanisms behind its pathogenesis. Currently, many believe that hEDS is a result of multigene heterogeneity [6]. The new and stricter diagnostic criteria in the 2017 classification were implemented in hopes of reducing heterogeneity in the hEDS population in order to find a genetic link [4].

Clinical Presentation

The multiple subtypes of Ehlers-Danlos syndromes each share common main traits, which are expressed differently across the subtypes. Skin hyperextensibility is defined as unusually

easy stretching of the skin that snaps back into place after release. Joint hypermobility is usually generalized and is characterized by the joints having a greater than normal range of motion. Tissue fragility can manifest as a variety of symptoms, such as easy bruising, generalized weakness, and hernias. Although each subtype shares varying degrees of these main traits, each type is differentiated depending on additional signs and symptoms [7].

We focus here on the clinical presentation of hypermobile EDS (hEDS), which can be highly variable between patients, dependent on age and gender. In 2010, three disease phases of hEDS were proposed, consisting of a "hypermobility" phase, a "pain" phase, and a "stiffness" phase, temporally separated throughout a patient's lifespan. These phases were based on a pilot study of 21 patients [14] and then supported by further observations of disease phases in other studies of patients with hEDS [15–17]. The hypermobility phase is present in the beginning of life and is characterized by exaggerated flexibility and a proneness to joint subluxation and dislocation. The pain phase begins between the second and fourth decade of life and is characterized by generalized musculoskeletal pain, as well as fatigue. The final "stiffness" phase presents later in life and is characterized by reduction of joint mobility, due to a variety of factors such as age, fatigue, and pain [6]. Multiple other symptoms are interspersed between these phases.

Symptomatic joint hypermobility can present at any age and is assessed using the Beighton score (discussed in "Diagnostic Criteria"). This symptom is not specific to hEDS, and therefore, it is important to consider other etiologies of joint hypermobility. Two commonly recognizable patterns of joint hypermobility presentation are either (1) a limited number of painful/unstable joints, with common subluxations/dislocations or (2) generalized musculoskeletal pain [6].

Skin hyperextensibility and tissue fragility are closely linked in hEDS. The skin is more hyperextensible than normal skin, yet not to the extreme degree as the other subtypes of EDS (extensibility > 2.0 cm is suggestive of other subtypes of EDS [4]). Therefore, critical examination of the skin is necessary when evaluating for the presence of the hyperextensibility criteria in patients with hEDS. The skin in hEDS patients has also been described as smooth and velvety, compared to normal patients. It has also been described as semi-transparent, yet not to the extent of vascular EDS. Patients with hEDS also have skin that is more fragile than normal skin, but again, not to the extent of other subtypes of EDS. Examples of skin fragility include easy bruising, poor wound healing, atrophic scarring, and striae atrophicae. However, these examples of fragility are not as extreme as those in other subtypes of EDS, such as classical EDS [6].

The pathogenesis of pain in hEDS is poorly understood, yet pain remains an important and common symptom in these patients. Proposed mechanisms of chronic pain include nociceptive pain, neuropathic pain, impaired proprioception, muscle weakness, and increased pain sensitization [16]. Several etiologies of pain have been suggested, such as spasms of connective tissue, nerve entrapment, osteoarthritis, and systemic or regional pain syndromes [6].

Fatigue is also a major complaint of patients with hEDS, with many patients meeting diagnostic criteria for chronic fatigue syndrome [18]. In a way, fibromyalgia, itself a condition that presents with vague symptomatology that cannot be objectively defined, is the framework for EDS and even POTS or MCAS. None of the conditions have any biomarker or objective test that can be used for diagnosis. For this reason, fibromyalgia has been called the "invisible" disease, even though it affects up to 2–4% of people with a significant female predominance. Patients experience physical fatigue, which can contribute to disability and increased risk for injury, as well as mental fatigue, which can affect cognition, mood, and quality of life [6]. It should be noted that we are not stating that all diseases must have a measureable laboratory parameter in order for it to be real. But in the absence of such an objective measurement, the clinical presentation must be clearly defined by stringent criteria, a requirement that either does not exist or is not often observed when making diagnoses of these vague conditions.

Patients with hEDS frequently complain of gastrointestinal symptoms, such as GERD, heartburn, bloating, recurrent abdominal pain, IBS, constipation, nausea, and diarrhea [19]. Definitive associations between hEDS and gastrointestinal symptoms were summarized in a 2017 review paper of multiple studies. The authors of this paper concluded that there is substantial evidence of this association for there to be gastrointestinal criteria included in future diagnostic criteria of EDS [20].

Autonomic dysfunction has also been posited to play a role in the clinical presentation of hEDS. Symptoms such as hypotension, orthostatic intolerance, palpitations, fatigue, exercise intolerance, dizziness, memory, and concentration problems can be explained by cardiovascular dysautonomia [6]. This will be discussed in more detail later, in its potential relationship to POTS and MCAS.

Multiple other symptoms have been described, such as sleep disturbance, urinary symptoms, pregnancy and childbirth issues, gynecologic issues, spinal issues, headaches, psychiatric issues, and temporomandibular joint and dental issues [6]. However, these symptoms have been described mostly under the broad grouping of EDS and are therefore not specific enough to be included in the scope of this review.

Diagnostic Criteria

Unlike the rest of the EDS subtypes, hypermobile EDS (hEDS) remains a clinical diagnosis, as there is no identifiable genetic defect that can be tested for. There is a substantial amount of overlap in symptoms between hEDS, joint hypermobility syndrome (JHS), and a newly established group of hypermobility spectrum disorders [21]. Therefore, diagnostic

criteria for hEDS must be strictly followed to prevent an incorrect or missed diagnosis. The 2017 classification for EDS identifies three criteria to be used in the diagnosis of hEDS. All three criteria must be met simultaneously. The criteria described here and summarized in Table 2 are adapted from Malfait et al. [4]. For comparison, the former Villefranche nosology diagnostic criteria for EDS hypermobility type are summarized in Table 3.

Criterion 1 The first criterion is generalized joint hypermobility (GJH). The current standard for measuring GJH is the Beighton score, portrayed in Table 4 [22, 23]. Unlike the Villefranche Nosology, the 2017 guidelines for Beighton scores take into account age-dependent joint mobility changes. As opposed to the former requirement of a Beighton score ≥5 for any patient [3], now a score of ≥6 for prepubescent children and adolescents, ≥5 for post-pubescent males and females up to age 50, and ≥4 for adults over age 50 is required to meet the criteria for GJH according to the new classification. The new criteria also take into account acquired joint mobility issues, such as injuries and surgeries, by incorporating Grahame and Hakim's Five-Point Questionnaire, portrayed in Table 5 [24]. With these updated criteria, if the Beighton score is one point under the requirement and the Five-Point Questionnaire is positive (2 positive items), a patient can be still be diagnosed with GJH [4].

Table 2 2017 Diagnostic criteria for hypermobile EDS. Adapted from Malfait et al. [4]

<table>
<tr><td colspan="4">Criteria: All 3 must be met</td></tr>
<tr><td colspan="2">CRITERION 1: GJH
Must meet Beighton Score for age</td><td colspan="2">CRITERION 2: At least 2 features must be present</td></tr>
<tr><td>Age</td><td>Beighton Score (see Table 3)</td><td rowspan="4">Feature A: Systemic manifestations of CTD (need ≥5)
1. Unusually soft/velvety skin
2. Mild skin hyperextensibility
3. Unexplained striae distensae/rubrae
4. Bilateral piezogenic papules of heel
5. Recurrent/multiple abdominal hernia
6. Atrophic scaring in ≥2 sites
7. Pelvic floor, rectal, and/or uterine prolapse in children, men or nulliparous women
8. Dental crowding and high or narrow palate
9. Arachnodactyly
10. Arm span-to-height ≥1.05
11. Mitral valve prolapse
12. Aortic root dilatation with Z-score > +2</td><td rowspan="4">Feature B: Family history (1 or more first degree relatives must meet criteria)

Feature C: MSK Complications (need ≥1)
1. MSK pain in ≥2 limbs, recurring daily for ≥3 months
2. Chronic widespread pain for ≥3 months
3. Recurrent joint dislocations or frank joint instability, in the absence of trauma (a or b)
a. ≥3 atraumatic dislocations in same joint or ≥2 more atraumatic dislocations in two difference joints occurring at different times
b. Medical confirmation of joint instability at two or more sites not related to trauma</td></tr>
<tr><td>Prepubescent or adolescent</td><td>≥6</td></tr>
<tr><td>Pubescent up until age 50</td><td>≥5</td></tr>
<tr><td>Over age 50</td><td>≥4</td></tr>
<tr><td>Patients with AJLs</td><td>BS 1 point under age requirements AND a positive 5PQ (see Table 4)</td></tr>
<tr><td colspan="4">CRITERION 3: All 3 prerequisites must be met</td></tr>
<tr><td colspan="4">1. Absence of unusual skin fragility.
2. Exclusion of other heritable and acquired connective tissue disorders. In patients with an acquired connective tissue disorder, additional diagnosis of hEDS requires meeting both Features A and B of Criterion 2. Feature C of Criterion 2 cannot be counted in this situation.
3. Exclusion of alternative diagnoses that may also include joint hypermobility by means of hypotonia and/or connective tissue laxity.</td></tr>
</table>

GJH generalized joint hypermobility, *AJL* acquired joint limitations, *BS* Beighton Score, *5PQ* Five-Point Questionnaire, *CTD* connective tissue disorder, *MSK* musculoskeletal, *hEDS* hypermobile EDS

Table 3 1997 Villefranche diagnostic criteria for EDS hypermobility type. Adapted from Beighton et al. [3]

Criteria	
Major criteria	Generalized joint hypermobility
	Skin involvement (hyperextensibility and/or smooth, velvety skin)
Minor criteria	Recurring joint dislocations
	Chronic joint/limb pain
	Positive family history

Criterion 2 The second criterion consists of three features (lettered A through C), and two must be positive for the criterion to be met.

Feature A is a list of systemic manifestations of connective tissue disorders, five of which must be present to be considered a positive feature. The following are directly from the 2017 classification paper [4]:

1. Unusually soft or velvety skin
2. Mild skin hyperextensibility
3. Unexplained striae such as striae distensae or rubrae at the back, groins, thighs, breasts, and/or abdomen in adolescents, men, or prepubertal women without a signification gain or loss of body fat or weight
4. Bilateral piezogenic papules of the heel
5. Recurrent or multiple abdominal hernia(s)
6. Atrophic scarring involving at least two sites and without the formation of truly papyraceous and/or hemosideric scars as seen in classical EDS
7. Pelvic floor, rectal, and/or uterine prolapse in children, men, or nulliparous women without a history of morbid obesity or other known predisposing medical condition [4]
8. Dental crowding and high or narrow palate
9. Arachnodactyly, as defined in one or more of the following: (i) positive wrist sign (Steinberg sign) on both sides and (ii) positive thumb sign (Walker sign) on both sides
10. Arm span-to-height ≥ 1.05

Table 4 Beighton Hypermobility Score. Adapted from Beighton et al. [22]

Task:
Passively dorsiflex 5th finger beyond 90°
Passively place thumb adjacent to anterior aspect of forearm
Hyperextend elbow joint beyond 10°
Hyperextend knee joint beyond 10°
Lay palms flat on the floor without bending the knees
Key: 1 point for the ability to perform each task (1 point per side of body, when applicable).

