

Hypermobility/Ehlers-Danlos Syndrome and the Parasympathetic and Sympathetic Nervous Systems.

DePace NL, Santos, L; Goldis M, Acosta CR, Munoz, R; Ahmad, G; Verma, A; DePace Jr. NL, Kaczmariski K, Colombo J.

ABSTRACT

Introduction. Ehlers-Danlos Syndrome/Hypermobility (EDSh) patients they demonstrate some degree of autonomic dysfunction (*a.k.a.*, dysautonomia). In general, dysautonomia is the effect of an imbalance between the two autonomic branches: the Parasympathetic and Sympathetic (P&S) nervous systems. **Methods.** From a suburban cardiology and autonomic clinic (Sicklerville, NJ) drawing patients from around the world, a cohort of 243 patients (223 female, 91.8%; average age 34.0 yrs, range 13 to 65 y/o; average BMI 27.3#/in²) previously diagnosed by Rheumatology with EDSh were followed from between November 2018 through May 2020. Baseline and at least two follow-up autonomic tests, with questionnaires, were administered. **Results.** While the etiology of EDSh is still being studied, the autonomic dysfunction, specifically both Parasympathetic and Sympathetic dysfunction caused by the results of the connective tissue disorder, may be documented, diagnosed, and treated. **Conclusion.** This is just the beginning of a research effort that must include many more patients from many more sources as EDSh awareness continues to grow.

Copyright: © 2022 by the authors. Submitted for open access publication under the Journal of Individualized Medicine and Therapies, of the Society of Individualized Medicine and Therapies, Inc.

INTRODUCTION

Ehlers-Danlos Syndrome/Hypermobility (EDSh) defines a spectrum of connective tissue disorders that are caused by defects in the genetic information that is used in humans to produce collagen. In both, the collagen is long and flexible, rather than short and stiff. This results in loose and “leaky” connective tissue. EDSh may be inherited, usually an autosomal dominant trait; however, acquired cases occur frequently. To date, there is no known cure for EDSh. However, there are a few characteristics that are well known (in no particular order): 1) it affects females significantly more than males; 2) in the young, the additional flexibility seems

advantageous due to the lack of significant symptoms; 3) generally, around the end of development (during later teens or early 20s), symptoms begin to present, and generally active and vivacious teenagers become sickly for no apparent reason with poor and, frequently, debilitating qualities of life.

Another primary characteristic of EDSh patients is that they demonstrate some degree of autonomic dysfunction (*a.k.a.*, dysautonomia). This may explain the last two characteristics listed above. During development, except for a couple of years around ages 8 and 15 when development slows down, the autonomic nervous system (ANS) is very active in development;

therefore, dysautonomia symptoms are masked and the symptoms that appear are attributed to current factors with largely unknown histories. Once development ends, in the late teens or early twenties, dysautonomia symptoms are unmasked and the effects of a persistently overactive ANS presents. In general, dysautonomia is the effect of an imbalance between the two autonomic branches: the Parasympathetic and Sympathetic (P&S) nervous systems. Here, we introduce a clinical cohort and some general characteristics of P&S function in 243 patients, predominantly female.

METHODS

From a single, suburban, cardiovascular and autonomic dysfunction clinic in the northeastern United States of America (Sicklerville, NJ, USA), 243 patients (223 female, 91.8%; average age 34.0 yrs, range 13 to 65 y/o; average BMI 27.3#/in²) previously diagnosed by Rheumatology with EDS_h were referred from November 2018 through May 2020. This patient cohort included a significant number of patients from across the USA and abroad. Detailed patient histories and physicals were taken as routine, including completing a Beighton Scoring test and the EDS_h Diagnostic Checklist from the Ehlers-Danlos Society (www.ehlers-danlos.com). Testing included Autonomic testing, including tilt-table testing, (TMFlow, Wake Forest, NC) and P&S Monitoring (Physio PS, Inc., Atlanta, GA); Vestibular testing; Mast Cell blood and urine work; Small Fiber Neuropathy (Sudomotor) testing; age- and symptom-specific cardiology testing; and serial P&S Monitoring (Physio PS, Atlanta, GA), which includes the Ewing challenges. P&S Monitoring includes LF_a as the direct

measure of Sympathetic (S) activity, RF_a as the direct measure of Parasympathetic (P) activity, and Sympathovagal Balance (SB=S/P, measured at rest as the average of ratios, not the ratio of averages) [1]. The blood and urine work were performed by labs, the remaining tests are easily performed in the out-patient setting.

