

Ehlers-Danlos Syndrome and Autonomic Dysregulation: "The Invisible Woman Has Significant Pathology and Morbidity."

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ABSTRACT

None

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INTRODUCTION

It is generally agreed that the most common types of abnormal collagen disorders are rheumatoid arthritis and lupus. However, Ehlers-Danlos Syndrome (EDS) is undoubtedly the most common inherited Collagen disorder [1]. While many geneticists consider EDS to be a rare disorder, and some state that its prevalence may be 1 in 5000, in clinical practice with proper recognition, we are seeing that it is much more common. It is usually transmitted as autosomal dominant with variable penetrance, and it appears females are both better transmitters and have more phenotype manifestations of the disorder for reasons that may reflect endocrine and neuro-cardiological bases. [2]

EDS, the name given to a group of more than 10 different inherited, clinically and genetically, heterogeneous connective-tissue disorders. It involves a genetic defect in collagen and connective tissue synthesis and structure. In 2017, a new international EDS classification was proposed with 13 different variants. EDS can affect the skin, joints, and blood vessels. This syndrome is

clinically heterogeneous and has been classically divided into six types (Classical, Hypermobile, Vascular, Kyphoscoliotic, Arthrochalasia, and Dermatosparaxis), with the underlying collagen abnormality being different for each type [3]. Those that do not qualify under the 2017 classification are classified as Hypermobility Spectrum.

What is the difference between EDS and Hypermobility Spectrum? While many experts lump the two together, the strict criteria published in the 2017 guidelines are used by purists to define EDS. Anything falling short of the 2017 criteria should be categorized as on the Hypermobility Spectrum if their Beighton score is 3/9 or higher [2]. However, there are individuals that have significant Hypermobility and have a very low Beighton score, < 3/9. They have subluxations of joints, pain syndromes, and flexibility and hypermobility, with other non-Beighton maneuvers such as arms and hands behind the back in a praying position, or placing their legs behind their head. In addition, there are those who have significant degenerative arthritis, and at one time may

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have fulfilled the Beighton criteria, but are not currently able. One must use judgement with these patients to classify if they would have fulfilled the EDS criteria. Needless to say, we have empirically observed that most patients with EDS or Hypermobility Spectrum have significant autonomic symptoms and dysfunction. Also, EDS has incomplete penetrance, genetically. When a patient gives a negative family history, further careful questioning may uncover Hypermobility in first-degree cousins and grandparents. This raises the question of whether the family history is positive. This is important, as there are many individuals that fall short of EDS criteria due to lack of family history.

EDS and its related disorders are a clinically variable and genetically heterogeneous group of hereditary monogenetic connective tissue disorders characterized by joint hypermobility, abnormal skin texture, and tissue fragility. This tissue fragility may include abnormal scarring, vascular fragility with easy bruisability, and a variable bleeding tendency. Other manifestations of generalized soft tissue fragility are also noted [1,4].

HISTORY OF EHLERS-DANLOS SYNDROME

EDS was described by two dermatologists; in 1891 by Alexander Nicolai Tschernogobov in Moscow and subsequently in 1900 by Edward Lauritz Ehlers in Copenhagen [5]. EDS was forgotten and rarely diagnosed until 1960 by Dr. Victor McKusick at Johns Hopkins University Medical School in Baltimore, MD. The two dermatologists basically grouped together signs that had been confirmed by other physicians who had also made these observations.

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The diagnosis of EDS is based on a joint rating system which is limited to a few joints that are not the most functionally important. This is known as the Beighton Test [6]. The Beighton system is often misinterpreted because of lack of sufficient training and clinical measurement even when a Goniometer is used. A Goniometer is rarely used in clinical practice.

In 2017, an international classification for the EDS recognized 13 subtypes. The majorities could be identified by genetic testing, except for the most common hypermobile-type [7]. Hypermobile EDS (EDSh) has no appreciable genetic etiology for which to test. Therefore, there is no gold standard. This reflects its genetic heterogeneity. With this syndrome, some individuals are asymptomatic and some are very symptomatic with joint laxity. A diagnosis of EDSh can only be assigned if they meet the criteria described in the Table in Figure 1, which is taken from the EDS website [8]. Generally, there is a 9-point scoring system for grading the Beighton system and the cutoff for EDSh definition is greater than or equal to 5 points out of 9. However, the joint range does decrease with age. This is Criterion 1.

In Criterion 2 (see Figure 1), there are three features (A, B & C). From Feature A, a total of 5 items out of 12 must be met. In Feature B (of Criterion 2 in Figure 1), a positive family history with one or more first-degree relatives independently meeting the current diagnostic criteria for EDSh must be met. Feature C involves musculoskeletal complications where at least 1 of 3 items must be met.

For Criterion 3, all of the following prerequisites must be met to diagnose EDSh. If the criteria are not met, but (1) an individual has Beighton score which is

considered significant, or (2) the clinical history is significant, then the definition of Hypermobility Syndrome is often given to the patient. When one looks at the differential diagnosis of EDS_h, one needs to exclude Marfan-related disorders, and oftentimes when an individual does not meet the strict criteria of EDS_h, according to Figure 1, they may be lumped in the category of other Hypermobility syndromes. Many physicians believe there was a



Diagnostic Criteria for Hypermobile Ehlers-Danlos Syndrome (hEDS)

This diagnostic checklist is for doctors across
all disciplines to be able to diagnose EDS



Patient name: _____ DOB: _____ DOV: _____ Evaluator: _____

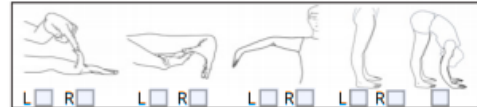
The clinical diagnosis of hypermobile EDS needs the simultaneous presence of all criteria, 1 **and** 2 **and** 3.

CRITERION 1 – Generalized Joint Hypermobility

One of the following selected:

- ☐ ≥ 6 pre-pubertal children and adolescents
- ☐ ≥ 5 pubertal men and women to age 50
- ☐ ≥ 4 men and women over the age of 50

Beighton Score: 0 /9



If Beighton Score is one point below age- and sex-specific cut off, two or more of the following must also be selected to meet criterion:

- ☐ Can you now (or could you ever) place your hands flat on the floor without bending your knees?
- ☐ Can you now (or could you ever) bend your thumb to touch your forearm?
- ☐ As a child, did you amuse your friends by contorting your body into strange shapes or could you do the splits?
- ☐ As a child or teenager, did your shoulder or kneecap dislocate on more than one occasion?
- ☐ Do you consider yourself "double jointed"?