Table 5 Five-Point Questionnaire for identifying hypermobility. Adapted from Hakim and Grahame [24]

Questions:
1. Can you now (or could you ever) place your hands flat on the floor without bending your knees?
2. Can you now (or could you ever) bend your thumb to touch your forearm?
3. As a child, did you amuse your friends by contorting your body into strange shapes, or could you do the splits?
4. As a child or teenager, did your shoulder or knee cap dislocate on more than one occasion?
5. Do you consider yourself double jointed?
Key: Two or more "yes" answers suggests joint hypermobility.

11. Mitral valve prolapse (MVP) mild or greater based on strict echocardiographic criteria
12. Aortic root dilatation with *Z*-score greater than + 2

Feature B is considered positive if there is a family history of hEDS, as it is an autosomal dominant syndrome. At least one first-degree relative must independently meet the criteria for hEDS.

Feature C is a list of musculoskeletal complications, one of which must be present to be considered a positive feature. The following are directly from the 2017 classification paper [4]:

1. Musculoskeletal pain in two or more limbs, recurring daily for at least three months
2. Chronic, widespread pain for ≥ 3 months
3. Recurrent joint dislocations or frank joint instability, in the absence of trauma (a or b)
   a. Three or more atraumatic dislocations in the same joint or two or more atraumatic dislocations in two different joints occurring at different times
   b. Medical confirmation of joint instability at two or more sites not related to trauma

Criterion 3 The third criterion is a list of prerequisites, all of which must be present for the criterion to be met. The following are directly from the 2017 classification paper [4]:

1. Absence of unusual skin fragility, which should prompt consideration of other types of EDS
2. Exclusion of other heritable and acquired connective tissue disorders, including autoimmune rheumatologic conditions. In patients with an acquired connective tissue disorder (e.g., lupus, rheumatoid arthritis), additional diagnosis of hEDS requires meeting both features A and B of criterion 2. Feature C of criterion 2 (chronic pain and/or

instability) cannot be counted towards a diagnosis of hEDS in this situation

3. Exclusion of alternative diagnoses that may also include joint hypermobility by means of hypotonia and/or connective tissue laxity. Alternative diagnoses and diagnostic categories include, but are not limited to, neuromuscular disorders, other hereditary connective tissue disorders, and skeletal dysplasia. Exclusion of these considerations may be based upon history, physical examination, and/or molecular genetic testing, as indication

Treatment

The treatment of patients with hypermobile EDS (hEDS) is centered on treating the symptoms and complications. Acute/emergency complications can include joint dislocations and acute pain episodes, and chronic complications can include fatigue, pain, and neuropsychiatric issues. Because these complications are vast and varied, coordination of care should be multidisciplinary [6].

Studies on the management of chronic pain in hEDS patients are lacking in number and substantial evidence [25]. Current methods on managing pain are similar to ones used in the general population [6, 25]. These center on prophylaxis of pain, treating the acute cause of pain and minimizing the sensation of pain. Physical therapy, exercise, and rehabilitation have been used in the prophylaxis of pain by improving joint stability and preventing muscle spasm [6]. In addition to physical therapies, cognitive behavioral therapy has also been utilized to help patients come to terms with chronic, intractable pain [25]. Pharmacological therapies have also been utilized in the management of pain in hEDS patients and follow the same guidelines as patients in the normal population. Included in these are non-steroidal antiinflammatory drugs (NSAIDS), acetaminophen, topical analgesics, muscle relaxants, and opioids. For more details, we refer to Chopra et al. [25].

The treatment of fatigue in hEDS is difficult, as there have been no pharmacological agents that have been shown to work. Management focuses predominantly on lifestyle changes, after ruling out other contributing causes of fatigue. Lifestyle changes include sleep management, pacing, relaxation techniques, and graded exercise therapy [26]. Measurement of the efficacy of these therapies is difficult, as fatigue is a subjective symptom.

Treating cardiovascular dysautonomic dysfunction, such as orthostatic intolerance, orthostatic hypotension, or postural orthostatic tachycardia syndrome, should start with non-pharmacologic interventions. These include minimizing triggers of symptoms, increasing dietary salt intake, using compression garments, and utilizing graded exercise therapy. Pharmacologic interventions include drugs that induce volume expansion (fludrocortisone), vasoconstriction (midodrine), and modulators of autonomic tone (beta-blockers) [27].

Lastly, it is important to treat the neuropsychiatric symptoms of patients with hEDS, because it is a chronic condition with no known cure. Cognitive behavioral therapy has been shown to be effective in a pilot study of 12 women with hypermobility EDS [28].

Postural Orthostatic Tachycardia Syndrome

History

Postural orthostatic tachycardia syndrome (POTS) is an orthostatic intolerance syndrome characterized by tachycardia in the absence of hypotension which results when assuming a standing position [29]. The term "POTS" was given to this syndrome in 1993 by Dr. Low at the Mayo Clinic [30]. Prior to the current nomenclature, POTS had many different names, including DaCosta's syndrome, soldiers heart, and the effort syndrome, neurocirculatory asthenia, and mitral valve prolapse syndrome [29, 31]. DaCosta first characterized a syndrome of palpitations, chest pain, cardiac uneasiness, headache, dimness of vision, and giddiness. Subsequently, more physicians began to describe similar syndromes and the nomenclature evolved [31]. Since then, researchers have refined their definition of POTS (discussed in the diagnostic criteria section), and it is now characterized as a syndrome of orthostatic intolerance.

Orthostatic intolerance is the development of symptoms when standing up, which are relieved when assuming a supine position. These symptoms can include syncope/presyncope, lightheadedness, fatigue, headache, changes in blood pressure, sweating, tremulousness, and nausea. POTS is a type of chronic orthostatic intolerance, characterized by the classic symptoms and excessive orthostatic tachycardia [32].

Epidemiology

The prevalence of postural orthostatic tachycardia syndrome is not known; however, it is estimated that POTS affects between over 500,000 and up to three million individuals in the USA [33–35]. Of these individuals, a strong female predominance has been noted. Multiple studies have concluded that the majority of POTS patients are female (80–85%) and are of child-bearing age (13–50 years) [36, 37].

Pathogenesis and Mechanisms

Despite the explosion of research on the etiology of POTS in the last two decades, its pathogenesis is still poorly understood. A variety of theories on the mechanism exist, but none have garnered substantial amounts of evidence. More recently,

the school of thought has moved towards the belief that the orthostatic tachycardia in POTS is the final pathway shared by multiple pathophysiological processes [38].

Before delving into the various theories behind the pathogenesis of POTS, it is valuable to explore the normal physiology of upright posture. When rising from a supine to standing position, approximately 500–1000 ml of blood volume shifts from the thorax to the lower abdomen and extremities [39]. Concurrently, 10–25% of plasma volume diffuses out of the vessels and into the interstitial space. The loss of volume in the vessels results in a temporary delay in cardiac filling and decrease in blood pressure. The decrease in blood pressure is detected in the baroreceptors of the carotid sinus and aortic arch, which unload and alter autonomic nervous system activity. Parasympathetic activity is downregulated and sympathetic activity is upregulated, resulting in an increased heart rate and vasoconstriction. Normal hemodynamic measurements of this compensatory mechanism are a heart rate increase of 10–20 bpm, a minimal change in systolic blood pressure, and an increase of approximately 5 mmHg in diastolic blood pressure [38, 40]. The goal of this normal compensatory reflex pathway is to maintain hemodynamics when changing from a supine to standing position. If, by some pathophysiological process, the reflex malfunctions or fails, orthostatic hypotension or tachycardia may result.

We now shift to the main proposed pathophysiological processes behind POTS symptoms. It is important to recognize that some authors have given subsets of patients, a "subtype" of POTS that is based on the profile of their symptoms and the believed mechanism behind their syndrome. However, it has been shown that there is much overlap between different subtypes of POTS, and there are no accepted criteria for each subtype. Therefore, these subtypes can be misleading and inaccurate [38].

The first possible pathophysiologic mechanism is partial sympathetic neuropathy, for which the "neuropathic" subtype of POTS is named. Some POTS patients have been found to have partial sympathetic denervation and an abnormal norepinephrine response in the lower extremities [41–43]. It has been suggested that this results in inadequate vasoconstriction, venous pooling in the legs, and compensatory sympathetic activation, which results in an increased heart rate.

Next is the hyperadrenergic state mechanism, for which the "hyperadrenergic" subtype of POTS is named. This theory is based on studies that show some POTS patients have elevated levels of plasma norepinephrine, secondary to partial dysautonomia or hypovolemia, or more rarely, excess sympathetic release. These patients have been shown to have plasma levels of norepinephrine of over 600 pg/mL while standing, which activates the sympathetic nervous system and leads to symptoms of POTS [36, 40, 44].

The genetic pathophysiologic mechanism stems from a deficiency in the presynaptic norepinephrine reuptake transporter (NET), which results in decreased norepinephrine clearance and prolonged sympathetic activation. Evidence for this theory consists of a handful of POTS patients and families that were found to have NET mutations [45, 46] or abnormal NET expression [47–49]. Interestingly, depression, attention deficit disorder, and fibromyalgia medications that affect NET transporters produce orthostatic tachycardia in non-POTS patients [50] and also exacerbate this symptom in POTS patients [51].

The "hypovolemic" subtype of POTS is named after the hypovolemia theory. The hypovolemia theory is based on a small study that showed POTS patients to have about a 13% deficit in blood volume compared to control patients, as well as an unchanged plasma renin activity and low aldosterone activity in response to low blood volume [52]. The persistence of hypovolemia is thought to contribute to the compensatory response of tachycardia to maintain blood pressure.

Many POTS patients have been found to have increased levels of deconditioning and poor exercise tolerance [53]. The deconditioning theory of POTS states that POTS patients respond to orthostatic stress in similar ways to patients with deconditioning, including tachycardia [38]. However, this is only a correlation, and it is unclear if POTS is a response to deconditioning, or if deconditioning is a result of inactivity due to symptoms of POTS.

These main theories and their convergence on the common pathway of POTS symptoms are depicted in Fig. 1, which is partially adapted from Arnold et al. [38].