All patients had a minimum of two follow-up P&S Monitoring tests. All HRV measures reported are computed based on the 1996 Standards established for HRV [2,3]. Cardiovascular Autonomic Neuropathy (CAN) indicates mortality risk. It may be demonstrated as all three of the Ewing Ratios being low [4] or as the resting Parasympathetic (P) activity < 0.1 bpm² [1]. In other words, CAN is due to a significant lack of P-activity to prevent excessive Sympathetic (S) activity (which may lead to unrecoverable Ventricular tachy-rhythms, or excessive inflammation, etc.). CAN is a normal part of life and is an eventuality, given age or duration of chronic disease. However, CAN with high SB (> 2.5) indicates high mortality risk [5,6] and is known to best predict Major Adverse Cardiovascular Events (MACE) when compared to nuclear stress and echocardiography (sensitivity 0.59 or 7.03 [Confidence Interval 4.59-10.78], specificity 0.83, positive predictive value 0.64 and negative predictive value 0.80) [7].

Exclusion criteria included: pregnancy, nursing, or refusal of testing. Also, the only known life-threatening form of EDS_h, Vascular EDS, was excluded. Inclusion criteria included: a Beighton score of ≥ 7/9 if younger than 25 to 30 or Beighton score of ≥ 5/9 if older than 30, or an EDS Diagnostic score of ≥ 5/12 with a positive family history. All patients consented to

testing and patient data were maintained according to HIPPA guidelines.

DIAGNOSIS

The typical patient presents with diffuse pain, especially in the shoulders, upper back, inter-scapular area, jaw, and hips. The patients oftentimes complain of their joints being quite flexible and oftentimes subluxing, or popping out. It is not unusual for the patients to have their knees, elbows, ankles, wrists, and even jaw pop out, or their cervical spine be hypermobile. Even hyperflexibility in the lumbar spine may make the patient able to touch the ground with their palms to the ground and knees straight quite easily. Patients typically complain of shortness of breath and palpitations. They do not stand for long periods of time and get dizzy and may have a history of fainting or near-fainting, and oftentimes have to lie down when trying to stand for periods of time. Oftentimes, the patients are extremely tired. They often complain of sleep difficulties, and they cannot get going in the morning. They complain of brain-fog or memory and cognitive difficulties. Bright light or sound may disturb them. These symptoms, not including the joint issues, are all symptoms of dysautonomia, including the possible amplification of pain and Fibromyalgia-like pain also due to dysautonomia.

Many patients state that they were quite athletic and were good dancers or good gymnasts during grade school and high school. They even comment that they believe they are double-jointed. A family history of this is often important in determining whether a person has Hypermobility or Ehlers-Danlos Syndrome. The skin is oftentimes soft and very hyperextensible (the skin on the non-dominant

forearm stretches more than 2 cm). The skin may also be velvety and mildly hyperextensible. Patients may have striae on their back, thighs, breast areas, and abdomen, and they may also have a history of recurrent hernias of the abdomen or inguinal area. Interestingly, some patients give a history of pelvic floor abnormalities with rectal or uterine prolapse as children. Some patients may present with arm spans greater than their height spans. However, other entities such as Marfan's Syndrome should be considered first with this presentation.

The combination of the Beighton score and the EDS_h Diagnostic Checklist provides a better diagnostic yield than either alone. Still, a detailed history and physical is important to find systemic features that reflect the syndrome, such as 1) family history, 2) many musculoskeletal complications such as pain in several limbs that has been occurring for more than three months, 3) pain that is widespread, or 4) recurrent (spontaneous) joint dislocations or joint instability without any trauma. In older EDS_h patients, including those in their 40s, arthritis and weight-gain due to exercise intolerance often limits mobility, making the detailed history more important.

Other possibilities that may mimic EDS_h must also be excluded, such as Lupus, Rheumatoid Arthritis, and Scleroderma. These other possibilities also have abnormal collagen and connective tissue as does EDS_h and can give joint laxity and hypermobility, but have other features, some of which can be life-threatening. Many rheumatologists refer patients whom they have evaluated for connective tissue disease and have excluded these other possibilities. The referrals are then for autonomic dysfunction. Also, the

inappropriate label “Fibromyalgia” oftentimes is applied to EDSH

Unfortunately, there is no blood test, lab test, or imaging modality that confirms a diagnosis; therefore, the diagnosis is completely clinical. There is no genetic testing that has been identified for EDSH.

What may complicate the issue is there are some patients who present with this syndrome complex *de-novo* and do not have a family history despite a careful search from the physician and clinician. These are the minority of cases, however, and the exact percentage is not known.

