**Abnormal Parasympathetic Responses to Stress Exacerbate Hypermobility and Ehlers-Danlos Syndrome Symptoms**

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**ABSTRACT**

**Introduction**. Ehlers-Danlos Syndrome/Hypermobility (EDSh) patients demonstrate abnormal parasympathetic responses to stressful stimuli. This has been labeled “Parasympathetic Excess” (PE). PE may be caused by the need in EDSh patients’ immune systems to be over-active due to the porous connective tissue. **Methods**. From a suburban cariology and autonomic clinic (Sicklerville, NJ, USA) 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. At follow-up testing autonomic therapy for PE, including low-and-slow exercise and very low dose anti-cholinergics. **Results**. From the questionnaires, PE is found to cause symptoms associated with a deconditioned heart, including: lightheadedness, fatigue, brain-fog, memory and cognitive difficulties, headache or migraine, sleep difficulties, and depression-like and anxiety-like symptoms. **Conclusion**. PE in EDSh patients exacerbates the debilitating nature of the disease and simply treating the symptoms often exacerbates the case. Therapy durations are among the shorter of the treatments for Dysautonomia, often lasting at least 6 to 9 months depending on the duration and severity of the disorder.

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**INTRODUCTION**

The connective tissue disorders, Hypermobility and Ehlers-Danlos Syndrome (EDSh), often present with symptoms of Dysautonomia, especially Orthostatic dysfunction; either Orthostatic Hypotension or Postural Orthostatic Tachycardia Syndrome. The disordered connective tissue leads to autonomic dysfunction [[[1]](#endnote-1),[[2]](#endnote-2)]. EDSh is a genetic disorder of collagen (hereditary – autosomal dominant – or less frequently, *de-novo*), which is long and stretchy rather than short and stiff. It is characterized by joints being quite flexible and oftentimes subluxing.

The abnormal collagen also causes connective tissue to be “leaky.” This leakiness compounds the autonomic dysfunction associated with EDSh [1,2]. In turn, the resulting autonomic dysfunction leads or contributes to many of the symptoms of EDSh. Pain and inflammation symptoms, characteristic of EDSh, are examples of contributions from autonomic dysfunction. For example, the “leaky” connective tissue permits foreign substances to enter the body that normally would not. This causes the immune system to be persistently hyperactive, which causes the Parasympathetic branch to become persistently hyperactive (*aka.*, Parasympathetic Excess or PE), which in turn causse secondary, hyper-reactive Sympathetic responses (*aka.*, Sympathetic Excess or SE, a beta-adrenergic response), amplifying the pain response and exacerbating the inflammatory response [[[3]](#endnote-3)]. Anxiety-like symptoms, headache, migraine, and GI difficulties may result directly or indirectly from PE. The remaining symptoms are considered direct results of autonomic dysfunctions, specifically Sympathetic Withdrawal (SW, an alpha-adrenergic response) [2], which may be masked by PE. Here, we describe PE and document its effect within a large clinical cohort of EDSh patients.

**METHODS**

From a single, suburban, cardiovascular and autonomic dysfunction clinic in the northeastern United States of America (USA), 569 patients (226 female, 94.2%; average age 30.4yrs, range 13 to 65 y/o; average height 64.5 in; and average weight 158.3#) previously diagnosed by Rheumatology with EDSh 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 EDSh Diagnostic Checklist from the Ehlers-Danlos Society (www.ehlers-danlos.com). Testing included Autonomic testing, including tilt-table testing, (TMFlow, Wake Forest, NC); Vestibular testing; Mast Cell blood work; Small Fiber Neuropathy 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 LFa as the direct measure of Sympathetic (S) activity, RFa 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) [[[4]](#endnote-4)]. These are all quick, in-office tests. All patients had a minimum of two follow-up tests. All HRV measures reported are computed based on the 1996 Standards established for HRV [[[5]](#endnote-5),[[6]](#endnote-6)].

Exclusion criteria included: pregnancy, nursing, or refusal of testing. Also, the only known life-threatening form of EDSh, cardiac-valvular EDS, was immediately ruled out in all patients (none was found within this cohort). 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 ≥ 12/?? with a family history. All patients consented to testing and patient data were maintained according to HIPPA guidelines.

The focus of this study is the prevalence and effects of Parasympathetic Excess (PE) on EDSh. PE is an abnormal Parasympathetic increase in response to a Sympathetic challenge (*e.g.*, Valsalva or upright postural change). Normally, the Parasympathetic response to a Sympathetic challenge is to decrease. Since the Parasympathetics set the threshold around which the Sympathetics react, PE often amplifies Sympathetic responses, thereby amplifying stress responses, such as pain, Anxiety (including palpitations and shortness of breath), inflammation, and histaminergic responses. The treatment to reverse PE used in this study included the low-and-slow, or graded, exercises in combination with low-dose anticholinergics [[[7]](#endnote-7)]. Once PE is relieved, due to the persistent nature of EDSh, a maintenance therapy was required to help maintain normal autonomic function.