In light of these multiple pathogenic theories, we refer to a recent systematic review article by Nagiub et al. that investigates all of the pathophysiological mechanisms proposed in the literature thus far. In this review, the regional neuropathy and hypovolemia theories were rejected on evidence-based qualitative analysis. Furthermore, the collagenic, autoimmune, and genetic theories were re-categorized as predisposing factors for POTS. Lastly, the authors posited that an imbalance in the angiotensin II receptor subtypes, AT1 and AT2, accounted for the neurohormonal, flow, nitric oxide, and baroreceptor theories of POTS. However, this was a recent article and has not yet been substantiated by other studies. For more details, we refer to the full article by Nagiub et al. [54].

Clinical Presentation

As discussed, postural orthostatic tachycardia syndrome predominantly affects females of child-bearing age. Another important trend to note is in the timing of the clinical presentation. Many POTS patients report mild symptoms of orthostatic intolerance beginning in their teens, which progress to more severe symptoms as they age. The onset of most POTS patients' symptoms is between their early teens and 5th decade of life, and different patients report that their symptoms developed acutely, subacutely, or insidiously [37]. This represents a heterogeneous timing for the onset of POTS symptoms. Many studies have also found that

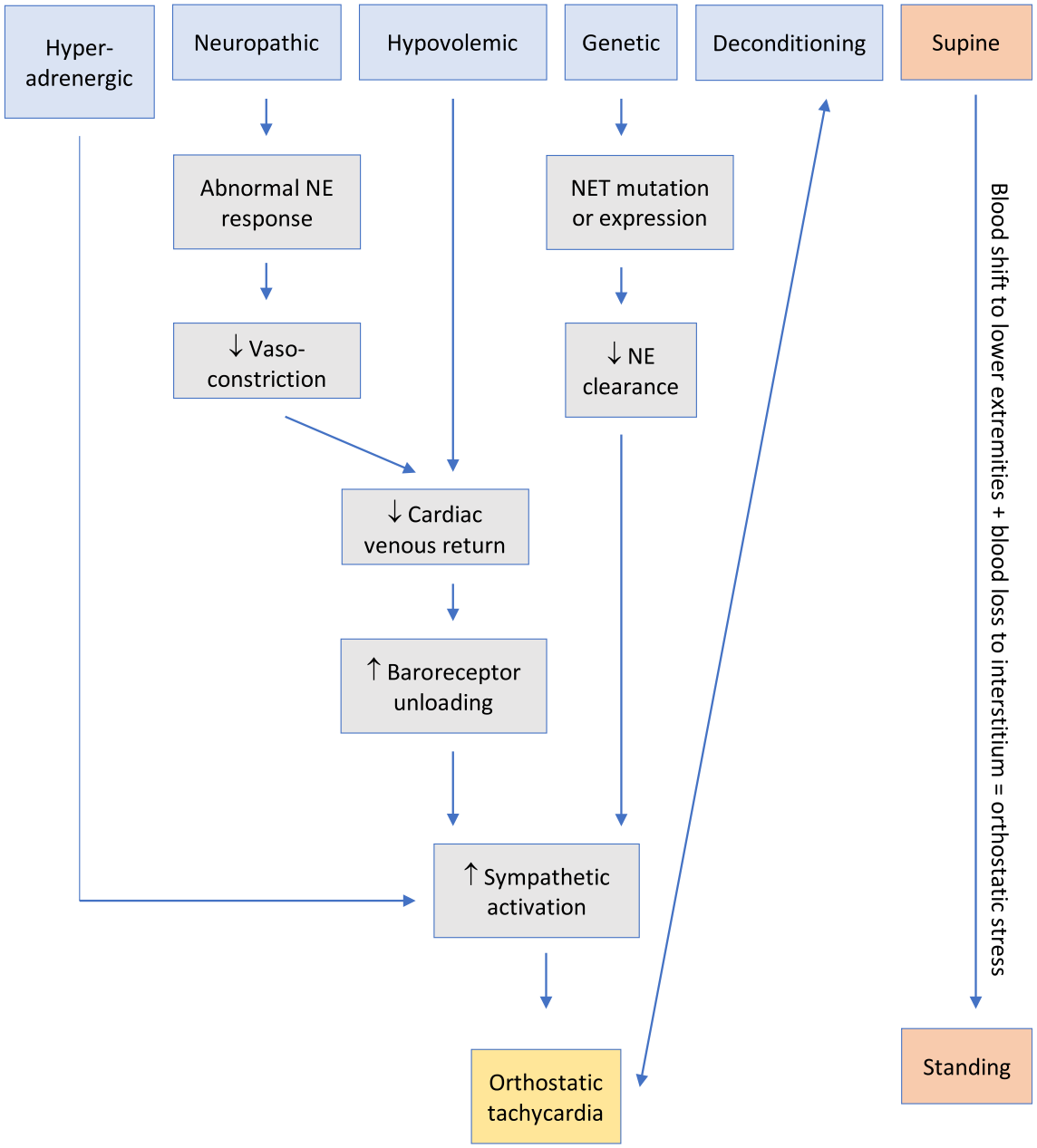

Fig. 1 Convergence of common POTS pathophysiological theories, partially adapted from Arnold et. al. [38]. This figure focuses solely on the principal symptoms of POTS, orthostatic tachycardia, omitting other symptoms of POTS. (*NE* norepinephrine, *NET* norepinephrine transporter)

a majority of POTS patients had a recent history of acute infection before the initial onset of their symptoms. In most cases, the infection was an upper respiratory or gastrointestinal virus [37, 55]. Other rarer preceding events reported are surgery, pregnancy, and concussions [56]. However, there are a large proportion of POTS patients who do not recall a precipitating event before onset of POTS symptoms.

As per criteria, POTS patients must have symptoms of orthostatic intolerance. These symptoms include impaired cognition, visual blurring, lightheadedness, vertigo, headache, changes in blood pressure, nausea, vomiting, diarrhea, chest pain, diaphoresis, and tremulousness [32, 56]. They are classified as symptoms of orthostatic intolerance when they are exacerbated upon standing and relieved by lying supine. Another orthostatic symptom reported in about 50% of patients in one study is acrocyanosis, which is dark-red blue discoloration of the legs upon standing [29].

POTS patients can also experience non-orthostatic symptoms. One of the most common non-orthostatic symptoms in POTS patients is fatigue, to the point where a subset of POTS patients is diagnosed at some point with chronic fatigue syndrome [56]. Sleep-related symptoms have also been reported in patients with POTS, such as sleep disturbance, fatigue, and excessive daytime tiredness [57].

Diagnostic Criteria

The most recent diagnostic criteria for postural orthostatic tachycardia syndrome were established in 2015 as part of an international consensus statement by the Heart Rhythm Society. The statement identifies three criteria to be used in the diagnosis of POTS. All three criteria must be met. The criteria described here and in Table 6 are adapted from Sheldon et al. [44].

> Criterion 1: The first criterion is a heart rate increase held for at least 30 s when transitioning from supine to standing position. The heart rate increase for adults must be at least 30 beats per minute and the minimum for adolescents age 12–19 years must be at least 40 beats per minute. If the patient's history is concurrent with POTS symptoms but orthostatic heart rate does not meet criteria, a head-up tilt table test may be utilized.
> Criterion 2: The second criterion is the absence of orthostatic hypotension. This is defined as the absence of systolic blood pressure drop of over 20 mmHg upon standing.
> Criterion 3: The third criterion is the presence of symptoms of chronic orthostatic intolerance for over six months. These symptoms can include lightheadedness, palpitations, tremulousness, generalized weakness, blurred vision, exercise intolerance, and fatigue.

Importantly, a diagnosis of POTS can only be given in the absence of other causes of tachycardia or orthostatic intolerance. Therefore, a thorough work-up and diagnostic evaluation are necessary in the evaluation of POTS. The 2015 statement has recommended a medical history, physical examination, orthostatic vitals, and a resting 12-lead electrocardiogram at the minimum for diagnosis.

Medical history is helpful in identifying predisposing factors or triggers of POTS symptoms, such as posture, temperature, exertion, menstrual cycle, or time of day [56]. The medical history is also helpful in identifying potential medications or medical conditions that can be causing similar symptoms. It is recommended that the physical examination includes cardiovascular, neurologic, autonomic, and dermatologic examinations. Orthostatic vital signs include blood pressure and heart rate measurements while the patient is supine for at least 5 min, as well as after 1, 3, 5, and 10 min of standing, or the head-up tilt table test. Lastly, a resting 12-lead electrocardiogram is recommended to rule out an accessory bypass tract or cardiac conduction abnormalities. In some patients, additional diagnostic evaluation is recommended, such as blood work, cardiovascular testing, head-up tilt table testing, and autonomic function tests [38].

Table 6 2015 Diagnostic criteria for postural orthostatic tachycardia syndrome. Adapted from Sheldon et al. [44]

Criteria: All 3 must be met and no other cause of tachycardia present
1. Heart rate increase: ≥ 30 bpm in adults ≥ 40 bpm in adolescents age 12–19
2. Absence of orthostatic hypotension
3. Symptoms of chronic orthostatic intolerance ≥ 6 months

Treatment

Although there is no cure for postural tachycardia syndrome, there are many methods available to help patients improve clinically. The treatment of POTS is multifaceted, consisting of non-pharmacological and pharmacological therapies. There are no FDA-approved medications for POTS due to lack of randomized clinical trials, but there are some small studies that offer evidence for some pharmacotherapies. Furthermore, the treatment of each POTS patient is individualized, as POTS is a heterogeneous disease. Although there is no standard treatment, it is agreed that non-pharmacological therapies should be utilized prior to starting medications [44].

The first non-pharmacological measure for POTS patients is to discontinue any medications that may be exacerbating their symptoms. These can include alpha- and beta-blockers, angiotensin-converting enzyme inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, diuretics, sympathomimetics, and anticholinergics [35, 44, 58]. There has also been growing evidence for the utilization of endurance exercise regimens in POTS patients [58–61]. It is recommended that POTS patients adhere to a supervised, structured exercise aerobic exercise program, which begins with non-upright exercises, such as rowing machines or swimming. This can later be modified to upright exercises, such as walking or jogging [44]. An additional non-pharmacological therapy consists of wearing compression garments to minimize blood pooling in the lower extremities [35].

The pharmacological therapies for POTS patients aim to improve the patients' quality of life. These therapies are targeted at reducing symptoms or alleviating the perceived cause of the patients' symptoms. There is no algorithm for treatment, and each patient will have an individualized optimal approach. However, one similarity between most patients is that a low dose of any therapy should be utilized first, as many POTS patients are sensitive to drugs [35]. These are several classes of drugs that have been shown to benefit POTS patients when used off-label. These classes include blood volume expanders, heart rate inhibitors, vasoconstrictors, sympatholytic drugs, and others.