CRITERION 2 – Two or more of the following features (A, B, or C) must be present

Feature A (five must be present)

- ☐ Unusually soft or velvety skin
- ☐ Mild skin hyperextensibility
- ☐ Unexplained striae distensae or rubae at the back, groins, thighs, breasts and/or abdomen in adolescents, men or pre-pubertal women without a history of significant gain or loss of body fat or weight
- ☐ Bilateral piezogenic papules of the heel
- ☐ Recurrent or multiple abdominal hernia(s)
- ☐ Atrophic scarring involving at least two sites and without the formation of truly papyraceous and/or hemosideric scars as seen in classical EDS
- ☐ 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
- ☐ Dental crowding and high or narrow palate
- ☐ Arachnodactyly, as defined in one or more of the following:
 - (i) positive wrist sign (Walker sign) on both sides, (ii) positive thumb sign (Steinberg sign) on both sides
- ☐ Arm span-to-height ratio ≥ 1.05
- ☐ Mitral valve prolapse (MVP) mild or greater based on strict echocardiographic criteria
- ☐ Aortic root dilatation with Z-score $> +2$

Feature A total: 0 /12

Feature B

- ☐ Positive family history; one or more first-degree relatives independently meeting the current criteria for hEDS

Feature C (must have at least one)

- ☐ Musculoskeletal pain in two or more limbs, recurring daily for at least 3 months
- ☐ Chronic, widespread pain for ≥ 3 months
- ☐ Recurrent joint dislocations or frank joint instability, in the absence of trauma

CRITERION 3 – All of the following prerequisites MUST be met

- ☐ 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 CTD (e.g. Lupus, Rheumatoid Arthritis, etc.), 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 toward a diagnosis of hEDS in this situation.
- ☐ 3. Exclusion of alternative diagnoses that may also include joint hypermobility by means of hypotonia and/or connective tissue laxity. Alternative diagnoses and diagnostic categories include, but are not limited to, neuromuscular disorders (e.g. Bethlem myopathy), other hereditary disorders of the connective tissue (e.g. other types of EDS, Loays-Dietz syndrome, Marfan syndrome), and skeletal dysplasias (e.g. osteogenesis imperfecta). Exclusion of these considerations may be based upon history, physical examination, and/or molecular genetic testing, as indicated.

Figure 1: Hypermobility-Ehlers-Danlos Diagnostic Checklist from the EDS website. See text for details. [reprinted from 8].

significant overlap of the other Hypermobility syndromes, especially since there are many factors which may prevent one from fulfilling all of the necessary criteria in the Table in Figure 1. To this end, we have developed another questionnaire with an eminent Rheumatologist which we feel is more complete (see Appendix).

EDS, as it affects collagen, can affect almost any organ system. As we will discuss later, oftentimes this is the result of a functional abnormality with the Autonomic Nervous System, specifically its two branches the Parasympathetic and Sympathetic (P&S) nervous systems, where innervation with all organs and organ systems occurs. For example, rapid heart rates due to autonomic dysfunction may cause a cardiomyopathy. As the left ventricular and diastolic dimension progressively increases, a cardiomyopathy can occur and decrease in the ejection fraction can be seen [9]. Another cardiac abnormality seen with EDS includes aortic root dilatation. This, however, is typically mild [10]. Based on the retrospective study of 302 patients with EDS between 1995 and 2006 with classic or EDS_h, 252 patients (83.4%) had more than one echocardiogram, 6% percent had mitral valve prolapse, which is mild in most patients and only mild to moderate in one, and 12 patients had mitral valve regurgitation: mild in 11 patients and moderate to severe in only one patient. Of 213 patients with aortic root measurements, only 10.8% had a dilated aorta, and this is generally mild. They conclude that mitral valve prolapse may be detected in patients with classical EDS, Hypermobile EDS, and hypermobility spectrum disorder. Another group of 209 patients [11] conclude that mitral valve prolapse may be detected in

patients with classical EDS_h and Hypermobility Spectrum syndromes, and they found the incidences of mitral valve prolapse at 6.2% and aortic root dilatation of 1.6%.

Since no genetic test is available, diagnosis of EDS_h (the hypermobile variant) requires the fulfillment of the criteria in the Table in Figure 1. However, genetic testing is required, and may be definitive in a proper clinical context, for many of the other 13 EDS subtypes (excluding EDS_h). A mutation of at least 19 genes have been linked to EDS. There are no known risk factors, and this appears to be a genetic disorder of collagen causing abnormal connective tissue. As connective tissue is involved in all organs and organs systems of the body, EDS and Hypermobility may affect more than one, if not all, systems of the body.

Various organ systems are affected functionally and anatomically with EDS. For example, mucosal involvement (*i.e.*, Mucosal Xerosis) is common in the EDS_h, most likely due to a consequence of autonomic dysregulation [12,13]. Xerostomia Xerophthalmia (dry mouth and dry eyes, respectively), Vaginal dryness, and Hyperhidrosis frequently accompany complaints of Mucosal Xerosis. Other comorbidities may involve cardiac structural abnormalities, such as Aortic Root dilatation, Mitral Valve Prolapse and tachycardia-induced Cardiomyopathy, GI functional abnormalities, such as gastroparesis and GI motility disorders of both the small and large bowel. Again, these abnormalities may be related to autonomic dysfunction, but not always.

The identification and nature of the connective tissue defects in relation to the function of the GI tract is an important question and still requires significant genetic and validation studies of both human and animal models to answer. There is the suggestion of a link between inflammatory bowel disease and EDS_h, but this is not yet conclusive [14]. Irritable bowel syndrome is the most common GI functional abnormality we see in clinic. It was found that Hypermobile EDS patients who attended a Hypermobility clinic had significant more GI symptoms compared to age- and sex-matched controls (37% versus 11%). Most common GI symptoms were nausea, abdominal pain, constipation, and diarrhea [15].

Neurological and spinal manifestations of the EDS have been detailed [16]. These investigators describe Chiari Malformation Type 1, and have demonstrated that the female-to-male proportion is higher (9:1) than in the general population (3:1). Also, headache is commonly seen in EDS, where causes include: migraines, muscle tension, intracranial hypertension, craniocervical instability, cervical spine disorders, temporomandibular joint disease, carotid dissections, and other physical condition. We oftentimes will do carotid ultrasounds on patients who have refractory headaches despite treatment to be certain there is no chronic carotid dissection. Some patients suffer status migrainous [17,18,19].

Dystonia has been described in 45% of EDS patients, according to a cohort study of 626 patients. These patients were treated with Levodopa and had improvement with Dystonia pain and fatigue [20]. Disorders of Proprioception have often been seen with EDS and have responded to treatment with tight garments, physiotherapy, and proprioceptive shoe inserts [21].