PE (whether Valsalva or stand) is associated with the following: difficult-to-control BP, blood glucose, hormone level, or weight; difficult-to-describe pain syndromes (including CRPS); unexplained arrhythmia (palpitations) or seizure; temperature dysregulation (both response to heat or cold and sweat responses); symptoms of depression or anxiety; ADD/ADHD; fatigue; exercise intolerance; sex dysfunction; sleep or GI disturbance; lightheadedness; cognitive dysfunction or “brain fog”; and frequent headache or migraine.

Occasionally PE, when associated with Vasovagal Syncope, may mask Orthostatic dysfunction (POTS in younger female patients, and Orthostatic Hypotension in older male patients). In these cases, both the Syncope and the Orthostatic dysfunction were treated simultaneously, since these responses are from two different portions of the nervous system.

**RESULTS**

Table 1 describes the patient demographics. While P&S balance for the cohort is well within normal limits (SB: 0.4 < SB < 3.0, unitless); preferred SB for younger, < 65 y/o, healthier patients is 1.0 < SB < 3.0; and preferred SB for older, ≥ 65 y/o, sicker patients is 0.4 < SB < 1.0; the latter is known to be cardio-protective [[[8]](#endnote-8)] and protective of bodily systems in general. The CAN threshold is defined as P-activity below 0.1 bpm2 [1]. In other words, CAN is due to a significant lack of P-activity to prevent excessive S-activity (which may lead to unrecoverable Ventricular tachy-rhythms, excessive inflammation, etc.) and indicates mortality risk. 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 [[[9]](#endnote-9),[[10]](#endnote-10)] 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) [[[11]](#endnote-11)]. Sympathetic Withdrawal (SW) occurs in approximately half (49.4%) of this cohort. The majority of patients presenting with PE are younger. This may be in part due to the heavy focus on dysautonomia within the representative practices.

Table 1: Hypermobility and Ehlers-Danlos Syndrome patient demographics and average, resting data, including: Heart Rates (HR), Blood Pressures (BP), and P&S data.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Age  (yrs)** | **N (#)** | **Female (%)** | **BMI (#/in2)** | **HR (bmp)** | **BP (mmHg)** | **P (bpm2)** | **S (bpm2)** | **SB** | **PE (#)** |
| < 20 | 32 | 93.8 | 24.8 | 88.2 | 115.5/70.7 | 6.5 | 7.7 | 2.3 | 10 |
| 20 – 29 | 86 | 95.3 | 25.3 | 86.2 | 121.2/76.5 | 6.8 | 6.9 | 1.9 | 44 |
| 30 – 39 | 52 | 96.2 | 29.0 | 84.7 | 123.2/79.3 | 7.5 | 6.6 | 2.4 | 30 |
| 40 – 49 | 29 | 86.2 | 30.5 | 79.7 | 124.1/80.3 | 1.9 | 2.5 | 1.7 | 21 |
| 50 – 59 | 29 | 89.7 | 30.6 | 75.0 | 137.6/83.5 | 1.5 | 2.0 | 2.6 | 16 |
| 60 – 69 | 7 | 85.7 | 25.6 | 69.6 | 137.5/78.0 | 0.7 | 0.9 | 2.3 | 6 |
| ≥ 70 | 8 | 50.0 | 27.6 | 75.9 | 136.7/71.7 | 0.2 | 0.5 | 2.0 | 5 |

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

**DISCUSSION**

Heretofore, independent, simultaneous measures of Parasympathetic and Sympathetic (P&S) assessment have been difficult and only total autonomic measures were available, forcing assumption and approximation to theorize independent, simultaneous P&S activity. With objective measures of independent, simultaneous P&S activity, no longer is the assumption that the two branches work in opposition required or appropriate (which only happens in truly normal cases). In fact, abnormally high Parasympathetic and Sympathetic activity (PE & SE, respectively) is now an observable possibility. In these cases, PE is always the primary autonomic disorder, even though the SE is often the clinical result (high BP, high HR, Anxiety, inflammation, etc.). PE is the primary because of the way in which the autonomic nervous system works [[[12]](#endnote-12),[[13]](#endnote-13)]. In this cohort, 132 (54.3%) of the patients demonstrate PE, whether upon Valsalva or Stand or both.

