**Hypermobility and Ehlers-Danlos Syndrome Symptoms are Explained by Abnormal Sympathetic Responses to Head-Up Postural Change**

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ABSTRACT

**Introduction**. Ehlers-Danlos Syndrome/Hypermobility (EDSh) patients demonstrate abnormal sympathetic responses to head-up postural change. This has been labeled “Sympathetic Withdrawal” (SW) an alpha-adrenergic dysfunction associated with the range of Orthostatic dysfunctions. **Methods**. From a suburban cariology 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. At follow-up testing autonomic therapy for SW was titrated, including fluids, electrolytes, compression garments, Alpha-Lipoic Acid and oral Vasoactives. **Results**. From the questionnaires, SW is associated with many of the symptoms of EDSh associated with poor cerebral perfusion, including: lightheadedness, fatigue, brain-fog, memory and cognitive difficulties, headache or migraine, sleep difficulties, and depression-like and anxiety-like symptoms. Additional symptoms of Orthostatic dysfunction due to blood pooling in the lower extremities are also common. **Conclusion**. SW in EDSh patients is often debilitating and simply treating the symptoms often exacerbates the case. Therapy durations are not short, lasting at least 9 months and perhaps up to 24 months depending on the duration and severity of the disorder.

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**INTRODUCTION**

Hypermobility and Ehlers-Danlos Syndrome (EDSh) often present with a constellation of symptoms that are thought to be associated with the connective tissue disorder, and they are, but not directly. The disordered connective tissue leads to autonomic dysfunction. EDSh is a genetic disorder of the collagen produced by the human body (hereditary – autosomal dominant – or less frequently, *de-novo*). It is characterized by 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 hypermobile. Even hyper-flexibility in the lumbar spine may make the patient able to touch the ground with their palms with straight knees quite easily. The flexibility is enabled by long, stretchy (rather than short and stiff) collagen, which also causes “leaky” connective tissue.

The leaky connective tissue leads, or contributes, to autonomic dysfunction [[[1]](#endnote-1),[[2]](#endnote-2)]. It is the autonomic dysfunction which leads or contributes to many of the symptoms of EDSh. These symptoms include: diffuse pain, especially in the shoulders, upper back, inter-scapular area, jaw, and hips; excess and persistent inflammation; shortness of breath and palpitations; lightheadedness perhaps with a history of fainting or near-fainting, and oftentimes having to lie down when trying to stand for periods of time; (extreme) fatigue; sleep and GI difficulties, and they cannot get going in the morning; brain fog or memory and cognitive difficulties; and bright light or sound may disturb them, including triggering headache or migraine.

The pain and inflammation symptoms 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 hyper-active, which causes the Parasympathetic branch to become persistently hyper-active which in turn causes hyper-reactive Sympathetic responses, amplifying the pain response and exacerbating the inflammatory response [[[3]](#endnote-3)]. Headache, Migraine, and GI difficulties may result directly or indirectly from autonomic dysfunctions. The remaining symptoms listed are considered direct results of autonomic dysfunctions. The main autonomic dysfunction that underlies these symptoms is known as Sympathetic Withdrawal (SW, an alpha-adrenergic dysfunction associated with the range of Orthostatic dysfunctions). Here, we describe SW 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 Sympathetic Withdrawal (SW) on EDSh. SW is an abnormal alpha-adrenergic (Sympathetic) decrease in response to upright postural change (sitting up or standing up). Normally, the alpha-adrenergic response to upright postural change is to increase. The treatment to reverse SW used in this study included the antioxidant r-Alpha-Lipoic Acid (rALA) [[[7]](#endnote-7)] in combination with low-dose oral vasoactive medications [[[8]](#endnote-8)]. Close observation is recommended during the early stages of therapy since the vasoactives tend to raise resting BP while the body acclimates to the restored vasoconstriction. Further, the restored vasoconstriction may also cause additional symptoms (*i.e.*, “goose-bumps” and “itchy” scalp) that may also be distracting. The patient needs to be reassured that these symptoms are indications that the therapy is working and they normally are relieved naturally in two weeks. To minimize these additional symptoms, and to maximize patient acceptance, the low dose vasoactives are titrated very slowly from even smaller doses. Once SW is relieved, due to the persistent nature of EDSh, a maintenance dose of rALA was required to help maintain normal autonomic function.