Chronic pain is also seen in EDS and is quite significant and disabling. This in conjunction with chronic fatigue is also experienced by most patients. These are two of the most disabling symptoms. The pain often presents as a diffuse body pain affecting almost any part of the body. It can be severe, and in one study, the pain prevalence was up to 90% [22]. The pain may be musculoskeletal or widespread. It may be acute or chronic, but is usually chronic. The pain is difficult to treat and is often associated with subluxation of many joints, predominately large joints, such as knees, elbows, and shoulders, but the fingers, ankles, and temporomandibular joints can also be severely affected. We commonly find patients who come to our clinic with a diagnosis of Fibromyalgia when in reality their pain is due to widespread pain from EDS and EDS_h syndrome, as they meet the criteria seen in the Table in Figure 1 when examined. We have even questioned whether Fibromyalgia is a real diagnosis; as with EDS, there is no gold standard test, such as a blood test or genetic test for this disorder, and many of the patients who come to our clinic with diffuse widespread pain do have laxity of their ligaments and joints, abnormal collagen, and are found to have EDS_h. The joint-musculoskeletal system is most affected and responsible for chronic pain in EDS by virtue of the fact that the collagen is abnormal.

Increased Sympathetic activity, regardless of the cause, will increase or amplify pain responses (see Figure 2). Regardless of the source, increased Sympathetic activity increases stress responses and thereby increases pain responses. Increased Sympathetic activity begets increased stress begets increased pain perception which begets more Sympathetic activity. This

cycle is meant to be transient, normally broken by a complimentary, short-term rise in Parasympathetic activity. However, this cycle may become chronic, causing persistent Sympathetic Excess (SE). Prolonged SE amplifies and prolongs the pain response, causing pain to become chronic. The underlying chronic SE also leads to increased blood pressure and heart rate and increased morbidity and mortality risk in chronic pain

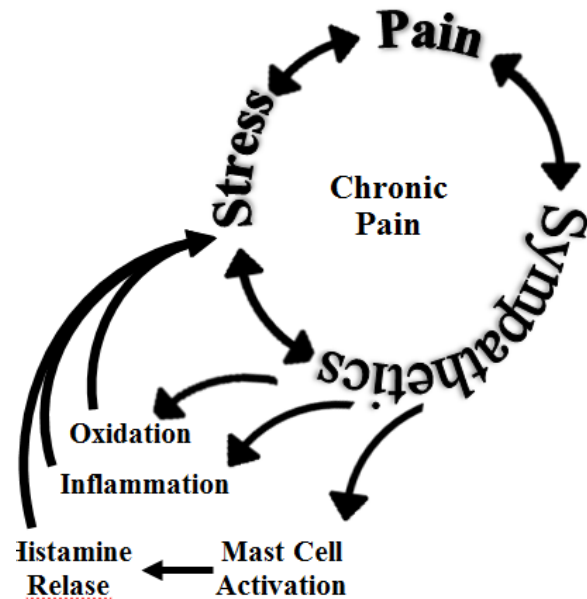


Figure 2: A schematic representation of the relationship between increased Sympathetic activity, regardless of the source of stress and pain. Increased Sympathetic activity begets increased stress responses begets increased pain perception which begets more Sympathetic activity. This cycle is meant to be transient, often broken by a complimentary, short-term rise in Parasympathetic activity for some reason. However, this cycle may become chronic, causing persistent Sympathetic Excess (SE). Prolonged SE amplifies and prolongs the pain response, and increased blood pressure and heart rate increase morbidity and mortality risk in chronic pain patients. Porous connective tissue due to abnormal collagen from EDS or Hypermobility Spectrum disorder increases and prolongs immune responses, which causes increased and prolonged Parasympathetic activation (Parasympathetic Excess, or PE). PE begets SE and is a reason for persistent pain responses in EDS and Hypermobility Spectrum patients. Normalizing PE helps to normalize SE and reduce pain.

patients. Porous connective tissue due to abnormal collagen from EDS_h or Hypermobility Spectrum disorder increases and prolongs immune responses, which causes increased and prolonged Parasympathetic activation (Parasympathetic Excess, or PE). PE begets SE and is a reason for persistent pain responses in EDS_h and Hypermobility Spectrum patients. Normalizing PE helps to normalize SE and reduce pain, as well as the associated morbidity and mortality risks of chronic pain.

EDS may also affect the bladder, but again, this is often due to Autonomic dysfunction with bladder urgency, frequency, or urinary retention. It also affects the hematological system with increased bruising and bleeding. As can be seen in the Table in Figure 1, hernias of varied types are common, as well as Hiatal hernias, although they are not mentioned in the Table. Hiatal hernias are seen in a higher percentage of patients with EDS symptoms. Abnormal collagen involves other organ systems including: ocular, reproductive (due to abnormalities in the barrier isolating gametes, in addition to vaginal dryness), the central nervous system due to abnormalities in the blood-brain barrier, and the skin, possibly causing severe scarring, fragile skin, soft velvety skin, and slow and poor wound healing. The development of Molluscoid Pseudotumors can be seen in various types of EDS.

Chronic fatigue, after chronic pain, may be the most disabling symptom of EDS_h. It is the belief that the chronic fatigue is most likely related or orthostatic intolerance and autonomic dysfunction that will be discussed later in more detail in this manuscript. Multiple studies have demonstrated chronic fatigue as a major contributor to disability in the joint Hypermobility syndrome and have

associated complaints of muscle weakness, sleep disturbances, and other features of chronic fatigue, including decreased exercise intolerance [23,24].

Figure 3 shows a schematic that details the extra-articular manifestation of the EDS_h type, which is alternatively termed Joint Hypermobility Syndrome [25] and is reprinted here. The schematic demonstrates the association of Joint Hypermobility Syndromes and EDS_h with chronic pain syndrome, chronic fatigue syndrome, functional gastrointestinal disorders, chronic headache disorders, pelvic dysfunction, exocrine gland dysfunctions, cardiovascular dysautonomias, and immune system dysregulation; the latter of which is an extremely important area of recent investigation. In addition, the association of EDS and Mast Cell Activation Syndrome is reasonably being recognized and will subsequently be discussed.

It is important to do a differential diagnosis if the diagnosis of Hypermobility or other types of EDS are not apparent. A search for other disorders of joint hypermobility, chronic pain, and fatigue should be sought as should bleeding disorders, such as Hemophilia and von Willebrand disease, pediatric and juvenile disorders associated with hypermobility, rheumatologic diseases, such as Ankylosing Spondylitis, Rheumatoid Arthritis, and Fibromyalgia, where again, we question Fibromyalgia as a valid disease entity. Also, Osteoarthritis of the knee should be considered. Other neurological diseases need to be excluded under differential diagnoses, including hereditary and acquired sensory, motor, or autonomic polyneuropathies, and other degenerative neurologic diseases, such as Multiple Sclerosis and Amyotrophic Lateral Sclerosis. More importantly, we oftentimes need to exclude vascular diseases once we

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have been comfortable that there is no question of a vascular type of EDS. These vascular type disorders, which can involve abnormal collagen, include: Marfan's disorder, Osteogenesis Imperfecta, Loeys-Dietz Syndrome, Larsen Syndrome, Ullrich Disease or Scleratonc Musculoskeletal Atrophy, Stickler Syndrome, DeBarsy Syndrome, Arterial Tortuosity Syndrome, Occipital Horn Syndrome, and Lateral Meningocele Syndrome.