It is not difficult to diagnosis hypermobile Ehlers-Danlos Syndrome (EDSH), but a very detailed history and physical examination is required. A very thorough family history is also required, and this may even involve examining some of the family members. Excluding other entities that present with abnormal collagen composition or other types of hereditary tissue diseases is extremely important and consultation with a skilled rheumatologist and a P&S nervous system expert is often needed. Generic testing may be useful to exclude vascular-type EDS, Marfan’s Syndrome, and other related connective tissue diseases.

RESULTS

Table 1 describes the patient demographics. P&S balance (at rest) for the cohort is well within normal limits (SB: $0.4 < SB < 3.0$, unitless). The preferred SB for younger, < 65 y/o, healthier subjects is $1.0 < SB < 3.0$.

Table 1: EDSH patient demographics and average, resting data, including: Heart Rates (HR) and Blood Pressures (BP), and P&S and HRV data.

Age (yrs)	N (#)	Female (%)	BMI (#/in ²)	HR (bpm)	BP (mmHg)	P (bpm ²)	S (bpm ²)	SB	LFnu (msec ²)	HFnu (msec ²)	LF/HF
< 20	32	93.8	24.8	88.2	115.5/70.7	6.5	7.7	2.3	64.4	35.6	2.7

20 – 29	86	95.3	25.3	86.2	121.2/76.5	6.8	6.9	1.9	63.1	36.9	2.5
30 – 39	52	96.2	29.0	84.7	123.2/79.3	7.5	6.6	2.4	62.8	37.2	3.0
40 – 49	29	86.2	30.5	79.7	124.1/80.3	1.9	2.5	1.7	64.1	35.9	3.7
50 – 59	29	89.7	30.6	75.0	137.6/83.5	1.5	2.0	2.6	63.4	36.6	3.0
60 – 69	7	85.7	25.6	69.6	137.5/78.0	0.7	0.9	2.3	56.9	43.1	2.7
≥ 70	8	50.0	27.6	75.9	136.7/71.7	0.2	0.5	2.0	57.5	42.5	1.8
Total	243	223	27.3	83.2	124.0/77.6	6.3	6.7	2.1	63.0	37.0	2.8

BMI, Body Mass Index; E/I, Exhalation/Inhalation; 30:15, Stand or upright posture; SB and LF/HF are unitless.

The preferred SB for older, ≥ 65 y/o, sicker patients is $0.4 < SB < 1.0$. The low-normal range for SB in older, sicker patients is known to be cardio-protective [8] and protective of bodily systems in general.

Overall, patients appear normal at rest. Perhaps their BPs are elevated, arguably due to the pain, but the rest of their resting results as taken from a typical office visit are well within normal limits. Here, we differentiate autonomic from P&S testing because most autonomic tests (*e.g.*, tilt-table testing) test only total autonomic function, forcing assumption and approximation to theorize specific P&S dysfunction, whereas P&S Monitoring specifies P from S dysfunction, objectively and quantitatively, and enables serial testing for trending and follow-up. In the case of this cohort, the resting autonomic test results (LF, HF, and LF/HF ratio) are well within normal limits.

The P&S results are within normal limits, but rather elevated in the 20s and 30s as compared to age-matched Normals (see Figure 1, below), and their balance (SB) is within normal limits throughout.

With specific P&S measures, a history of the P&S responses to EDSH is possible and helps to frame an understanding of the effects of the disorder. First, consider more common measures of the ANS. EDSH patients' resting HRs (bpm) and BPs (mmHg, Systolic or SYS, and Diastolic or DIAS) are displayed in Figure 2, plotted against age (in years). On average, both HR and BP measures are within normal limits throughout the history of the disease. This contributes to the perceived, apparent normalcy of these patients. Many of these patients are often not believed by their physicians because all of the (resting) office measures are within normal limits.

Unfortunately, EDSH is one of the diseases or disorders (like Fatigue or Anxiety) that do