Increasing blood volume in POTS patients can be achieved in many ways. It is recommended that patients drink 2–3 L of water per day and increase salt intake or supplementation to

10–12 g per day [44]. Fludrocortisone, desmopressin, and erythropoietin have also been shown to improve blood volume expansion in POTS patients [35]. To help lower heart rate, low-dose beta-blockers are recommended, with most studies focusing on propranolol. Other studies have also shown ivabradine and pyridostigmine to be effective for tachycardia in POTS patients [35]. Vasoconstrictor drugs that have been recommended in the pharmacological treatment of POTS are midodrine, octreotide, and droxidopa. Some stimulants have also been shown to be useful in increasing blood pressure and cognition in POTS patients. Lastly, sympatholytic drugs may be useful in patients who are believed to have "hyperadrenergic" POTS. We refer to a recent review article for a more detailed description of the suggested approach to the pharmacological management of POTS by Miller et al. [35].

Although there is no cure for POTS, it is important to note that POTS is believed to be a chronic condition that is not associated with increased rates of mortality [44]. Furthermore, it is believed that POTS patients improve over time. Multiple studies have reported either patients with symptomatic improvement or patients no longer meeting POTS diagnostic criteria at a later follow-up date [62–64].

Mast Cell Activation Syndrome

History

Over the last decade, diseases of mast cell activation have garnered much interest. There has been an explosion of patients diagnosed with mast cell activation syndrome. Interestingly, this term was only coined recently in 2007.

Mast cells were first described as granular cells seen in frog mesenteries in 1863 by Dr. Friedrich von Recklinghausen and were given the name *mastzellen* in 1877 by Dr. Paul Ehrlich. A few years later, mast cells were first tied to a pathologic state when they were found by Dr. Alfred Sangster to be distributed in the lesions of a patient with urticaria pigmentosa. It was not until 1949 that mast cells were connected with an internal disease, when mast cells were discovered by Dr. John Ellis in multiple organs at the autopsy of a one-year-old child who died of cachexia. This was the first description of systemic mastocytosis [65]. Over the next few decades, researchers sought to define mast cell functions, hematopoietic lineages, and the mediators they created and released. In 1988, a classification scheme for mastocytosis was proposed by Travis et al. [66], and this was recognized in 1991 by the NIH as the first standard classification scheme for mastocytosis [67].

Until recently, mast cell diseases were thought to be a result of mast cell over-proliferation, along with the resulting mast cell mediator release. It was in 1991 that pharmacologists John Oates and Jack Roberts theorized that there was a subset of mast cell disorders in which over-proliferation was absent [68].

In 2007, this theory was tested after Valent et al. described two patients with who developed severe hypotension after insect stings but had normal tryptase levels and no history of mastocytosis. However, they both had some minor criteria of systemic mastocytosis, although they did not completely meet criteria. Their syndrome was named "monoclonal mast cell activation syndrome" (MMAS), and a definition and diagnostic criteria were applied [69–71].

Following this, increasing numbers of patients were thought to have symptoms of mast cell activation but were not associated with mastocytosis or any underlying disease. In 2010, a conference was organized with the objective of updating and defining the classification and diagnostic criteria for mast cell disorders, specifically those of mast cell activation syndromes. The umbrella term "mast cell activation disorder" (MCAD) was given to these disorders characterized by either abnormal number or function of mast cells. It was agreed upon that "mast cell activation syndromes" (MCAS) and mastocytosis were diseases of abnormal mast cell activation and fell under the term MCAD. Mastocytosis had already been well defined, but MCAS also needed to be defined and assigned criteria. It was in this conference that primary, secondary, and idiopathic MCAS were defined, and these will be discussed in the classification and diagnostic criteria sections of this paper [72]. Two years later, Valent et al. released an update to the criteria [73]. In 2016, the WHO released an updated classification of mastocytosis, but our review will focus on MCAS, of which the most recent classification and criteria guidelines are from 2012 [74].

Epidemiology

There is a lack of epidemiologic studies to confirm the incidence and prevalence of both mastocytosis and mast cell activation syndromes. The recognition and ability to diagnose mastocytosis have improved in the last two decades, so estimates of the prevalence of mastocytosis have increased. The prevalence of mastocytosis is currently estimated to be one in 10,000 individuals [75]. Mastocytosis affects both males and females equally and can occur at any age. However, it has been shown that in approximately 55% of patients with mastocytosis, the disease onset was within the first two years of life [76].

There have been no epidemiologic studies on mast cell activation syndromes either, and the epidemiology of these syndromes has been even more difficult to estimate, as they have only recently been defined. The incidence and prevalence of patients with monoclonal mast cell activation syndrome and idiopathic mast cell activation syndrome are unknown [75].

Classification and Diagnostic Criteria

This review is centered on mast cell activation syndromes, but it is helpful to expand on the classification of MCAD as a whole, due to the confusing nature of the nomenclature. The classification of MCAD is still being refined today, as it is a relatively new spectrum of disorders. MCAD includes mastocytosis and MCAS. MCAS is further broken down into primary, secondary, and idiopathic MCAS, as specified by the 2012 consensus proposal. In the same proposal, MCAS and mastocytosis were integrated into the global classification of mast cell related disorders [73]. The global classification of mast cell related disorders, with an emphasis on MCAS, is depicted in Fig. 2.

The global classification of mast cell–related disorders includes mast cell hyperplasia, myelomastocytic conditions, mastocytosis, and MCAS [73]. Mastocytosis and MCAS are both disorders of mast cell activation. Mastocytosis is characterized by an increased number of (mono)clonoal mast cells in one or more organ systems. Mastocytosis is categorized into cutaneous mastocytosis, systemic mastocytosis, and mast cell sarcoma, each of which must meet their own diagnostic criteria and are also divided into subcategories. For more detailed classification and diagnostic criteria for systemic mastocytosis, we refer to the 2016 updated WHO classification, reflected in Table 7 [74].

We now shift our focus to the classification of mast cell activation syndromes (MCAS), which were most recently defined in 2012. MCAS is divided into primary, secondary, and idiopathic MCAS. Each category of MCAS must meet the criteria for mast cell activation (MCA), as well as additional criteria for their individual category.

There are three criteria necessary for the diagnosis of MCA. The following are the criteria from the 2012 consensus proposal, which are also listed in Table 8 [73].

The first criterion is the presence of clinical symptoms that are thought to be caused by mast cell activation. These symptoms consist of flushing, pruritus, urticaria, angioedema, nasal congestion, nasal pruritus, wheezing, throat swelling, headache, diarrhea, and hypotension. However, these symptoms are non-specific to mast cell activation, so they must be recurrent and not caused by any other known diseases to meet the first criterion.

The second criterion is an increase in serum tryptase levels during or within 4 h of a symptomatic period. The increase in serum tryptase levels must be 20% above baseline plus 2 ng/ml. It is important to measure the baseline level prior to and after the symptomatic episode to confirm a temporary increase that may be causing symptoms. It is also important to note that patients with systemic mastocytosis have an elevated basal level of tryptase [77]. Therefore, measuring the baseline tryptase is important in excluding patients with this disorder.

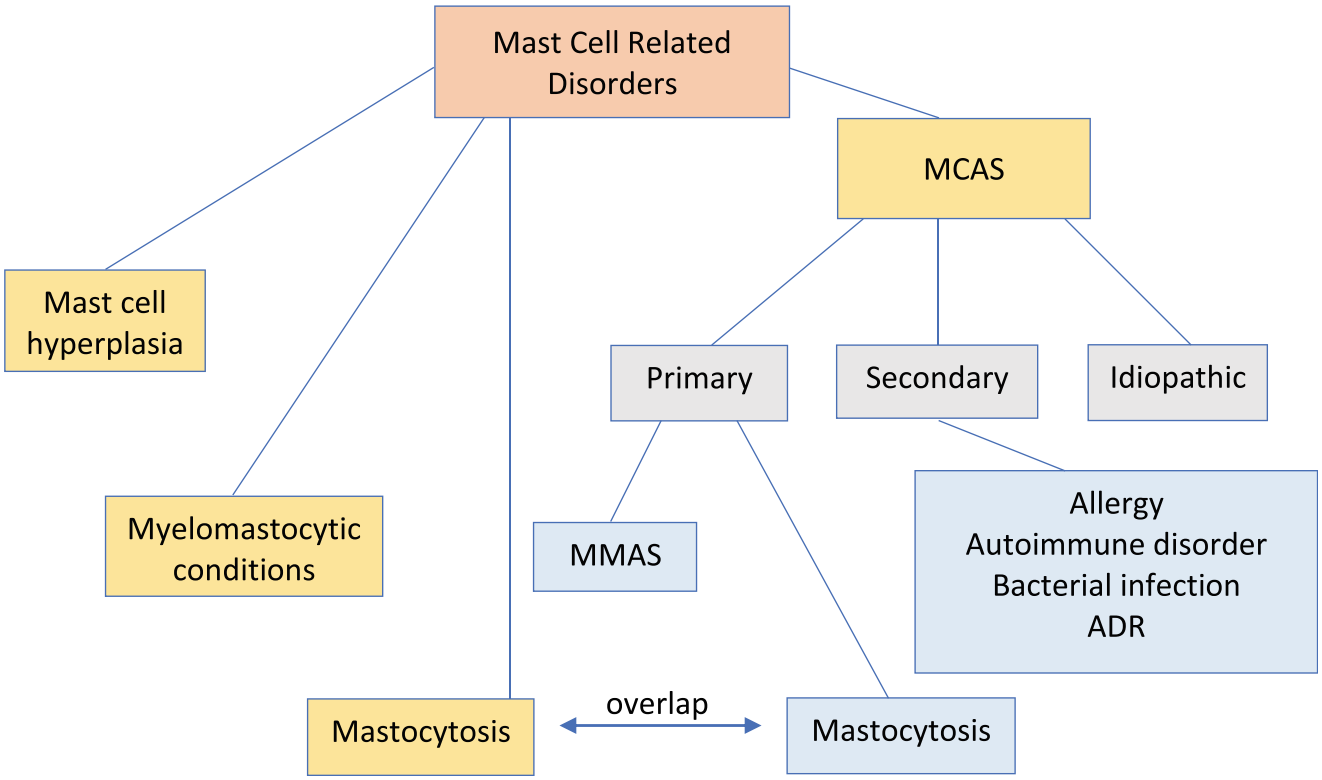

Fig. 2 Global mast cell related diseases classification, with an emphasis on MCAS. (*MCAS* mast cell activation syndrome, *MMAS* monoclonal mast cell activation syndrome, *ADR* adverse drug reaction)

Table 7 2016 Updated WHO diagnostic criteria for systemic mastocytosis. Adapted from Valent et al. [74]. One major and one minor or three minor criteria must be met

Criteria:	
Major SM criterion	Multifocal dense infiltrates of mast cells in bone marrow biopsies or other extracutaneous organs
Minor SM criteria	1. Over one-fourth of all mast cells are morphologically atypical
	2. KIT point mutation at codon 816
	3. Mast cells that exhibit CD2 and/or CD25
	4. Baseline serum tryptase level > 20 ng/mL

Although tryptase is the ideal mediator for the second criterion, it was agreed upon by members of the consensus that the elevation of other mediators should be considered in the event that tryptase levels cannot be taken or are ambiguous. It was agreed that 24-h urinary histamine metabolites and 24-h urinary levels of PGD_2 or its metabolite $11\beta\text{-}PGF_{2\alpha}$ should be taken into consideration. However, it was also agreed upon that there was a need for further validation of these measures in mast cell activation.