Occasionally, SW may be masked by an excessive Parasympathetic response to upright posture. In these cases, both the SW and the PE were treated simultaneously, since these responses are from two different portions of the nervous system.

**RESULTS**

Table 1 and Table 2 describe the patient demographics. While resting P&S balance (SB) for the cohort is well within normal limits (SB: 0.4 < SB < 3.0, unitless); preferred SB for younger, < 65 y/o, healthier subjects is 1.0 < SB < 3.0; and preferred SB for older subjects, ≥ 65 y/o, and sicker patients is 0.4 < SB < 1.0; the latter is known to be cardio-protective [[[9]](#endnote-9)] 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 [[[10]](#endnote-10),[[11]](#endnote-11)] and is known to best predicted 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) [[[12]](#endnote-12)]. While on average, none of the age groups demonstrate CAN, only 3 of 11 (27.3%) of those over the age of 65 demonstrate CAN (Table 2), and none of those three also demonstrate high SB, so their risk is normal. More patients (14.4%) demonstrate AAD with at least one patient in each decade demonstrating AAD. Sympathetic Withdrawal (SW) occurs in approximately half (49.4%) of this cohort. The majority of patients presenting with SW are younger. This may be in part due to the heavy focus on dysautonomia within the representative practices.

The HRV data, known as the Ewing Ratios or Time-Domain Ratios, are standard autonomic measures taken during standard (Ewing) challenges of the autonomic nervous system and are presented in Figure 1. The solid lines represent the average EDSh patients’ responses by age and the same color, broken lines represent the threshold between normal and abnormal for the same measures. All of these measures indicate that on average, the P-activity is normal throughout the years, further contributing to the perceived normalcy of these patients.

Comparing the change in the other HRV measures of LF and LF/HF from rest to head-up posture with the change in BP over the same time periods, 104 patients demonstrate a decrease in BP, indicating Orthostatic Hypotension (OH) or pre-clinical OH. Under the same conditions, the change in LF indicates that 151 patients are at risk for OH (19.3% false positive and 48.1% false negative, p = 0.116) and the change in LF/HF indicates that 81 patients

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

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Age  (yrs)** | **N (#)** | **Female (%)** | **BMI (#/in2)** | **HR (bmp)** | **BP (mmHg)** | **E/I Ratio** | **Valsalva Ratio** | **30:15 Ratio** |
| < 20 | 32 | 93.8 | 24.8 | 88.2 | 115.5/70.7 | 1.3 | 1.5 | 1.4 |
| 20 – 29 | 86 | 95.3 | 25.3 | 86.2 | 121.2/76.5 | 1.3 | 1.6 | 1.4 |
| 30 – 39 | 52 | 96.2 | 29.0 | 84.7 | 123.2/79.3 | 1.3 | 1.6 | 1.3 |
| 40 – 49 | 29 | 86.2 | 30.5 | 79.7 | 124.1/80.3 | 1.2 | 1.6 | 1.3 |
| 50 – 59 | 29 | 89.7 | 30.6 | 75.0 | 137.6/83.5 | 1.2 | 1.6 | 1.2 |
| 60 – 69 | 7 | 85.7 | 25.6 | 69.6 | 137.5/78.0 | 1.2 | 1.3 | 1.1 |
| ≥ 70 | 8 | 50.0 | 27.6 | 75.9 | 136.7/71.7 | 1.1 | 1.6 | 1.3 |

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

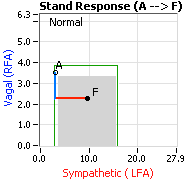
Table 2: Hypermobility and Ehlers-Danlos Syndrome patient demographics and average, resting P&S data.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Age  (yrs)** | **N (#)** | **P (bpm2)** | **S (bpm2)** | **SB** | **AAD**  **(#)** | **CAN**  **(#)** | **SW (#)** |
| < 20 | 32 | 6.5 | 7.7 | 2.3 | 1 | 0 | 11 |
| 20 – 29 | 86 | 6.8 | 6.9 | 1.9 | 4 | 0 | 37 |
| 30 – 39 | 52 | 7.5 | 6.6 | 2.4 | 5 | 0 | 26 |
| 40 – 49 | 29 | 1.9 | 2.5 | 1.7 | 3 | 0 | 13 |
| 50 – 59 | 29 | 1.5 | 2.0 | 2.6 | 12 | 0 | 22 |
| 60 – 69 | 7 | 0.7 | 0.9 | 2.3 | 5 | 1 | 4 |
| ≥ 70 | 8 | 0.2 | 0.5 | 2.0 | 5 | 2 | 7 |