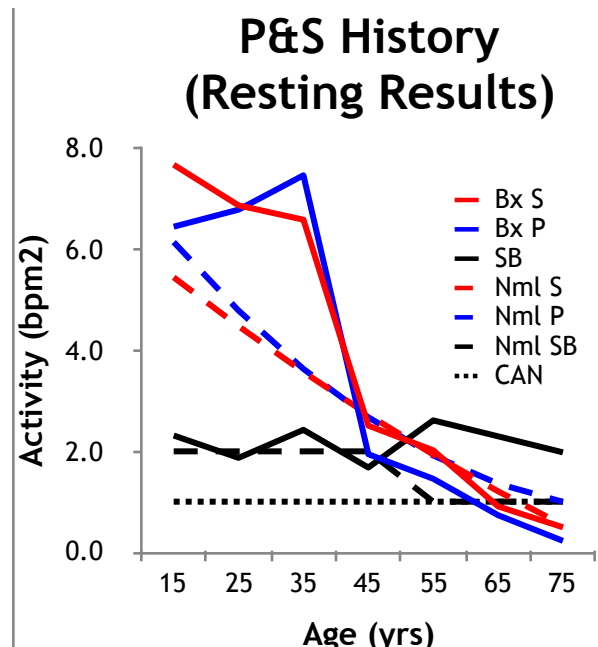


Figure 1: Resting P&S measures from this EDSH cohort (solid blue and red lines, respectively) compared with normal, age-matched subjects (broken blue and red lines, respectively) compared over time (black lines represent SB). The dotted black line at 1.0 represents CAN (see text for details).

not present as abnormal at rest. Rather, the associated dysautonomias are manifested while active (which is the usual condition of the ANS; it rarely rests, as one branch or the other is always active).

HRV measures include the normalized spectral analysis measures: LFnu, HFnu, and LF/HF. These are commonly measured at rest (Bx1). LFnu is assumed to be a measure of Sympathetic activity, when in actuality, it is a mixed P&S measure. HFnu is assumed to be a measure of Parasympathetic activity, when in actuality, it is a measure of noise (signals not from the ANS) with Parasympathetic activity

sometimes included if the breathing frequency is high enough. The LF/HF ratio is considered to be a measure of autonomic balance. On average, all of these measures are also normal throughout the years (Figure 2). For these spectral HRV measures, the

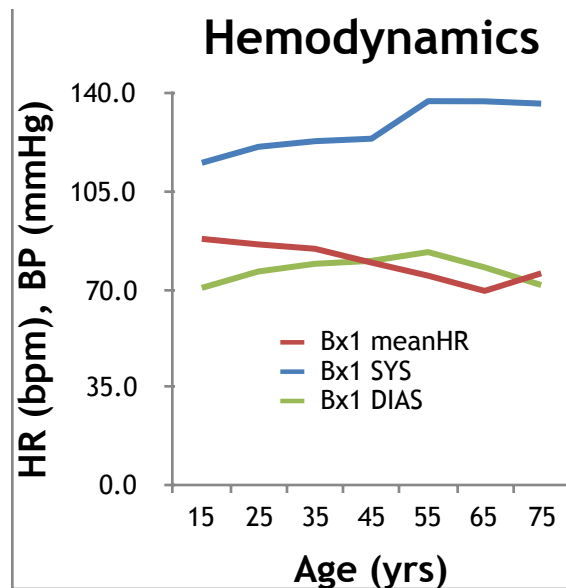


Figure 2: HR and BP are often considered as measures of Sympathetic activity; however, they are the net result of the activity of both autonomic branches.

apparent normalcy is due to the fact that they are mixed measures and as long as the balance is within normal limits (as measured by the LF/HF ratio), the two ANS branches average out to be normal.

EDSh patients' resting P&S data are displayed in Figure 3. For comparison, the P&S history of 302 normal, age-matched subjects (Nml, 55.6% Female) are included. Normal is defined as not under physician care and not on any prescription medications. On average, younger EDSh patients' P&S activity is high-normal compared with Normals. Eventually, the EDSh patients' resting P&S activity normalizes, as compared with the Normal subjects' resting P&S activity. Note, however, the Normals' resting P-activity is higher or virtually equal to their resting S-activity; whereas, the EDSh patients' resting P-activity is lower than their resting S-activity, indicating a higher morbidity risk, a

complimentary reduced quality of life, and ultimately a higher mortality risk. On average, EDSh patients cross the CAN threshold up to 20 years earlier than