Besides the chronic pain, chronic fatigue, and many of the other organ system abnormalities, which are both functional and structural and cause symptoms and disabilities within patients, one of the most prevalent and disabling problems is Autonomic Dysfunction, which is also caused by EDS.

II: AUTONOMIC DYSFUNCTION AND EHLERS-DANLOS SYNDROME.

Patients with EDS_h or Hypermobility Spectrum disorders have a significant amount of Dysautonomia symptoms as seen in Table 1 (this table is the questionnaire that we use in our office clinic). Many of these symptoms are related to Chronic Fatigue, Orthostatic Intolerance, Cognition or Brain-Fog, sweating, Salivary Gland dysfunction, pain, temperature dysregulation, and Urinary Tract symptoms. Also, Syncope and pre-Syncope are common Dysautonomia symptoms. Dysautonomic Syncope has been reported to occur in patients with Joint Hypermobility Syndrome and include symptoms of Syncope, pre-Syncope, palpitations, chest discomfort, fatigue, heat intolerance, Orthostatic Hypotension, Postural Orthostatic Tachycardia Syndrome (POTS), and uncharacterized Orthostatic Intolerance-type symptoms [26]. It is thought that connective tissue laxity seen in hypermobility patients allows for a greater

EDS & AD

than normal degree of vascular dispensability, leading to an exaggerated amount of blood pooling in the lower extremities during upright posture

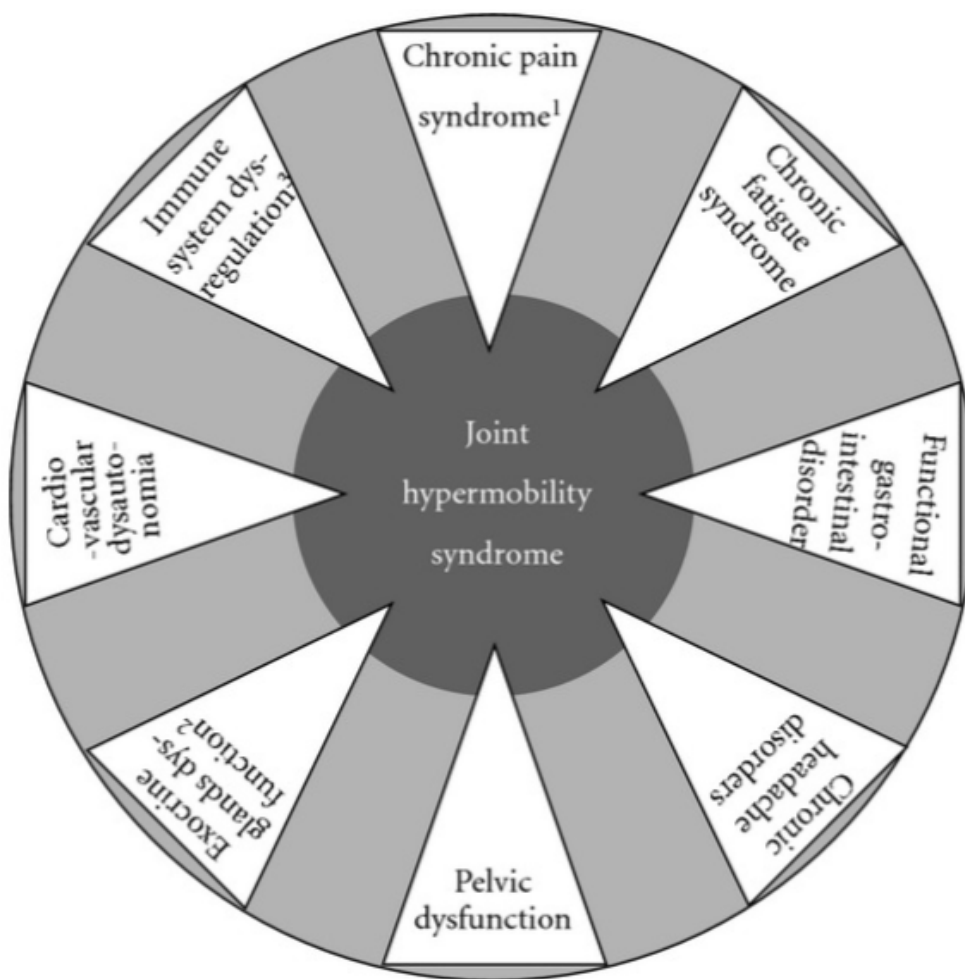


Figure 3: A schematic representation of extra-articular manifestations of Hypermobility type EDS (alternatively termed Joint Hypermobility Syndrome). The dark grey circle symbolizes the phenotypic spectrum of this condition, which includes a series of functional somatic syndromes and tissue- and organ-specific dysfunctions (i.e., the white triangles, whose tips are indeed comprised within the dark circle). Outside the clinical spectrum of Hypermobility type EDS, the single phenotypic components may be observed in isolation or perhaps in incomplete associations within the general population (the larger and light grey circle). It is expected that, in the future, the study of heritable dysfunctions of the connective tissue will move from the dark gray circle to the light gray one, as a prominent field of interest. 1. Mostly including Fibromyalgia, Myofascial pain, and Complex Regional Pain Syndromes. 2. Comprising Xerophthalmia, Xerostomia, Vaginal Dryness, and abnormal sweating. 3. Asthma, Atopy, gluten sensitivity, Inflammatory Bowel Disease, and recurrent Cystitis are all possible manifestations of an underlying immune system dysregulation. [reprinted from **25**, p 28, open access]

Table 1: Common Dysautonomia symptoms. Circle the symptoms you experience.

1. Lightheaded	2. Fainting and near fainting	3. Fatigue	4. Brain Fog or Mental cloudiness
5. Difficulty finding words	6. Short term memory loss	7. Hypersensitive to light, sound, motion, touch	8. Pins and needles in arms/legs
9. Numbness in hands and feet	10. Coat-hanger pain in neck and shoulders	11. Migraine or Headache	12. Tension headaches
13. Nausea or vomiting	14. Difficulty standing	15. Chest pain or Palpitations	16. Short of breath
17. Hypermobility, Joints pop out	18. Depression or Anxiety	19. Sweat too much or too little	20. Insomnia or Sleep Difficulty
21. Salivate too little, or Dry mouth	22. Cold hands or feet	23. Dimmed vision	24. Dimmed hearing or ringing in ears
25. Hot or cold weather bother you	26. Hands or Feet turn colors (Red, White, or Blue) in cold temperatures	27. Chronic Pain	28. Diarrhea or Constipation

[27,28,29]. But it appears that more than just venous pooling may be responsible for the severe orthostatic intolerance, pre-Syncope, and Syncope-type symptoms seen in Ehlers-Danlos patients and other Hypermobility Spectrum patients. This is where autonomic dysfunction and the lack of Sympathetic activity with standing occurs, the so-called Sympathetic withdraw.