The third criterion is a decrease of clinical symptoms in response to a pharmacological therapy that acts against mast cells or their mediators. Histamine receptor inverse agonists are the preferred pharmacologic therapy to meet this criterion. A complete response to a variety of other antimediator drugs may be considered as indirect evidence of mast cell activation. However, response to these drugs is not specific to solely mast cells, so only after long-lasting resolution of symptoms can this response be counted.

The three subcategories (primary, secondary, and idiopathic) of MCAS must meet MCA criteria, as well as separate criteria. These are defined by the 2012 consensus statement and depicted here in Table 9.

Patients with primary MCAS must also have evidence mast cell (mono)clonality. Specifically, the expression of CD25 and/or detection of the *c-KIT* mutation, D816V, must be present. Primary MCAS is further classified into mastocytosis or monoclonal mast cell activation syndrome (MMAS). MMAS is diagnosed when (mono)clonality of mast cells is present,

Table 8 Diagnostic criteria for mast cell activation. Adapted from Valent et al. [73]

Criteria: All 3 must be met
1. Presence of recurrent clinical symptoms associated with mast cell activation
2. Serum total tryptase increased 20% plus 2 ng/ml above baseline after a symptomatic period
3. Decrease in clinical symptoms to histamine receptor blockers or other antimediator drugs

Table 9 Classification of mast cell activation syndromes (MCAS). Adapted from Valent et al. [73]

MCAS category	Subcategories	MCA criteria fulfilled plus additional criteria:
Primary	Mastocytosis MMAS	Mast cell (mono)clonality present
Secondary	Allergy, autoimmune disease, bacterial infection, ADR	Criteria met for diagnosis of a disease that can produce symptoms of mast cell activation
Idiopathic	None	Does not meet criteria of any other disease that can produce symptoms of mast cell activation

MCAS mast cell activation syndrome, *MMAS* monoclonal mast cell activation syndrome, *ADR* adverse drug reaction

but the patient does not meet systemic mastocytosis criteria completely.

Secondary MCAS patients are patients who meet MCA criteria, but who also meet the criteria of an underlying process that can cause MCA symptoms, such as allergy, autoimmune diseases, bacterial infections, and drug reactions.

Idiopathic MCAS patients meet MCA criteria but do neither meet any criteria of mastocytosis nor have any identifiable underlying disease that could lead to MCA symptoms. This is a diagnosis of exclusion, reached only after an extensive work up.

It is important to note the areas of overlap within the classification of mast cell diseases. Primary MCAS mastocytosis type, by nature, overlaps with mastocytosis. In addition, patients with secondary MCA can also have idiopathic MCA at a different time point [73].

Pathogenesis and Mechanisms

It is important to briefly cover the normal physiologic functions of mast cells in order to understand the proposed pathogenic mechanisms of MCAS. Mast cells are involved in multiple physiologic and pathologic processes. Mast cells are derived from mast cell progenitors in the bone marrow, and travel to tissues, where they finish maturing [78]. Their development, maturation and phenotypes are influenced by multiple variables, such as transcription factors, growth factors, cytokines, and stimuli in the local microenvironment. Mast cells are widely distributed throughout the body, concentrated especially at immunologically vulnerable sites where the host is exposed to the external environment [79]. Mast cells employ a variety of mediators to achieve their functions. Preformed mediators are stored in cytoplasmic granules and included biogenic amines, lysosomal enzymes, proteases, proteoglycans, cytokines, chemokines, growth factors, peptides, and other enzymes/proteins. Neoformed mediators are formed

from membrane lipids. These include prostaglandins, leukotrienes, and platelet activating factor. Lastly, neosynthesized mediators are newly formed based on the stimuli that the mast cells encounter. These include cytokines, growth factors, reactive oxygen species, and complement proteins [79].

The normal physiologic functions of mast cells include roles in homeostasis, tissue repair, angiogenesis, the nervous system, innate and adaptive immunity, and immune tolerance. Normal mast cell activation and release of their mediators are necessary to maintain normal homeostasis; however, there are instances in which mast cells are not regulated. Aberrant mast cell function and activation result in a wide spectrum of disorders. The most well-defined and studied pathologic role of mast cells is in allergy, when mast cells inappropriately respond to harmless antigens. However, a whole new spectrum of mast cell activation diseases has been characterized recently. This spectrum includes mastocytosis and mast cell activation syndromes. Mast cell activation becomes problematic when they are abnormally produced, due to a clonal mutation in a mast cell progenitor, or produced with a hypersensitivity to normal conditions. Clonal abnormalities, the most common being a *c-KIT* point mutation, can result in overproduction of mast cells or abnormal mast cells [74, 80]. Mastocytosis and monoclonal MMAS are both defined as having clonal mutations in mast cells. While the pathogenic mechanisms of mastocytosis have been relatively well defined, the mechanism of MMAS has not been as clearly elucidated. Furthermore, in idiopathic MCAS, no mutations have been found, and its pathogenesis is an even more perplexing mystery. Pathogenic mechanisms are further clouded by the vast symptomatology of these patients, as described in the following section.

Clinical Presentation

The clinical presentation of mast cell activation syndrome (MCAS) is very similar to the presentation of other mast cell related diseases, such as allergy and systemic mastocytosis. The difference, however, is that patients who have been diagnosed with MCAS generally have vague symptoms that neither are consistent with either allergy or systemic mastocytosis nor can they be found to have an underlying condition causing their symptoms [81].

The timeline of clinical presentation in patients diagnosed with MCAS varies. These symptoms usually manifest in childhood or adolescence but go unrecognized as symptoms of mast cell activation. Due to the non-specific and varying nature of symptoms, it is often not until much later that patients are ultimately stamped with a label of MCAS [65, 81].

The symptoms frequently experienced by MCAS patients are non-specific to mast cell activation; therefore, multiple symptoms are more supportive of a diagnosis, as well as meeting the other diagnostic criteria. The symptoms also span across many different organ systems, as well as vary in severity. This results in a very heterogeneous clinical presentation of MCAS. The validated symptoms of mast cell activation are flushing, pruritus, urticaria, angioedema, nasal congestion, nasal pruritus, wheezing, throat swelling, headache, diarrhea, and hypotension [73]. However, many patients also commonly complain of other symptoms, including tachycardia, abdominal cramping, nausea, vomiting, dermographism, and ocular itching [65, 72, 80–82]. Even these symptoms have been reported in diseases related to mast cell release, such as anaphylaxis. It is when patients begin to complain of vague and subjective symptoms, such as fatigue, malaise, lack of concentration, "brain fog," and mild cognitive problems, where the diagnosis becomes problematic.

Patients also report that certain triggers stimulate their symptoms of mast cell activation. Antigenic triggers include certain drugs, alcohol, radiocontrast media, hymenoptera stings, and environmental allergens. Other triggers include extreme temperatures, excess exertion or exercise, trauma, emotional stress, and electrostatic shocks [65, 83, 84].

Treatment

The management of mast cell activation syndrome is highly individualized, as each patient suffers from a large constellation of symptoms and severity. However, a similarity in the treatment of all patients is the avoidance of triggers. Patients should be encouraged to learn their triggers and to avoid them when necessary. In some cases, an allergy workup can be done to guide patients on what they should be avoiding. For patients with a history of anaphylactic events, immunotherapy to their allergens may be indicated. In addition, patients with a history of anaphylaxis or mastocytosis should be provided with self-injectable epinephrine in case of emergency [80].

The pharmacologic management of patients is also highly individualized; patients may need to try various agents in a drug class, as well as different doses. Medications should also be trialed one at a time, to reduce confusion between responses to drugs. Patients should also be told that an initial response to therapy may take a few weeks to notice [83, 84]. There have been multiple stepwise approaches proposed for the treatment of MCAS patients [83, 85]. A similarity between approaches is the first-line use of histamine receptor 1 or 2 antagonists. The next adjunct therapy is usually a mast cell membrane stabilizing agent, such as sodium cromolyn. Ketotifen can also be used, as it has both antihistamine and mast cell stabilizing effects. Leukotriene receptor blockers are also utilized in MCAS therapy. More recently, non-steroidal immunosuppressant drugs and monoclonal antibodies have been utilized in MCAS therapy. Examples of these include azathioprine, cyclosporine, glucocorticoids, and omalizumab [85, 86]. Multiple other agents have been utilized in the therapy of MCAS patients; however, the pool is vast and out of the

scope of this paper. We refer to Molderings et al. and Cardet et al. for a more detailed approach to MCAS therapy [83, 85].

Evaluating MCAS, hEDS, and POTS

MCAS

Categorizing the classification of mast cell activation disorders into mastocytosis and MCAS has been beneficial to patients who did not fit into a previously defined category. However, the classification of MCAS is somewhat confusing and repetitious. The first category, primary MCAS, can be divided into MMAS and mastocytosis. The latter subcategory, primary MCAS mastocytosis type, is simply mast cell activation symptoms secondary to mastocytosis. Classifying these patients as mastocytosis patients, rather than MCAS patients would simplify matters for both the patient and diagnosticians. Similarly, secondary MCAS is defined by mast cell activation symptoms secondary to other conditions, such as allergy, autoimmune diseases, bacterial infections, and drug reactions. It would further simplify matters to classify these patients as having the primary disease and not another syndrome. To summarize, both primary MCAS mastocytosis type and secondary MCAS have known causes; therefore, it would be simpler to classify them as so. However, the categories of primary MMAS and idiopathic MCAS are still unaccounted for. It is necessary to understand how the classification for these entities came into existence before potentially revising them.

The first mast cell activation disorder described and defined was mastocytosis and its subtypes. By nature, patients with mastocytosis were said to have increased proliferation of mast cells [67]. In 1991, Roberts and Oates were the first to explore the existence of a "new" type of mast cell activation disorder, without evidence of proliferation. Their hypothesis cited data from a study done in 1988 that carefully counted cutaneous mast cells from biopsies of a spectrum of patients. Patients biopsied included patients with a diagnosis of mastocytosis, patients with symptoms of mast cell activation, but who did not meet histologic criteria, and normal patients. It was found that symptomatic patients not meeting criteria had average numbers of mast cells in between that of normal patients and patients with a diagnosis of mastocytosis [87]. The conclusion of the 1991 paper was a call for more investigation into what they called a "mild form" of mastocytosis [68]. Following this observation, more patients were reported with mast cell activation symptoms, but no evidence of mast cell proliferation.