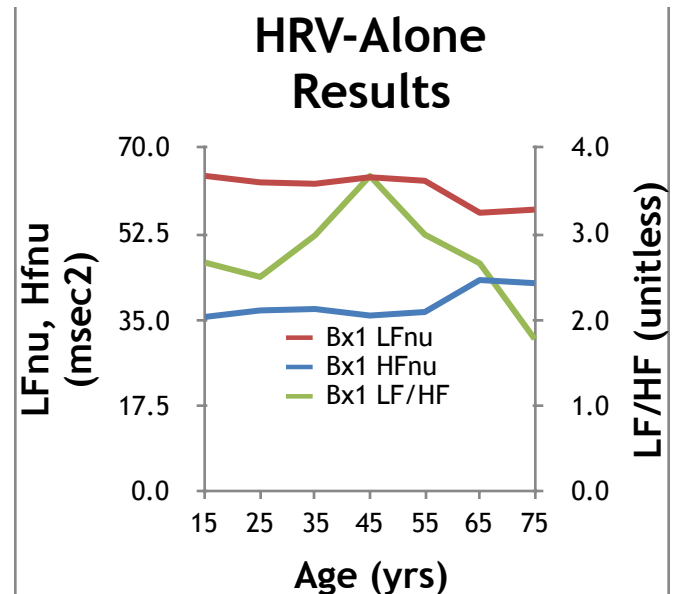


Figure 3: Normalized, resting spectral measures of HRV from this EDSh cohort are presented. LFnu is the normalized low frequency measure often assumed to be the Sympathetic measure. HFnu is the normalized high frequency measure often assumed to be the Parasympathetic measure. LF/HF ratio is sometimes considered a measure of autonomic balance. On average throughout this cohort, the normalized spectral analysis measures of autonomic activity are normal.

Normals. CAN indicates higher morbidity and mortality risk. In their latter years, EDSh patients' SB is significantly elevated as compared with Normals. With vascular EDSh excluded, the presence of only 3 EDSh patients demonstrating CAN (see Table 2) supports the point that the vast majority of EDSh is not lethal. The more common form of resting autonomic

dysfunction is Advanced Autonomic Dysfunction (AAD). Of the EDSh population, 14.4% demonstrated AAD (see Table 2). AAD is demonstrated throughout the ages, but mostly in older patients (≥ 50 y/o, Table 2). Again, this further demonstrates the general consensus that EDSh is not life-threatening.

Since the P&S nervous systems are dynamic in nature, we consider the two most prevalent, dynamic P&S dysfunctions: Sympathetic Withdraw (SW) & Parasympathetic Excess (PE) (see Table 2). Of the EDSh population, 49.4% demonstrated SW and 54.3% demonstrated PE. Along with AAD & CAN, both SW & PE may be involved in high BP and Hypertension (HTN). SW contributes to all types of Orthostatic dysfunction, including Neurogenic Orthostatic Hypotension (NOH, SW with a BP drop upon standing $> 20/10$ mmHg), Orthostatic Intolerance (OI, SW with a BP drop upon standing $0/0$ mmHg $<$ BP $< 20/10$ mmHg), and Postural Orthostatic Tachycardia Syndrome (POTS, SW with an abnormal increase in HR upon standing: $> a 30$ bpm change or > 120 bpm average). Also, SW is associated with the constellation of symptoms that result from cardiac and cerebral hypo-perfusion. PE contributes to Vasovagal Syncope (VVS) and a constellation of symptoms that result from cerebral hypo-perfusion. Not all Orthostatic dysfunction includes SW (*i.e.*, others may be due to venous valve or wall dysfunction or thromboses). We define Orthostatic BP Dysfunction (OBPD) as abnormal BP responses to upright postural change (including standing) with or without SW. Of the EDSh population, 79.0% presented with OBPD, including 9.5% that presented with clinical Orthostatic

Hypotension (OH, defined as a BP drop of $20/10$ mmHg or more upon standing with or without SW), and 33.8% demonstrated VVS (see Table 2).

All patients with SW had either OBPD or POTS. Of the EDSh population, 3.7% presented with POTS (see Table 2). The difference between OBPD and SW in Table 2 indicates that 72 patients (29.6%) presented with OBPD not due to SW. PE may mask SW; however, PE with an abnormal BP response to stand is a clue that SW may be masked. Masked or not, SW & PE may be demonstrated together; therefore, POTS and VVS may present together, and this occurs in 7/9 of the EDSh patients with POTS. Similarly, OBPD & VVS may present together, and this occurs in 67/192 of the EDSh patients with OBPD. Of course, all patients with POTS presented with Tachycardia, but not all patients with Tachycardia (12.3%) presented with POTS. Of the EDSh population, 20.2% present with HTN. Often HTN is a compensatory mechanism for stand or postural change abnormalities. In these cases, it seems that the higher resting BP helps to prevent too low a cerebral perfusion pressure when the patient's BP drops upon assuming an upright posture [9].