For decades, patients with symptoms of Chronic Fatigue, Orthostatic Intolerance (which we now know refers to a lack of cerebral blood flow to the brain on upright position), Anxiety, GI symptoms, and other Autonomic dysfunction symptoms (as listed in Table 1), especially women, were often thought of as functional or having invisible symptoms. We term these patients “the invisible women” because the majority of them were women. They had Chronic Fatigue and pain all over. In reality, this is exactly what we see with EDS patients, predominately female, that present to our clinic with chronic pain, subluxation of joints, Anxiety, palpitations, chest pain, Orthostatic Intolerance, pre-Syncope, and many other symptoms as seen in Table 1.

Why are these individuals invisible? One reason is that there is no gold standard to diagnose EDS, no blood test, or genetic testing marker that can be used. This is also a reason for its low diagnosis and the reason why many patients are mislabeled as Anxiety or Fibromyalgia. Second, only a minority of physicians are even familiar with Autonomic Dysfunction and know that there is testing available, such as cardio-respiratory testing, sudomotor testing, tilt testing, even old-style HRV testing or a “Poor Man's tilt test” performed in the office where individuals lie down, sit down, and stand and vital signs are taken at appropriate

intervals is better than nothing. Therefore, not only are EDS and Hypermobility syndromes not diagnosed in the outpatient setting, but Autonomic Dysfunction is also not diagnosed, and therefore the patient appears invisible with symptoms that can be easily attributable to something such as Anxiety, Fibromyalgia, or psychological causes. Many patients are also diagnosed with conversion reactions. This is unfortunate, since these diagnoses should be made by psychiatrists as some of the disorders such as we are describing are excluded.

Dysautonomia in EDS is often apparent and is seen when patients tire easily, usually after activity or after they eat a heavy meal. Oftentimes, these patients are misdiagnosed with Hyperthyroidism, Hypoglycemia, Depression, and Fibromyalgia. As mentioned, the majority of these are female. They often have pre-Syncope or Syncope, low blood pressure, cold intolerance, disorientation, or poor memory, concentration, or brain fog. These are symptoms of Dysautonomia. If blood pools in the lower extremity veins, and the Sympathetic nervous system is not properly activated when an individual stands (this condition in autonomic terms is known as Sympathetic Withdraw (SW) [30]), it leads to improper blood perfusion of the brain and these symptoms all result. One study found that 60% of patients with Chronic Fatigue Syndrome had Joint Hypermobility compared to 24% of controls [31]. Another study noted that 64% of adults with Fibromyalgia really had Joint Hypermobility [32]. In a third study [29], Joint Hypermobility spectrum patients were more likely than controls to have Syncope, pre-Syncope, palpitations, chest discomfort, heat

intolerance, and when undergoing autonomic testing, Orthostatic disorders, including Orthostatic Hypotension, Postural Orthostatic Tachycardia, and uncategorized Orthostatic Intolerance symptoms. Orthostatic disorders were found in 70% of Joint Hypermobility patients in contrast to 10% of controls. These authors concluded Dysautonomia was due to extra-articular manifestations of Joint Hypermobility syndrome or Hypermobility type 3 EDS syndrome.

In a study [33] of 39 females with EDS_h and 35 age-matched controls, all of whom underwent autonomic function testing using a heart rate variability and baroreflex sensitivity analysis, the EDS_h patients showed Autonomic Dysregulation with increased Sympathetic activity at rest and reduced Sympathetic reactivity to stimuli. Increasing resting activity was indicated by a higher LF:HF ratio as compared to controls: 1.7 ± 1.23 versus 0.9 ± 0.75 ($p=0.020$). Decreased reactivity was indicated by a greater systolic blood pressure fall during Valsalva: $-19 \text{ mmHg} \pm 12$ versus -8 ± 10 ($p<0.001$). The systolic fall was accompanied by a smaller initial diastolic blood pressure during tilt: 7% versus 14% ($p=0.030$). Orthostatic Intolerance was significantly more prevalent in EDS Hypermobility patients than control: 74% versus 34%. The Orthostatic Intolerance was most frequently expressed as Postural Orthostatic Tachycardia. Low QSART testing (Sudomotor or Small Fiber testing) responses suggested that Sympathetic neurogenic dysfunction was more common in EDS Hypermobility patients, which explained their Dysautonomia. The conclusions are that Dysautonomia consisting of Cardiovascular and Sudomotor dysfunction is present in EDS_h patients. Neuropathy and connective

tissue laxity were implicated as playing a role in the development.

It is undisputed that patients with EDS_h have high incidents of Autonomic Dysfunction symptoms and higher prevalence of abnormal Autonomic testing. Testing on Aortic continuous wave doppler ultrasound measurements for Aortic wall compliance and Joint Hypermobility support that there are connective tissue abnormalities in dependent blood vessels which distend excessively in response to ordinary hydrostatic pressures [28,34]. Therefore, as mentioned earlier, abnormal connective tissue and dependent blood pressure traction with veins distending excessively in response to standing leads to venous pooling. This has hemodynamic and symptomatic consequences which lead to cerebral hypoperfusion. Cerebral hypoperfusion leads to symptoms of Orthostatic Intolerance: brain fog and cognitive difficulties, pre-Syncope, and at times even overt Syncope. Evidence [29] indicates that these symptoms are due to alpha-adrenergic and beta-adrenergic hyper-responsiveness. Subsequently, a hyperadrenergic state was identified in 29% of cases of Postural Orthostatic Tachycardia with Hypermobility syndrome [35]. We have found that using cardiorespiratory testing, Sympathetic Withdraw (alpha-adrenergic hypo-responsiveness) is a major mechanism operative in patients who have EDS with venous pooling on assuming the upright position, regardless of their resting Sympathovagal Balance (beta-adrenergic state) [36].

Abnormal cardiovascular autonomic profiling in EDS_h patients was confirmed [37], as well as a higher baroreflex sensitivity as a potential disease marker. The response to cardiovascular reflex comprising of deep breathing, Valsalva

maneuvers, handgrip test, and head-up tilt test (providing the 30:15 ratio) was studied in 35 EDS patients. Heart rate and blood pressure variability were investigated by spectral analysis and compared to a controlled group. At tilt, 48.6% of the patients showed Postural Orthostatic Tachycardia, 31% showed Orthostatic Intolerance, and 20% showed normal results. Only one patient had Orthostatic Hypotension. The spectral analysis showed significantly higher baroreflex sensitivity values at rest compared to controls. Small Fiber neuropathy was commonly found in the EDS patients [38], suggesting that Small Fiber Neuropathy may be a cause of neuropathic Postural Orthostatic Tachycardia. However, a phase 4 overshoot of the Valsalva maneuver was commonly demonstrated. This would suggest a more complex mechanism for the Postural Orthostatic Tachycardia seen in EDS. The phase 4 overshoot reflects Parasympathetic activity.