In 2007, Sonneck et al. described two cases of patients who suffered severe hypotension after hymenoptera stings. Both patients had normal tryptase levels, normal bone marrow histology, and normal tryptase immunohistochemistry. The first patient did not meet any minor systemic mastocytosis criteria. The second patient met two minor systemic mastocytosis (SM) criteria at the time. The criteria met were the presence of morphologically atypical mast cells and the expression of CD25 on mast cells. Criteria not met were the major criterion of multifocal dense infiltrates of mast cells demonstrating by histologic staining, and minor criteria of *c-kit* mutation at codon 816 and elevated serum total tryptase concentration. The authors tentatively termed this disorder, defined as meeting two minor systemic mastocytosis criteria, monoclonal mast cell activation syndrome (MMAS) [71].

Similarly, in the same year, Akin et al. published a study which described two patients who suffered severe hypotension and only met two minor criteria for systemic mastocytosis. The two minor criteria met were presence of morphologically atypical mast cells and expression of CD25 on mast cells. Criteria not met were the major criterion of multifocal dense infiltrates of mast cells demonstrating by histologic staining and minor criteria of *c-kit* mutation at codon 816 and elevated serum total tryptase concentration [88]. The criteria missing mirrored the ones missing in the case of the patient described by Sonneck et al. in the same year.

This discussion brings up the need for investigation into patients currently diagnosed with MMAS and idiopathic MCAS. What criteria are these patients missing in that they received a diagnosis of MMAS or idiopathic MCAS? Are they the same ones as Sonneck et al. and Garriga et al.'s patients? If these patients have the two minor criteria of morphologically atypical mast cells and expression of CD25, they are only missing one minor criterion to be diagnosed with systemic mastocytosis (Table 7). The missing minor criteria include a *c-kit* mutation at codon 816 and elevated serum total tryptase concentration. It has been posited that there could be mutations other than KIT D816V responsible for mast cell activation syndromes [65, 71]. There have also been cases of patients diagnosed with systemic mastocytosis that had unusual KIT mutations other than D816V [89–92]. Commercial testing for other KIT mutations may not be available, or these mutations may not be able to be detected with the techniques used when diagnosing these patients. A future area of research would be to investigate other mutations that may be contributing to symptoms of patients with MCAS. Perhaps idiopathic MCAS or MMAS can be explained by an unrecognized KIT mutation. If other mutations are uncovered and patients with a diagnosis of MMAS or primary idiopathic MCAS are discovered to have the novel mutations, they may fit criteria for systemic mastocytosis.

Further research could potentially eliminate the need for MCAS as a diagnostic framework, while still fitting these patients into another diagnostic category, such as mastocytosis, allergy, or another underlying disorder. However, more research into mutations may be fruitless, leaving some patients with unmet criteria for a diagnosis. In that case, we would support the categories of idiopathic MCAS or

MMAS. However, we propose that primary MCAS due to mastocytosis be called mastocytosis, and secondary MCAS due to allergy, autoimmune disorders, etc. be called by their causative disorder. This would simplify matters.

This new perspective on the need to revise the mast cell activation syndromes stems from the recent explosion of patients diagnosed with MCAS. Criteria for MCAS have been loosely adhered to, and the lines delineating the symptoms have been blurred. This may be due to the fact that symptoms of mast cell activation, such as itching, flushing, headache, and gastrointestinal symptoms, are non-specific and incongruent. Symptoms such as brain fog, irritability and fatigue are common complaints of patients who believe they have MCAS, yet these have not been substantiated as legitimate symptoms typical of mast cell activation [73]. Furthermore, the diagnosis of MCAS has garnered explosive support through social media and the Internet, because it gives patients with non-specific patterns of symptoms a diagnosis to carry. Although there are benefits to creating a new category for patients that do not meet other criteria, it has opened up the door to many patients complaining of a myriad of vague symptoms. We are not sure if this complicated new scheme of mast cell disorders helps or complicates matters for these patients.

hEDS

The diagnostic criteria and classification for hypermobile Ehlers-Danlos syndrome (hEDS) are still being refined. The years between the Villefranche nosology and new 2017 nosology for the classification of EDS were marked by confusion in differentiating EDS hypermobility type (EDS-HT, the old nomenclature for hEDS) from joint hypermobility syndrome (JHS). At this time, both disorders shared some of the same diagnostic criteria, including the Beighton score and symptoms such as joint hypermobility, joint pain, joint dislocations, and skin involvement [4, 93]. It was in 2009 that Tinkle et al. addressed the similarities between the two entities. The authors agreed that patients with JHS and EDS-HT were part of a distinct group of hereditary connective tissue disorder patients; however, they could not be phenotypically distinguished from each other. It was in this paper that the authors also posited that multiple members of the same family may be diagnosed with either JHS or EDS-HT [94]. In 2014, Castori et al. published a study on 23 families, 21 of which the members shared diagnoses of JHS, EDS-HT, and JHS + EDS-HT. It was then concluded that JHS and EDS-HT were the same clinical entity, creating a diagnostic dilemma [95].

The 2017 updated diagnostic criteria for hEDS reflected a response to this dilemma. The stricter, more specific criteria sought to distinguish hEDS from JHS. However, this new classification left many symptomatic patients without a diagnosis, because they did not meet all of the criteria for hEDS. This matter was addressed by another article in the same issue that the updated classification was released. The article by Castori et al. proposed a new group of hypermobility spectrum disorders (HSDs). A continuous spectrum of phenotypes was created, ranging from asymptomatic joint hypermobility, through various HSDs in the middle of the spectrum, to hEDS at the severe end of the spectrum. The spectrum was described as dynamic, where individuals can phenotypically move forwards or backwards on the continuum, depending on how their symptoms change throughout life [21]. The dynamic nature of this spectrum and the ability of individuals to move between diagnoses raise the issue of whether hEDS is a true syndrome or just a severe manifestation of a hypermobility spectrum disorder. It is a difficult question to answer, as hEDS, or the multiple HSDs, have not yet been associated with a causative genetic defect.

Relatedly, in the 2017 updated classification, every EDS subtype except for hypermobile type was defined by the causative gene of the syndrome. Because hEDS has not been associated with any known genetic defect, it also did not fit into the new pathogenetic classification proposed in the 2017 consensus. To account for this discrepancy, the authors sought to improve its clinical definition by updating the diagnostic criteria for hEDS. The new criteria are more difficult to meet, with the aim of reducing heterogeneity in the hEDS patient population to facilitate future research [4].

This raises the issue of patients with a former diagnosis of EDS hypermobility type. The former and current criteria are contrasted in Tables 2 and 3. It is clear that the new criteria are more numerous and strict than the former. To our knowledge, there have been no studies on how many patients previously diagnosed with EDS hypermobility type fit into the new classification for hEDS. Because the criteria differ vastly, this should be an area of future study. We suspect that it will discovered that a substantial number of "hEDS" patients do not fit the new criteria for hEDS. These patients may meet criteria for an HSD that is lower on the newly created spectrum for joint hypermobility disorders. Therefore, the additional classification of hEDS may not be warranted. Instead, these patients may be classified with a severe manifestation of an HSD.

POTS

Of the three conditions discussed, POTS is the most well established and recognized. It is estimated that that POTS affects between over 500,000 and up to three million individuals in the USA, which is a substantial number of individuals [33–35]. However, it is not known if all of these patients underwent extensive diagnostic testing, as recommended in the 2015 guidelines, to rule out other causes.

POTS diagnostic criteria are objective and exclusive. However, in the most recent consensus update, reproducibility

was not mentioned as part of the criteria [44]. Meeting POTS criteria multiple times should be required as part of diagnosis. This is similar to the specifications that high blood pressure can only be diagnosed as hypertension after multiple blood pressure measurements. We believe this is important, because once a patient undergoes a single positive test for POTS and is diagnosed, they carry that diagnosis for the rest of their lives.

More research into the pathophysiological mechanisms of POTS is warranted as well. There are many unproven, proposed mechanisms of POTS symptoms. Currently, POTS symptoms are believed to be the final result of the convergence of multiple pathological pathways. It will be necessary in the future to determine whether POTS is a disease in itself or rather a symptom of one or more pathological processes.

Discussion

The Relationship Between hEDS, POTS, and MCAS

There have been multiple descriptions in the literature regarding the association between two of or all three of these clinical entities. In order to evaluate potential associations between these conditions, we must examine whether or not patients truly meet criteria for each diagnosis. As previously discussed, many criteria for these conditions are vaguely subjective or difficult to meet. If patients are being misdiagnosed with hEDS, MCAS, or POTS, no associations can be made between the three.

To begin, we presume that many patients with a prior diagnosis of EDS hypermobility type do not fit the new criteria for hEDS. The former and current criteria for hEDS are compared in Tables 2 and 3. It is clear that it is more difficult for patients to meet the new criteria. Most studies to data associating hEDS with other conditions did not use current criteria.

The first description of an association between orthostatic intolerance (including POTS) and EDS was in 1999 by Rowe et al. The study initially was examining the association between chronic fatigue syndrome (CFS) and EDS, but the authors also identified a subset of 12 patients with EDS out of approximately 100 patients with orthostatic intolerance and CFS. Six patients were classified as having classical type EDS, and six patients were classified as having hypermobility type EDS. No genetic testing was utilized for either diagnosis, as none were developed at the time. Instead, the Villefranche nosology was utilized in establishing these diagnoses [96].

It is necessary to reevaluate this study in context of recent changes to the criteria for all types of EDS. The 2017 criteria now require genetic evidence for classical EDS and the fulfillment of much stricter criteria for hypermobile EDS. The patients in this study no longer meet EDS criteria for either diagnosis. Since the publication of the 1999 article, many other authors have cited associations between joint hypermobility syndromes and orthostatic intolerance syndromes [97–99]. However, these studies are based on the former diagnostic criteria, which are less strict. A 2017 study by Miglis et al. on the association between POTS and hEDS was recently published after the release of the new guidelines for diagnosis of hEDS; however, this study again used the former diagnostic criteria to diagnose hEDS [100]. This highlights the need for widespread re-evaluation of patients with a former diagnosis of EDS hypermobility type.

As it has recently gained more attention and recognition, MCAS has been associated with both EDS and POTS. The first study aiming to establish an association between MCAS and POTS was done in 2005 by Shibao et al. It was hypothesized that because flushing is both a symptom in POTS and MCAS, that MCAS may contribute to the pathogenesis of POTS. A group of eight female patients out of 177 patients was identified with both symptoms of MCA and POTS. The criteria for this group were as follows: at least six months of orthostatic intolerance, increase in heart rate of over 30 bpm after standing, absence of underlying disease, a history of flushing, and urine methylhistamine of over 230 μg/g creatinine associated with a flushing episode. As a result, the authors recommended the consideration of MCA in POTS patients [101]. However, these patients did not meet the established criteria for any type of MCAS. Since then, associations between MCAS and POTS have been noted in review papers on the individual conditions [29, 38, 40]. The most recent article on the potential relationship between mast cells and POTS was accepted in 2018. The article examines the possible relationship between the two and concludes with a call for better characterization of the mechanisms behind POTS and MCA [102]. Of note, the only study cited in the review that reports a comorbidity of the two conditions is the study from 2005 by Shibao et al. We believe that more investigation into patients that meet both criteria for POTS and MCAS is warranted before this association is made.