DISCUSSION

From Figure 3, younger EDSh patients' P&S activity is high-normal possibly due to their heightened immune state and their body's attempt to heal the "leaky" connective tissue. The initial high-normal S-levels, higher than the P-levels (the opposite is typical), may be why there is persistent inflammation starting in the earlier years, a characteristic of EDSh patients. Typically, given that P-activity is more involved in

development and pregnancy, P-activity is higher during these years, as in the normal subjects through the 20s and 30s. Allergies, Mast Cell activation, Arthritis, Small Fiber disorder, etc. all involve S-activity. Histaminergic and inflammatory responses are Sympathetic functions. As the Sympathetics are the reactionary branch, S-activity is normally short-lived. Persistent or inflated S-activity, therefore, leads to histaminergic and inflammatory disorders. In EDSH cases, S-activity is typically inflated by the elevated P-activity and the additional S-activity drives the additional inflammation. S-activity is also involved in the pain response. Amplified S-activity, due to abnormal, excessive P-activity¹⁰, also amplifies the pain response, especially in “Fibromyalgia-like” pain syndromes. Since the majority of EDSH patients are female (91.8% of this total population), P-activity (and therefore S-activity) remains higher during childbearing, and may be the reason for the persistence of the elevated P&S activity into the middle-age years. Subsequently, the EDSH patients’ resting P&S activity normalizes, as compared with

that of the Normal subjects. However, the EDSH patients’ resting S-activity remains high compared with resting P-activity.

EDSH is believed to not be life-threatening, except for one form of EDS (the vascular form). However, based on these sample populations, EDSH may perhaps reduce length of life an average of 10 years, given that they cross the CAN threshold up to 10 years earlier than Normals. Again, P-activity is protective. The more reduced P-activity in the EDSH patients may be the cause of the reduced life span. It may indicate an immune system that has fatigued earlier or it may be responsible for earlier onset MACE-risk (heart attack, stroke, heart failure, etc.). The higher mortality-risk is reflected in the CAN with SB > 2.5 condition [1,11] in the EDSH patients starting around age 60, on average (see Table 2). CAN with SB > 2.5 is therefore an indicator that therapy should be more aggressive about establishing and maintaining low-normal SB: $0.4 < SB < 1.0$; e.g., increasing dosages of

Table 2: Numbers of EDSH patients presenting with abnormal resting or dynamic (or challenge) P&S or hemodynamic responses, by age. Patients that demonstrate autonomic abnormalities may demonstrate one or more of the following: AAD, CAN, SW, or PE. These autonomic abnormalities may result in one or more of the following: HTN, OBP, Tachy, POTS. (For definitions, see below the Table and see text for details).

Age (yrs)	AAD	CAN	SW	PE	HTN	OBPD	Tachy	POTS	VVS
< 20	1	0	11	10	1	15	4	5	6
20 – 29	4	0	37	44	11	64	15	4	32
30 – 39	5	0	26	30	13	40	7	0	17
40 – 49	3	0	13	21	5	26	2	0	11

50 – 59	12	0	22	16	13	27	1	0	12
60 – 69	5	1	4	6	3	10	0	0	2
≥ 70	5	2	7	5	3	10	1	0	2
Total	35	3	120	132	49	192	30	9	82
Total %	14.4	1.2	49.4	54.3	20.2	79.0	12.3	3.7	33.8

AAD, Advanced Autonomic Dysfunction, similar to Diabetic Autonomic Neuropathy without the blood sugar and insulin issues, indicates increased morbidity risk; CAN, Cardiovascular Autonomic Neuropathy, indicates increased mortality risk; HTN, Hypertension (resting BP > 140/90 mmHg); OBPD, Orthostatic BP Dysfunction, includes SW with a drop in BP upon standing and a drop in BP without SW; PE, Parasympathetic Excess, an excessively abnormal increase in Parasympathetic activity in response to a Sympathetic challenge (*i.e.*, Valsalva challenge >400%, or Stand > 10%) as compared with rest.; POTS, Postural Orthostatic Tachycardia Syndrome, SW with stand Tachycardia; SW, Sympathetic Withdrawal, a < 10% increase in Sympathetic activity in response to stand or upright posture as compared with rest, and alpha-adrenergic response; Tachy, a resting Tachycardia, resting HR ≥ 100 bpm; VVS, Vasovagal Syncope, PE with stand Sympathetic Excess, a beta-adrenergic response.

Sympatholytics or reducing stress, including Psychosocial stress. Overall, the P&S data are a better match to the natural history and progression of EDSH.

Many patients present with prior diagnoses of depression and anxiety or psychiatric illness attributed to them, but they know they have something real and abnormal that is not purely psychiatric. The patients hurt all over and have diffuse pain, which keeps them from functioning properly. They are often diagnosed as “Fibromyalgia” or “Chronic Pain Syndrome.” Many cannot perform any gainful employment. Certainly, they become anxious and depressed because of their non-functional status.

Dysautonomia features, such as exercise intolerance, orthostatic intolerance (where one cannot stand up without getting brain fog or dizzy), and chronic or persistent fatigue are almost universally present in these patients. There is a high percentage of females with this problem, but we do also see males in addition, since it is believed that if a person has this disorder, they can

transmit it genetically to one or two of their children (autosomal dominant transmission).