A strong association has been shown [39] between several forms of cardiac dysfunction, including Postural Orthostatic Tachycardia, and Joint Hypermobility in a review of ten papers. This study found that it is important to screen for hereditary connective tissue disorders in Dysautonomia patients who have Orthostatic Intolerance disorders. The screen is to rule out higher mortality risks, including due to Marfan Syndrome and vascular EDS. This is important, even though vascular EDS is a much rarer form of EDS. Also, Marfan Syndrome is much less common than EDS. Marfan Syndrome can be identified by applying the criteria for Marfan Syndrome and doing genetic testing for Marfan Syndrome. The more important issue is to identify EDS patients who have Autonomic Dysfunction. Not that the severity of the

morality risks is unimportant, but the degradation of quality of life and productivity is far more prevalent. Identifying Autonomic Dysfunction (specifically, differentiating Parasympathetic from Sympathetic dysfunction) enables more specific therapy plans to better treat patient comorbidities, such as chronic pain, chronic fatigue, and joint laxity, and also to give them a better understanding of their disease. This also prevents the misdiagnoses of Fibromyalgia, Anxiety, Depression, and so forth.

In addition to Postural Orthostatic Tachycardia and Orthostatic Intolerance, Orthostatic Hypotension and Neural-Mediated Hypotension also refer to Vasovagal Syncope or Neurocardiogenic Syncope and should also be assessed for Ehlers-Danlos patients [40]. It is possible that low blood pressure, increased peripheral venous dilatation of blood pooling, low-circulating blood volume, medications, elevated circulating catecholamines, autoimmunity, and excess levels of histamine are caused by a rare brain or spinal cord impingement from a Chiari syndrome or cranial cervical instability. The impingement may also contribute in one way or another to Autonomic Dysfunction mechanisms seen in patients with EDS. It is noted that histamine can induce hypotension and tachycardia. Mast Cell activation is excessive histamine release and has been identified in cases of EDS [41,42]. There has been controversy regarding Mast Cell disorders in EDS. Mast Cells reside in connective tissue, helping to protect from foreign substances invading the body. A review of the biological feasibility of how Mast Cell Activation can contribute to symptoms in patients with Ehlers-Danlos syndrome [43] demonstrated a relationship between Mast Cell Activation Syndrome,

EDS, and Postural Orthostatic Tachycardia Syndrome; the latter being a form of Dysautonomia.

One of the types of Mast Cell found residing in the connective tissue contains Tryptase. Its granules express Interleukin 5 and Interleukin 6. EDS functional Gastrointestinal disorders, Eosinophil Gastrointestinal disorders, and an increased prevalence of Asthma and Neuropsychiatric conditions, Osteoporosis, and Orthostatic Intolerance can result and be linked to abnormal Histamine production (a function of Mast Cells). The subpopulation of EDS patients that have been found to have Mast Cell Activation disease have many of the above functional disorders. An increased number of mast cells in the eyelids has been found in patients with connective tissue diseases [44]. However, (generalized) connective tissue disease patients previously diagnosed with EDS Hypermobility type that no longer meet the newer restricted criteria for EDS may for a less severe Hypermobility syndrome [45]. They feel the evidence-based pathophysiological mechanism between Mast Cell Activation Syndrome and EDS is not quite as clear, especially when POTS is also included. However, EDS, POTS, and Mast Cell Activation Syndrome are not very common disorders by themselves, and when found in aggregates, suggest there is a common mechanism amongst them. Further research is needed.

When a dysautonomia is detected by clinical evaluation and autonomic testing in the laboratory, an etiology is sought. For example, in a study [46] of 91 POTS patients evaluated using the 2017 EDS criteria, 28 met the criteria for EDS (31%). The initial 24% of participants had generalized hypermobility without meeting EDS criteria. Therefore, in patients

diagnosed with Postural Orthostatic Tachycardia, one should search for Hypermobility syndromes. However, potential etiologies for dysautonomia also include: Amyloidosis, Antiphospholipid Syndrome, Celiac Disease, Charcot-Marie Tooth disease, Chiari Malformation, Chronic Inflammatory Demyelinating Polyneuropathy, Crohn's Disease and Ulcerative Colitis, deconditioning, Delta Storage Pool Deficiency, Diabetes and pre-Diabetes, EDS, Mast Cell Disorders, Mitochondrial disease, Paraneoplastic syndromes, Parkinson's Disease, Sarcoidosis, Sjogren's Syndrome, and toxicity from alcohol, chemotherapy, and heavy metals which may also damage the autonomic nerves. Also, physical trauma, surgery, and pregnancy need to be considered. In addition, one should consider vitamin deficiencies [47]. Therefore, not all individuals with Dysautonomia, especially if they are female, and even if they have chronic pain and some degree of hypermobility of joints, may necessarily have EDS as the cause of their Dysautonomia, and one must still exclude the other possibilities. Many of the other abnormalities are much more rare than EDS. Diabetes and deconditioning are much more common.

Chronic fatigue is a significant symptom of Autonomic Dysfunction. We believe it is due to Orthostatic Intolerance from lack of proper cerebral blood flow and is often due to venous pooling in the lower extremities with abnormalities of the Autonomic Nervous System that cause the lack of appropriate compensation. Mainly, Sympathetic Withdraw occurs and the Sympathetics do not respond appropriately. Many patients with chronic fatigue respond simply to compression stockings and fluids and often low-dose vasoactive agents, such

as Midodrine and Florinef. These are regimens that are effective for all forms of Orthostatic Intolerance, whether they be POTS, Orthostatic Hypotension, or even delayed Orthostatic Hypotension (Vasovagal Syncope). Chronic fatigue is reported in 84% of patients with EDS [48]. The impact of fatigue on daily life is just as traumatic as chronic pain, if not more. Sleep disturbances, concentration problems, social functioning, and pain severity are also seen in EDS patients with chronic fatigue [48]. Muscle weakness has been shown to be associated with fatigue [49,50]. This fatigue worsens with exercise and affects gait pattern [51,52]. It is noted that the orthostatic intolerance in POTS often seen in patients with EDS relates increased Sympathetic activity at rest and reduced Sympathetic activity to stimuli, as discussed earlier [53]. Chronic fatigue may be a manifestation of acquired Mitochondrial disorder. When the Mitochondria function well during exertion, Lactic Acid is quickly converted back to Glucose by Pyruvate and the Lactic Acid burn disappears. The Glucose conversion to Lactic Acid produces two molecules of ATP for the body to use, but the reverse process requires six molecules of ATP. If there is no ATP available, such as with an acquired myocardial disorder, or when the Mitochondria fail, the Lactic Acid may persist for minutes, or indeed hours, causing pain, and this may be one of the mechanisms responsible for chronic fatigue, mainly, acquired Mitochondrial Dysfunction [54]. This is one rationale for using mitochondrial cofactor cocktails which involve Coenzyme Q10, L-carnitine, and Alpha Lipoic Acid. Some have recommended measuring Coenzyme Q10 levels, SOD ASE levels, Glutathione levels, Peroxidase levels, L-carnitine levels, NAD levels, and cell-free

DNA. Cell-free DNA may be the most useful as it may reflect severity of illness. There are tests known as mitochondrial function profiles that are available for research purposes that can measure these.