The Parasympathetics set the threshold around which the Sympathetics react. Since SE is secondary, but largely the apparent cause of the clinical result, SE tends to be treated as the primary. When this is the case, patients tend to become more labile, more difficult to manage, and apparently non-responsive or non-compliant, and higher doses of therapy only serve to exacerbate the condition. By treating the PE as the primary, lower doses typically work better, causing fewer side-effects, and in time, SE will be relieved organically, and then, in time, the clinical result will be relieved organically, assuming no end-organ dysfunction. Part of the problem with treating SE as the primary in cases where it is secondary to PE is that by limiting the Sympathetics, any extant feedback control by the Sympathetics on the Parasympathetics is reduced, permitting the Parasympathetics to become more excessive, forcing the body to defeat the Sympathetic therapy, since not all Sympathetic pathways may be blocked by medicine.

In cases of Dysautonomia, PE often masks SW in just this way. The PE forces the threshold for a Sympathetic response to be higher. When high enough, as compared with normal, the resulting Sympathetic response is greater than the resting (baseline) Sympathetic response, causing the stand Sympathetic response to appear normal. Yet the patient is (mildly) symptomatic, and perhaps even the BP drops or at least does not increase normally. Unmasking the SW may occasionally exacerbate symptoms at first until the SW is addressed and itself reversed. In these cases, treating both PE and SW simultaneously is helpful.

PE upon standing may also involve Vasovagal Syncope (p = 0.026). From P&S Monitoring, a (beta-) Sympathetic Excess may also be detected upon standing, indicating another form of Dysautonomia in addition to Orthostatic Dysfunction. Fortunately, treating PE often relieves not only the Vagal component of the Syncope, but the SE component as well, organically, relieving Vasovagal Syncope with low dose therapy. This does not rule out other forms of Syncope.

The Parasympathetics are well known as the “rest and digest” branch; however, it is also the “protective” branch. For example, “a little more” Parasympathetic activity (at rest) is known to be cardio-protective [[[14]](#endnote-14)]. This may help to explain PE with the Valsalva challenge, a challenge that models all forms of mental and physical, Sympathetic stressors, including healthy stressors such as exercise and food. For better or for worse, the Parasympathetics are attempting to protect from stress, but stress often does not go away. We were not designed for chronic stress. For example, patients with PE often complain of exercise intolerance as one of the many symptoms. They tend to report that even though they exercise, they do not lose weight. In fact, the harder the exercise, the more weight they gain, and it is not muscle mass. The reason for this is that the Parasympathetics work to preserve fat stores in times of stress and shunt blood from the periphery to the core. So, while exercising, even mild to moderate exercise, the patient is fighting their own body and not benefitting from the exercise.

Some patients seem to be able to exercise strenuously, however, they “crash”, as they report, afterwards for hours to days because their systems are not able to support the exertion and efficiently restore the body to baseline. In effect, PE seems to decondition the heart (Valsalva PE and low resting diastolic BP are well correlated; p = -0.026). This may be associated with the observation that PE with Valsalva is also associated with a decrease in BP with Valsalva, indicating Baroreceptor Reflex dysfunction (p = -0.009). Using this as a clue, we have found that in addition to very low-dose anti-cholinergic therapy, six months of low-and-slow exercise (*e.g.*, a slowly titrated version of the Modified Dallas Program) helps to relieve PE and enable patients to exercise again thereafter. The reason for the slow titration of the Dallas Program is due to the fact that the original intent of the Modified Dallas Program was to recover astronauts after returning from space with deconditioned hearts. Astronauts are very healthy people with an acute problem. EDSh patients are not healthy people and with a chronic problem and need longer to adapt to the low-and-slow exercise regimen.

The Parasympathetics control or coordinate immune responses and provide the memory for the immune system. Due to the lack of a strong connective tissue barrier from the outside world, the immune system may be persistently overactive in EDSh patients. As a result, the Parasympathetics may be persistently overactive in EDSh patients. This contributes to the fact that EDSh patients may require persistent maintenance therapy to maintain P&S balance.

**CONCLUSION**

Parasympathetic Excess (PE) is a largely unrecognized autonomic disorder that is best measured by independent, simultaneous measures of the autonomic nervous system. PE is relatively easy to treat, once documented, requiring low-dose pharmaceuticals or temporary lifestyle modification. PE in EDSh patients exacerbates the debilitating nature of the disease and simply treating the symptoms often exacerbates the case. Therapy durations are among the shorter of the treatments for Dysautonomia, often lasting at least 6 to 9 months depending on the duration and severity of the disorder. However, due to the “leaky” nature of the disordered connective tissue in EDSh, maintenance dosing is often required since the Parasympathetics are constantly being pulled out of balance. More research is needed to find a cure for the EDSh directly, but for the time being, a means of restoring quality of life and productivity in these patients is possible.

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