It is well known that the P&S is, generally, very active during development. This level of activity, masking any effects of excessive P&S activity, may explain why symptoms do not present until after development. It has been postulated that “leaky” connective tissue permitting foreign items to leak in causes a persistently heightened immune response. This in turn leads to a persistent state of Parasympathetic Excess (PE), mostly while active, as well as for periods of time when younger at rest (see Figure 3), as measured as high-normal SB ($2.0 < SB < 3.0$; see Table 1). The persistent and prolonged stress on the more exposed and longer Parasympathetics (Vagal) nerves, including Oxidative Stress [12], tends to cause them to weaken first and fastest. The relative PE also forces a relative Sympathetic Excess (SE) which not only multiplies symptoms, but amplifies symptoms, such as Sympathetically-mediated pain and inflammation.

Unfortunately, there is no cure for P&S imbalance in these patients. Typically, with many other diseases and disorders, once P&S balance is established, then the nervous system “learns” this new condition and maintains it until some other clinical event occurs. Unfortunately, in EDSH, the next clinical event, *per se* (such as the next infection), is only moments away once it leaks into the body. Therefore, there is also no real cure for P&S imbalance due to EDSH, only the ability to treat it to maintain P&S balance as much as possible as the system continues to degrade more rapidly than normal. Fortunately, once the protocol for the individual patient is determined, it may be implemented immediately should a significant clinical event occur, including pregnancy, where patients may need to suspend treatment during that time.

Fatigue, exercise intolerance, shortness of breath, palpitations, and chest pains with which many patients with EDSH present are often the result of P&S dysfunction. This goes hand in hand with the EDSH. Even the amplified and generalized pain and inflammatory responses (not only in the joints), anxiety, brain fog, memory and cognitive difficulties, sleep difficulties, and GI motility issues, may be secondary to P&S dysfunction caused by EDSH. Many patients develop Small Fiber Disease, which is an inflammation or dysfunction of unmyelinated small, type C nerve fibers which carry autonomic and sensory, including pain, signals. Also, EDSH is associated with Mast Cell hyperactivity, which manifests as episodic histaminergic over-production. Mast Cell may be associated with Celiac disease and food allergies or sensitivities. Leaky Gut Syndrome may be involved either as a result

of histaminergic excess or leaky connective tissue. Histaminergic over-production may be associated with persistent or excessive Sympathetic activity secondary to PE. This may be tested for objectively and serially, with diagnostic test modalities that provide quantitative information. This, in turn permits more individualized titration of therapy given the then current state of the patient’s nervous system.

One reason for the lack of understanding and recognition of the P&S dysfunctions underlying EDSH is the fact that virtually all of the data collected from patients are collected while the patient is at rest. The ANS, specifically the P&S nervous systems, is never at rest. (In fact, it may be argued that they are most active when you are sleeping, resting.) As a result, the common thread behind the constellation of symptoms associated with EDSH is lost. It is well known that the Sympathetic nervous system is the reactionary branch of the ANS and is not supposed to be chronically active. It is also well known that the Parasympathetic nervous system is the ANS branch that establishes the metabolic threshold around which the Sympathetic branch reacts and then works to quiet the Sympathetic branch. Under normal resting conditions, as one branch is activated, the other becomes less active.

This is not the case in most abnormal conditions and is not the case under abnormal dynamic conditions. There are two significant, dynamic P&S abnormalities (P&S dysfunctions that present when not at rest) that are, apparently, caused by EDSH and serve to exacerbate the symptoms of EDSH. One is known as Sympathetic Withdrawal (SW), which is an abnormal alpha-Sympathetic response to head-up

postural change (sitting or standing) which leads to poor cardiac and cerebral perfusion which lead to fatigue, exercise intolerance, shortness of breath, palpitations, and chest pains, and anxiety, brain-fog, memory and cognitive difficulties, and sleep difficulties; respectively. The other is known as Parasympathetic Excess (PE), which is an abnormal Parasympathetic response to a stress (a beta-Sympathetic) response. PE not only may exacerbate symptoms caused by SW, but it also amplifies the Sympathetic disorders, including pain and inflammatory responses (including in the joints). It may also cause, or be the cause of, Mast Cell hyperactivity leading to unexplained rashes, Mast Cell Activation Syndrome (MCAS), and Small Fiber disorder.