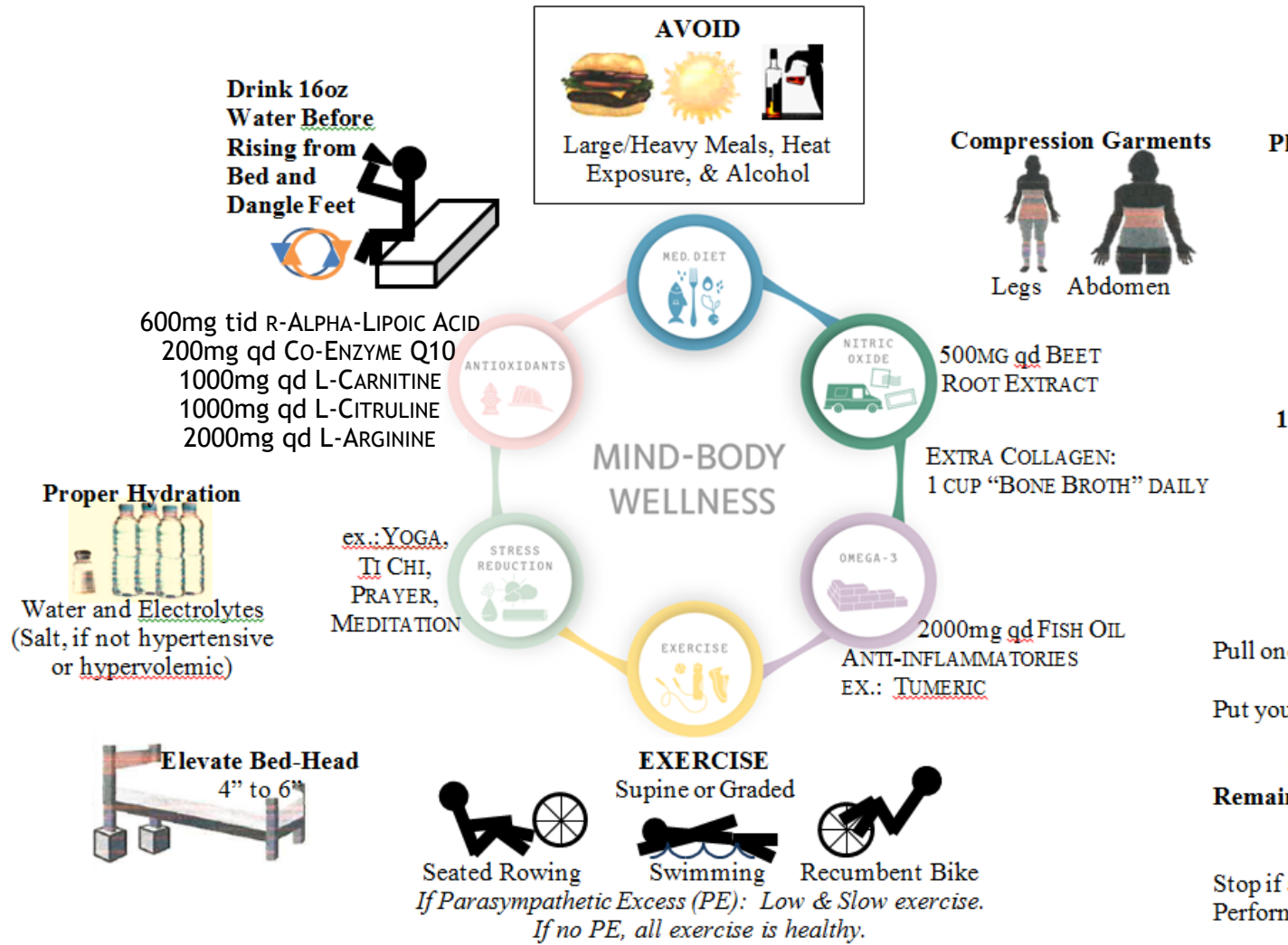
III: TREATMENT

Treatment for Autonomic Dysfunction with EDS is quite complex. First, education and a patient's awareness that they have a true disorder and not a functional or psychological disorder is of paramount importance. Second, correcting an incorrect diagnosis, such as Fibromyalgia or Depression, must be done. Third, appropriate autonomic testing in an experienced autonomic lab is helpful in identifying both the presence and severity of abnormalities, specifically in Sudomotor testing and in heart rate variability or cardiorespiratory testing. Fourth, 48-64 ounces of fluid with electrolytes is preferred if there is no contraindication, and we use a 13-point algorithm (Figure 4) [54]. The 13-point algorithm starts with patients, first thing in the morning, dangling their feet over the edge of the bed, drinking 12-16 ounces of water (with no electrolytes), and taking any of their pharmacology before even standing. Their pharmacology is usually a vasoactive agent such as low-dose Midodrine. The water is to replace the water that is breathed out overnight. If Sympathetic Withdraw and venous pooling is operative, we use compression stockings, oftentimes at multiple levels as more than one level has been shown to normalize tilt-test abnormality results [55].

A recent publication on Corlanor in Hyperadrenergic-POTS has raised the question of whether this may be more beneficial than Propranolol or vasoactive agents. However, for Orthostatic Intolerance disorders, we use vasoactive

agents preferentially. First, Midodrine is preferred over Florinef. However, sometimes using both together at low doses while taking the proper precautions [reference our paper on Northera and Midodrine in press] helps as they are synergistic. A graded or low-and-slow exercise program is often recommended as many of these patients have concomitant Vagal disorders effecting their responses to exercise, including health exercise. Low-and-slow exercise may also be recommended in chronic fatigue states where patients need to conserve their energy and exercise slowly to recondition their hearts, nerve fibers, and vessels. Antioxidants have been shown to improve autonomic function, [56,57,58] and we have found an antioxidant cocktail of Alpha Lipoic Acid, L-carnitine, and Coenzyme Q10 to be very useful. In regard to fatigue in EDS, one should evaluate for concomitant drugs, poor sleep habits, Obstructive Sleep Apnea, and secondary mitochondrial

SUPPLEMENT AND LIFESTYLE THERAPY ALGORITHM FOR DYS



Proper Exercise and Hydration are most important for long-term relief

We understand that this is a lot, but there is a lot going on with you, so let's get started!