In multiple literature reviews on each individual condition, there is mention of comorbidity of one or both of the other conditions. The first article that focused solely on the association between all three of the conditions was published by Cheung and Vadas in 2015, titled “A New Disease Cluster: Mast Cell Activation Syndrome, Postural Orthostatic Tachycardia Syndrome, and Ehlers-Danlos Syndrome.” However, the association posited by the authors is weak at best, and the study had multiple limitations. The authors recruited 15 patients with POTS and EDS from a patient support group, which is a small, potentially biased population. A diagnosis of EDS based on a Beighton score and skin biopsy was determined in nine patients. They did not follow the EDS diagnostic criteria at the time of publication, and these patients also do not meet current EDS diagnostic criteria; skin biopsy and Beighton score do not determine a diagnosis of any type of EDS. Next, a diagnosis of POTS was diagnosed by a

cardiologist in 12 patients. The methods used by cardiologists were not described. Nine patients were diagnosed with both EDS and POTS. Patients were then given a questionnaire for symptoms of mast cell activation. Six out of nine patients were said to have validated symptoms of a mast cell disorder [103]. There are obviously multiple limitations of this study including the patient population, lack of a validated diagnosis of MCAS based on criteria, and use of incorrect diagnostic criteria for EDS. This study was later cited as evidence for an association between MCAS and EDS in a 2017 review article.

The review article, titled "Mast Cell Disorders in Ehlers-Danlos Syndrome," was published by Seneviratne et al. and examined a potential association between the two conditions. The authors explored possible mechanisms to explain a link between the two conditions and discussed mast cells and their relationship with connective tissue. However, they did not offer sufficient evidence of a patient population that exhibited both conditions. The only patient population referenced was the nine patients in the study by Cheung and Vadas, which as previously discussed, had many limitations. The rest of the references in the review cited complaints experienced by patients with EDS that can somehow be related to mast cell activation. These complaints were non-specific and included naso-ocular symptoms, increased incidence of asthma, gastrointestinal symptoms, neuropsychiatric conditions, and orthostatic intolerance [84]. Although these non-specific complaints can be related to mast cell activation, shared symptoms cannot be used as evidence for an association between the two conditions. Shortly after its publication, in a reply letter to the editor, Vengoechea expressed his concerns with the associations that had been made. He described the evidence for an association between MCAS and EDS as "thin" and raised similar concerns with the Cheung and Vadas study [104].

Vengoechea also referenced an issue that one of the authors has experienced in his own professional experience; the link between MCAS, POTS, and hEDS can be appealing to certain patient populations. Due to the publication of articles on the association of these three conditions, numerous patients are surfacing who believe they have mast cell activation syndrome. We believe the association for these three conditions has garnered support through the Internet. There has been an explosion of non-evidence based material on the Internet regarding mast cell activation syndrome, and patients are enthralled by it. Patients are presenting to allergy and genetic clinics claiming to have MCAS and requesting antihistamine treatments recommended for this condition [104]. Often, their chief complaints is "my mast cells are producing too much histamine". However, the use of these agents cannot be justified with evidence-based support, which leaves many patients feeling frustrated and neglected.

We believe that the reason behind the association of these three clinical entities stems from an overlapping pool of symptoms. The symptoms for each of these entities are non-specific and vague. Figure 3 represents the symptoms that have been reported by patients with these conditions and highlights the similarities between the three. It is very evident that there is a large overlap between patient-reported symptoms of these three entities and we suspect that the overlap may have been misconstrued to reflect comorbidity.

Scientific Approach to the Relationship Between hEDS, POTS, and MCAS

Methods and Search Results

A PubMed search was conducted individually for the terms, "MCAS," "mast cell activation syndrome," "mast cell activation," and "mast cell disorder." Searching MCAS yields 826 papers.

Searching "POTS," "postural orthostatic tachycardia," "postural tachycardia," and "postural orthostatic tachycardia syndrome" yielded 2820 papers.

Searching "EDS," "hEDS," "hypermobile EDS," "hypermobile Ehlers-Danlos syndrome," and "Ehlers-Danlos syndrome" yielded 16,167 papers.

A search of combinations of the search terms above was conducted using two different strategies. The number of papers yielded from both search strategies is as follows.

Strategy 1 A total of 136 searches were done on the following terms and combinations on PubMed: "MCAS," "mast cell activation syndrome," "mast cell activation," "mast cell disorder," "POTS," "postural orthostatic tachycardia syndrome," "postural orthostatic tachycardia," "postural tachycardia," "EDS," "hEDS," "hypermobile EDS," "hypermobile Ehlers-Danlos syndrome," and "Ehlers-Danlos syndrome." These are not specific for hypermobile type.

A maximum of 28 papers were found in any of these searches, with significant overlap. Overall, 40 unique papers were found. Of those 40, seven were completely out of scope for this paper, three were case reports, 19 were review papers, two were letters to authors/responses to letters, and nine were original research papers. Of the nine original research papers, there were no papers that resulted from a combination of three search terms for the three conditions.

Strategy 2 A total of 88 searches were done on the following terms and combinations on PubMed: "MCAS," "mast cell activation syndrome," "mast cell activation," "mast cell disorder," "POTS," "postural orthostatic tachycardia syndrome," "postural orthostatic tachycardia," "postural tachycardia," "hEDS," "hypermobile EDS," and "hypermobile Ehlers-Danlos syndrome." This search is specific for hypermobile form of EDS.

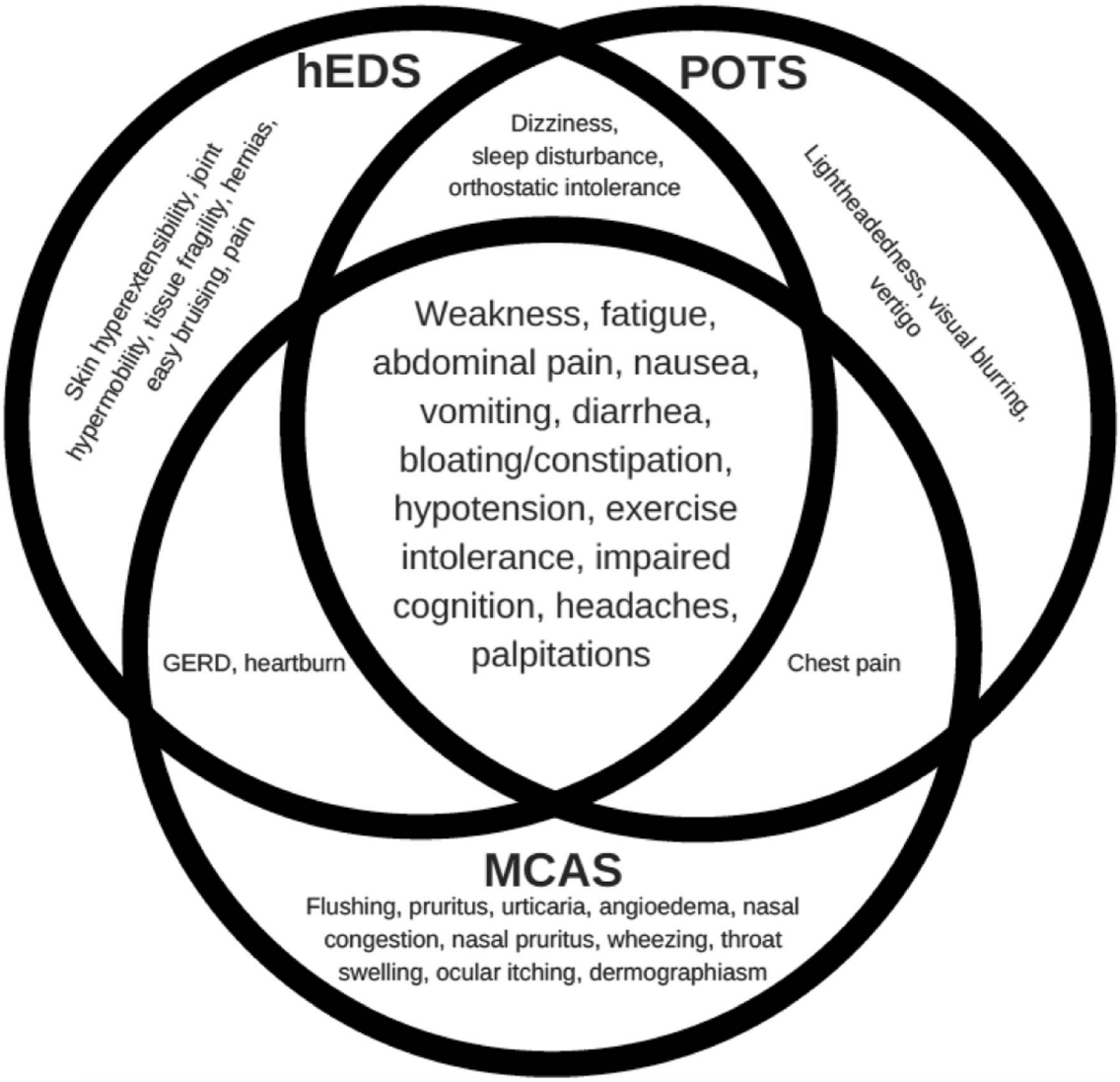

Fig. 3 Patient reported symptoms in hEDS, POTS, and MCAS. (*MCAS* mast cell activation syndrome, *POTS* postural orthostatic tachycardia syndrome, *hEDS* hypermobile Ehlers-Danlos syndrome)

A maximum of 12 papers were found in any of these searches, with significant overlap. Overall, 19 unique papers were found. Of these, two were completely out of scope for this paper, two were case reports, 11 were review papers, and four were original research papers. Of the four original research papers, there were no papers that resulted from a combination of three search terms for the three conditions.

No epidemiological studies were found addressing the coexistence of mast cell activation disorder, hypermobile EDS, or POTS using the current criteria. A relationship between hEDS, POTS, and MCAS can only be undeniably substantiated with scientific evidence linking the three conditions. There would have to be a proven commonality between all three conditions that contributes to the pathophysiology of each. We do not believe there is substantial evidence that a common pathologic mechanism exists.