PE may be a primary disorder caused by EDSH. It is well known that the Parasympathetics control and coordinate immune responses, including providing the “memory” for the immune system. Since EDSH enables foreign substances to “leak-in” to the body all of the time, the immune system is always on constant, heightened “alert” and thereby forces the Parasympathetics to remain overactive. Dynamically, PE forces the Sympathetic response to also be excessive (Sympathetic Excess or SE), secondarily. Unfortunately, since most clinical office measurements are Sympathetically-based (HR, BP, etc.), only the SE is recognized (high HR and high BP) and therefore treated. However, this results in more PE because the complimentary Sympathetic activity is reduced, enabling the increase in PE. This often leads to

unresponsive or labile patients which are often misinterpreted. In these patients, when PE is recognized as a primary autonomic dysfunction, and treated as such, the secondary SE is often relieved organically, in time, and then the Sympathetically-based symptoms are often relieved organically, in time, assuming no end-organ effects.

A final thought for now: Since the human body will assimilate foreign, ingested, collagen (*i.e.*, from bones, shellfish shells, and other animal connective tissue), perhaps this is a basis for some relief of EDSH. The (normal) animal collagen may help to “plug the leaks” caused by the abnormal native collagen. Many patients empirically find relief of symptoms with intake of collagen products.

CONCLUSION

As mentioned before, there is no genetic testing or lab testing that is diagnostic of EDSH. That is not to say that we will not in the future hone down on a specific gene loci or other biomarkers that may be supportive of hypermobile Ehlers-Danlos Syndrome. However, to date, there are none. We use a scoring system developed by the EDS Society. For now, it is possible to re-establish P&S balance and thereby help to restore an improved quality of life that permits a productive lifestyle, with less pain and better sleep [1,8]. This is just the beginning of a research effort that must include many more patients from many more sources as EDSH awareness continues to grow.

REFERENCES

1 Colombo J, Arora RR, DePace NL, Vinik AI. Clinical Autonomic Dysfunction: Measurement, Indications, Therapies, and Outcomes. Springer Science + Business Media, New York, NY, 2014.

- 2 Malik, M. The Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability, standards of measurement, physiological interpretation, and clinical use. *Circulation*. 1996; 93:1043-1065.
- 3 Malik, M. and the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability, standards of measurement, physiological interpretation, and clinical use. *European Heart Journal*. 1996, 17: 354-381.
- 4 Pafili K, Trypsianis G, Papazoglou D, Maltezos E, Papanas N. Simplified Diagnosis of Cardiovascular Autonomic Neuropathy in Type 2 Diabetes Using Ewing's Battery. *Rev Diabet Stud*. 2015 Spring-Summer;12(1-2):213-9. doi: 10.1900/RDS.2015.12.213. Epub 2015 Aug 10. PMID: 26676669; PMCID: PMC5397991.
- 5 Murray G and Colombo J. Ranolazine therapy reduces non-ST-segment elevation myocardial infarction and unstable angina in coronary disease patients with angina (2016) *Int J Angiology* 25: 159-164. <https://doi.org/10.1055/s-0036-1572364>
- 6 Murray LG and Colombo J. Routine measurements of cardiac parasympathetic and sympathetic nervous systems assists in primary and secondary risk stratification and management of cardiovascular clinic patients. *Clinical Cardiol Cardiovascular Med*. 2019; 3: 27-33.
- 7 Curtis B and O'Keefe J. Autonomic tone as a cardiovascular risk factor: the dangers of chronic fight or flight (2002) *Mayo Clinic Proc* 72: 45-54. <https://doi.org/10.4065/77.1.45>
- 8 Umetani K, Singer DH, McCraty R, and Atkinson M. Twenty-four hour time domain heart rate variability and heart rate: Relations to age and gender over nine decades. *JACC*. 1998; 31(3), 593 – 601.
- 9 Arora RR, Bulgarelli RJ, Ghosh-Dastidar S, Colombo J. Autonomic mechanisms and therapeutic implications of postural diabetic cardiovascular abnormalities. *J Diabetes Science and Technology*. 2008; 2(4): 568-71.
- ¹⁰ Normally, P-activity decreases then S-activity increases. Under certain abnormal conditions (Dysautonomias), P-activity increases (presumably as a protective mechanism), forcing the reactionary S-activity to increase even more, amplifying the resultant S-response (*e.g.*, pain, inflammation, stress, HR, BP, etc.). This abnormal increase in P-activity is detectable during S-challenges (under stress) and is known as P-Excess (PE).
- 11 Murray LG and Colombo J. Maintenance (r) alpha lipoic acid reduces sudden cardiac death in geriatric diabetes mellitus II patients. 2020; *Clin Cardiol Cardiovasc Med* 4: 6-12.
- 12 DePace NL, Colombo J. Autonomic and Mitochondrial Dysfunction in Clinical Diseases: Diagnostic, Prevention, and Therapy. Springer Science + Business Media, New York, NY, 2019.