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Figure 4: A 13-point therapeutic algorithm for treating Autonomic Dysfunction [54].

dysfunction. Also in EDS, the muscles are tense and constantly attempt to stabilize at rest, and ligaments provide no tension and stability; this needs to be addressed. Muscle relaxants have not been shown to be very effective in treating chronic pain in EDS.

Pain control is more difficult in EDS patients, but is important because pain increases Sympathetic activity inappropriately. Turmeric and Fish Oil as anti-inflammatories are recommended. Oftentimes, we use nonsteroidals (*e.g.*, Tylenol). Tricyclics in very low dose at 10 mg a day, SNRIs such as Cymbalta also in low dose (20 mg a day), or, rarely, Gabapentin and Lyrica and occasionally low-dose Naltrexone, is recommend. Medical marijuana (for pain control, higher CBD levels and lower THC levels are recommended) has shown promise empirically in many of our patients: THC for sleep and CBD for pain relief. It is known that the human body has two types of receptors, CB1 and CB2. CB1 receptors are found in the brain. CB2 receptors are found in the rest of the body, the immune cells, and glia cells in the central nervous system. Chemicals that cause inflammation in the peripheral parts of the body are modulated by cannabinoids, and therefore, cannabis applied topically is helpful in the form of CBD oil. Also, medical Marijuana does not affect Mast Cell Activation Syndrome as much as nonsteroidals and Opioids, in our experience. Low dose Naltrexone is a competitive antagonist of Opioid receptors. It has for many years been used for addiction. It depresses the effects of CNS glia which helps central nervous sensitizations. There have been numerous articles reported on using 1.75 to 4.5 mg and the trial should last at least six months, avoiding Opioids or Tramadol [59,60,61].

In our database of over 600 EDS patients, performing Cardio-Respiratory testing, beat-to-beat blood pressure, and Sudomotor testing in a majority of patients, we have found the most common Autonomic Dysfunctions present to be: (1) Sympathetic Withdraw, (2) Vasovagal Syncope profile at rest or provocation, and (3) Postural Orthostatic Tachycardia response. Sudomotor testing has shown a high prevalence of both inflammation of small nerve fibers consistent with Small Fiber inflammation or deficiency of Small Fibers consistent with Small Fiber Disease in half the patients.

Further research is needed in characterizing the types of Autonomic Dysfunction an individual has, for there may be a combination of several types, such as Postural Orthostatic Tachycardia Syndrome and Vasovagal Syncope, and also the best treatments available for the Dysautonomia. Also, Autonomic Dysfunction in other organs must be taken into consideration if a patient has Orthostatic Intolerance; for example, GI side-effects such as constipation where Mestinon (Pyridostigmine) may be more appropriate than Midodrine as a vasoactive agent.

APPENDIX

Questionnaire on Hypermobility Syndromes (EDS and Related Disorders)

Please Circle Yes or No.

1. Do you develop pain in joints that is continuous or intermittent that is difficult to relieve and causes discomfort and also possibly have abdominal discomfort or migraines? **Yes or No**
2. Do you have significant fatigue during the day or on awakening? **Yes or No**
3. Do your limbs feel like lead and become heavy at times? **Yes or No**
4. Do you get bouts of drowsiness or sleepiness? **Yes or No**
5. Do you have difficulty standing up for long periods of time? **Yes or No**
6. Do you have profuse sweating? **Yes or No**
7. Do you get chills or cold extremities? **Yes or No**
8. Do you believe that you have a drop in blood pressure periodically? **Yes or No**
9. Do you bruise easily or have bleeding from your gums, mouth, nose, or heavy periods? **Yes or No**
10. Are you hypersensitive to sound, smells, sudden positional changes, flickering lights, or any cutaneous stimulation? **Yes or No**
11. Do you have problems with blurred vision or does the image ever split? **Yes or No**
12. Does your vision at times feel as though it gets tired? **Yes or No**
13. Do you get shortness of breath on minimal exertion? **Yes or No**
14. Do you have memory deficits? **Yes or No**
15. Do you get brain fog, orientation difficulties, concentration difficulties, or have attention deficit problems? **Yes or No**
16. Are you clumsy when you walk? Do you fall? **Yes or No**
17. Do you get frequent sprains, dislocate or sublux your joints, such as your ankles, knees, jaw, or any other joints? Please list joints that are affected. **Yes or No**
18. Have you suffered numerous miscarriages (if female)? **Yes or No**
19. Do you have urological problems, such as losing urine or retaining urine? **Yes or No**
20. Do you have sleep disturbances? **Yes or No**
21. Do you get pneumothoraces? **Yes or No**
22. Have you ever had swelling of the legs or lymphedema? **Yes or No**
23. Have you ever had a history of arterial aneurysms? **Yes or No**
24. Do you have excessive elasticity or stretchability of your skin? **Yes or No**
25. Do you bruise easily? **Yes or No**
26. Does your skin scar easily? **Yes or No**

27. Did you have stretch marks before pregnancy (if female) or do you get stretch marks easily? **Yes or No**
28. Do you have delayed healing? **Yes or No**
29. Do you have thin skin? **Yes or No**
30. Do you have transparent skin? **Yes or No**
31. As a child, did you participate or excel in gymnastics, swimming, or cheerleading? **Yes or No**
32. Do you get fractures often? If so how many fractures ____ **Yes or No**
33. Do you or a family member have diverticulitis or diverticulosis? **Yes or No**
34. Do you have a cleft lip or cleft palate? **Yes or No**
35. Are the whites of your eyes discolored either blue-gray or off-white? **Yes or No**
36. Do you have hernias? **Yes or No**
37. Do you have Scoliosis? **Yes or No**
38. Do you have herniated, ruptured or bulging discs? **Yes or No**
39. Do you have mitral valve prolapse? **Yes or No**
40. Do you have family history of Ehlers-Danlos, Marfan's osteogenesis imperfecta, sickle cell syndrome, or pseudoxanthoma elasticum? **Yes or No**
41. Do you develop cigarette paper skin after a cut, stitches, or when you form a scar? **Yes or No**
42. Are you double-jointed, such as being able to touch your thumb to your wrist or put your palms on the floor when bending at the waist without bending your knees? **Yes or No**
43. Can you put your thumb through your closed fist and have it come out the other side? **Yes or No**
44. Can you pull the skin out from your elbow more than 2 cm? **Yes or No**
45. Is your hair very thick? **Yes or No**
46. Is your hair very thin? **Yes or No**
47. Are your nails weak and fragile? **Yes or No**
48. Are your nails strong and grow back fast? **Yes or No**
49. Does your chest cave in, does it appear to cave in, or have you had any family members who had to have their chest bone or sternum removed because it was pushing on their heart? **Yes or No**

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