We begin with the physiology behind joint hypermobility, the defining characteristic of hypermobile EDS (hEDS). Joint hypermobility has no single defined cause. It stems from a variety of factors affecting the mechanical properties of the extracellular matrix, specifically leading to an imbalance between stiffness and elasticity in tissues. The arrangement of collagen fibrils mediates stiffness and the arrangement of elastic fibrils mediates elasticity. It is believed that multiple different mutations in the genes encoding the extracellular matrix are responsible for shifting the balance towards elasticity, resulting in a hypermobile phenotype [105]. Hence, why many have posited that genes involved in the production and expression of collagen are involved in the pathophysiology, as well as elastin, fibrillin, tenascin-X, and other proteins affecting the connective tissue [106]. In order to establish a relationship between hEDS and MCAS, evidence that mast cell mediators affect the production, metabolism, or composition of

connective tissue must exist. To our knowledge, there is no evidence of mast cell mediators contributing to hypermobility. In fact, several studies have found that mast cells stimulate both collagen synthesis and fibrosis, which would decrease mobility. Hyperactive mast cells have been shown to play a role in lung, cardiac, renal, and adipose tissue fibrosis [107, 108]. A recent review on mast cells and their role in fibrosis by Bradding and Pejler came to the following conclusion: clinical human and in vitro studies are in favor of a pro-fibrotic role for mast cells; however, animal studies were inconsistent in determining a pro-fibrotic role for mast cells [109]. Evidence for a pro-fibrotic role results from multiple studies showing that mast cell mediators may play a role in this process.

Tryptase, a major mast cell mediator, has been shown to stimulate fibrosis by increasing fibroblast proliferation, as well as increase the production of type I collagen [110, 111]. Histamine, another mast cell mediator, has been demonstrated to have similar effects on the proliferation of fibroblasts and production of collagen [111–114]. Another study showed that mast cell mediators prostaglandin D2, leukotriene D4, carboxypeptidase A, and tryptase also increased proliferation of fibroblasts and synthesis of type I collagen [115]. This is evidence in favor of mast cells shifting the balance towards stiffness, rather than elasticity, which would not result in a hypermobile state. This, in combination with the paucity of evidence linking mast cell mediators and hypermobility, makes it difficult to substantiate the theories behind mast cell activation leading to hypermobility of joints. Lastly, individuals with hypermobile EDS are always hypermobile; however, their purported MCAS symptoms are separated temporally, so a link between them seems even more unlikely.

We now ought to examine any potential scientific link between MCAS and POTS. It is known that mast cells and the nervous system have a complex interplay, as outlined in Doherty and White's work on relating MCAS to POTS. There are multiple proposed mechanisms in which mast cells affect nerve activity and vice versa [102]. However, it may be premature to map out relationships between the two conditions, because we are still unsure of both their pathogeneses. Another mechanism between the two was proposed by Shibao et al., when the first purported subset of patients with both MCAS and POTS was discovered. The mechanism consisted of a positive feedback loop, in which mast cell degranulation would release histamine, a vasodilator, leading to a compensatory increased in sympathetic activity. Sympathetic activity would result in increased vascular resistance, tachycardia, and release of norepinephrine and neuropeptide Y, which would lead to an increase in mast cell degranulation, beginning the cycle again [101]. However, the role of neuropeptide Y in this pathway is hypothetical and unproven. It is also hard to form conclusions when looking at this mechanism in light of the clinical timeline. In order for this theory to have merit, one of two scenarios would have to be observed. One, there would have to be evidence of mast cell degranulation occurring at abnormally increased levels when transitioning from a supine to standing position. Or two, upon standing, both POTS symptoms and MCAS symptoms would have to be present. At the present time, there is no evidence for the former scenario (mast cell degranulation triggered by positional change). While the latter scenario may be experienced on the basis of overlapping symptoms, MCAS symptoms are also reportedly experienced at multiple times of the day, not just when transitioning from supine to standing.

Lastly, the potential links between POTS and hEDS must be examined. To our knowledge, mechanisms between these two have not been explored. However, mechanisms between dysautonomia and hEDS have been explored. This mechanism states that potential abnormalities in connective tissue, specifically blood vessels, in patient with hEDS result in abnormalities in circulation, leading to sympathetic activation and orthostatic symptoms [96, 98, 99, 116]. Evidence against this mechanism lies in the fact that the vascular and vascular-like types of EDS (Villefranche nosology) have not been linked to POTS thus far in the literature [98]. Furthermore, authors were not able specify exactly what "connective tissue abnormalities" were present in hEDS patients. Some proposed abnormalities in connective tissue are speculated to be due to mutations that would affect collagen or elastin, which make up the matrix of vessels. However, no mutations or abnormalities in hEDS patients have been characterized yet. These hypotheses are mere conjecture until they are backed by evidence. More research must be done in characterizing the specific changes in connective tissue caused by hEDS and whether or not they are linked to altering nerve activity.

Recently, a new proposed mechanism to tie all three clinical entities together has surfaced, as summarized in a recent review by Bonamichi-Santos et al. [117]. The proposed mechanism centers on an autosomal dominant mutation in the gene that encodes α-tryptase. In 2014, Sabato et al. published data on a three generation family of seven members. All seven members had an elevated baseline tryptase level following autosomal dominant inheritance, and four members met criteria for a diagnosis of MCAS (one primary and three idiopathic type MCAS) [118]. In the same year, Lyons et al. described a similar population consisting of 33 individuals in nine families with elevated baseline tryptase levels following an autosomal dominant pattern. Of these 33 individuals, 78% of patients reported symptoms of mast cell activation, such as urticaria, flushing, and abdominal symptoms, but none met formal criteria for diagnosis of MCAS. Of these 33 individuals, 70% of patients had connective tissue abnormalities and 30% of patients were found to have autonomic dysfunction [119].

In 2016, the same authors identified germline duplications and triplications in the *TPSAB1* gene, which encodes α-tryptase, in 96 patients in 35 families with elevated baseline

tryptase levels and multisystem symptoms. Of the 96 individuals, 51% of patients had recurrent flushing/pruritus, 26% of patients had congenital skeletal abnormalities (including EDS), and 46% had elevated composite autonomic dysfunction scores (including POTS). It is important to note that neither EDS nor POTS were specifically diagnosed. Rather, these were fit into the categories congenital skeletal abnormality and autonomic dysfunction, respectively. Furthermore, these patients did not meet formal MCAS criteria; they only reported symptoms of mast cell activation. The authors also discovered that a triplication in the *TPSAB1* gene was associated with a higher baseline tryptase level and more symptomatic patients, when compared with a duplication in the *TPSAB1* gene, suggesting a gene-dose effect [120]. The mechanism behind increased levels of α-tryptase leading to these symptoms has not yet been discovered. Nonetheless, identifying this common genetic defect is helpful in elucidating a common mechanism between how these seemingly unrelated symptoms are linked. However, we believe that this genetic mutation will most likely only explain a very small subset of purported MCAS, EDS, and POTS patients.

The Subject of Gut Dysbiosis

A frequent claim of patients who have unexplained constitutional and gastrointestinal symptoms is that they have mast cell–induced gut dysbiosis. This is another concept that has found a life of its own, despite the lack of scientific evidence for this association. The role of tissue-based mast cells in human disease is extremely complex, and it is too presumptive to conclude that mast cells are the culprit in patients who present with gastrointestinal symptoms such as diarrhea or bloating. Mast cells have been demonstrated to have immune effects in vitro, which are not only limited to release of preformed and newly synthesized mediators but also include their effects on innate immunity through their expression of toll-like receptors (TLRs) [121–123] and their chemotactic functions [124, 125]. However, simply because one can detect these effects in a test tube does not translate to clinical effects in vivo.

Mast cells are tissues based cells, and they are not normally found in circulation. However, it is unclear how to interpret the presence of mast cells in tissues. One would normally expect to find some mast cells in biopsy specimens from the gastrointestinal tract. Previous studies have suggested that mast cell numbers of greater than 20 cells/high power field are abnormal, but it is not clear if this is pathogenic or an epiphenomenon [126]. In systemic mastocytosis diagnosed in patients that satisfy current diagnostic criteria, immunoreactivity for CD25 in gastrointestinal mast cells may be a validated marker for disease [127]. However, in the case of chronic diarrhea, colonic mast cell counts may be of limited diagnostic value, as demonstrated in a study of 76 patients with chronic diarrhea of unknown etiology. In this case, although the patients with chronic diarrhea had significantly higher average mast cell counts per hpf than control subjects (31 versus 24), no discriminatory cutoff value could be established to determine if mastocytic enterocystic enterocolitis is a true condition [128]. This was confirmed in another recent study in patients with irritable bowel syndrome [129].

The term gut dysbiosis refers to a microbial imbalance or anomalous microbiota in the gastrointestinal tract. While microbial variations have been detected in patients with various conditions ranging from eczema to autoimmune diseases, there is no evidence that an abnormal microbiome plays a pathophysiologic role in the various symptoms that affect patients who have been diagnosed with mast cell activation syndrome. There is even less evidence that mast cell activation syndrome leads to gut dysbiosis. Leaky gut syndrome is another dubious condition with little scientific basis. This refers to a condition in which a defect in intestinal mucosa permeability allows bacterial, toxins, metabolites, and toxins to "leak" into the circulation. This is again a condition with no scientific evidence for its existence, but patients with mast cell activation syndrome often cite leaky gut as a reason for their diarrhea and other symptoms and attempt to link this with mast cell dysfunction.

There is currently insufficient evidence to conclude that the gut microbiome is in anyway related to mast cell dysfunction. There is no scientific evidence that leaky gut is a real condition [130].

Conclusions

There is currently no scientific evidence of any association between MCAS, POTS, or hEDS. We are not refuting the claims that a possible association between these clinical entities may exist; we are simply arguing the need for reevaluation of these associations in light of new considerations, such as updated diagnostic criteria and updated guidelines for each. Furthermore, a scientific approach is warranted in linking these clinical entities. An evidence-based, common pathophysiologic mechanism between any of the two conditions, much less all three conditions, has yet to be described. Overlapping symptoms between the conditions cannot be utilized as adequate evidence to create an association between these entities. There may very well be a mechanism linking the three clinical entities. However, the patients reportedly affected by all three entities must be evaluated strictly before a diagnosis is made. Any vague or unquantifiable symptom must be treated with a degree of skepticism. Diagnostic criteria must be created to minimize false positives and carefully and strictly adhered to. Otherwise, a symptom such as fatigue may be attributed to chronic fatigue syndrome, EDS, or a myriad of other conditions.

Another concern is the variability of presentation. The vague symptomatology leads to patients with different phenotypes being grouped into one study, leading to conclusions derived in the presence of confounding variables and unclear patient selection. Any well-designed clinical trial must follow one of the basic caveats of the scientific method, which is to define a population that is truly uniform that can be studied without any fear of arriving at the wrong conclusion. Once a more homogenous population is established, further research into a potential pathophysiologic mechanism linking the conditions can be explored.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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