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

are at risk for OH (9.5% false positive and 29.2% false negative, p = 0.067). This is in keeping with the findings of the standards articles, that the LF/HF ratio is better than LF in indicating risk of OH. The change in the P&S measure of Sympathetic activity, LFa, under these same conditions indicates that 120 patients are at risk for OH (6.6% false positive and 3.3% false negative, p = 0.009). A normal P&S stand response is depicted in Figure 2 (top panel). Normally, the Parasympathetics decrease first to potentiate and minimize the (alpha-)Sympathetic response. Then, the Sympathetics respond positively to cause the vasoconstriction required to defeat gravity and coordinate the Orthostatic response to head-up postural change (*e.g.*, standing). An example of SW is depicted in Figure 2 (bottom panel), where even though the Parasympathetics decrease as normal, the Sympathetics decrease also. As a result, the Orthostatic response is abnormal, typically resulting in abnormal hemodynamic responses, including Orthostatic Hypotension (OH, SW with a drop in BP upon standing) or Postural Orthostatic Tachycardia Syndrome (POTS,

Figure 1: The Ewing Ratios are presented for this EDSh cohort. The E/I Ratio is the exhalation/inhalation ratio of heart beat intervals (HBIs) measured at peak exhalation and peak inhalation during a paced breathing exercise where the patient is directed to breathe at six breaths per minute (five-second inhalation and five-second exhalation). The Valsalva ratio is the longest HBI during a 15 second Valsalva maneuver over the shortest HBI during that same maneuver. The 30:15 ratio is the HBI at 30 seconds following a rapid head-up postural change (standing) over the HBI at 15 seconds. All three ratios are always greater than 1.0 and are thresholded quantitative measures of Parasympathetic activity, where more is considered better with no known upper limit. (Too much Parasympathetic activity is also not healthy, but is unknown in these cases). On average throughout this cohort, the Ewing ratio measures of Parasympathetic activity are normal.   
EDS DB raw 12May20



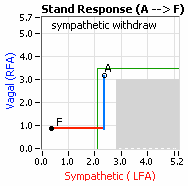


Figure 2: Sample PC (stand) response plots demonstrating the normal (top) and the abnormal (bottom) SW states. See text for details. InteractiveRespPlots

SW with an excessive increase HR upon standing) or Orthostatic Intolerance (OI, SW with a normal hemodynamic response upon standing).

SW was reported in 120 of the 243 (49.4%) patients in this cohort. Relieving SW relieved symptoms in over 85% of this sub-population and helped to restore their quality of life and productivity in society. The remaining EDSh patients in this sub-population had other dysautonomias and confounding disorders that prolonged their therapy.

**DISCUSSION**

Orthostatic dysfunction is often the first and arguably the most debilitating form of autonomic dysfunction [[[13]](#endnote-13),[[14]](#endnote-14)]. The autonomic nervous system, including its two branches, the Parasympathetic and Sympathetic (P&S) nervous systems, is a very dynamic system and never actually “rests.” In fact, when the body is at rest, as in sleeping, it may be argued that the P&S systems are most active. This is important because most autonomic dysfunctions are not well documented when the patient is at rest. In fact, the primary autonomic dysfunctions documented at rest are much later stage dysfunctions, such as Diabetic Autonomic Neuropathy (DAN, *aka.*, Advanced Autonomic Dysfunction, AAD, for non-diabetics) and Cardiovascular Autonomic Neuropathy (CAN). These are conditions indicating that patients are already at increased morbidity [[[15]](#endnote-15)] and mortality [[[16]](#endnote-16)] risk, respectively. This may be a reason why EDSh symptoms have failed to be associated with autonomic dysfunction, because these tend to be younger patients, tested at rest, before most would consider AAD or CAN. The lack of any patients in this cohort with CAN with high SB helps to confirm that EDSh does not seem to effect longevity. On the other hand, AAD is more prevalent (14.4%) in this population, with even one of the teenagers demonstrating AAD. As expected, EDSh seems to affect morbidity and thereby quality of life and productivity, even though common physiologic measures (*i.e.*, HR & BP) are well within normal ranges.

To compound the problem that most autonomic dysfunctions are not well documented when the patient is at rest is the fact that Heart Rate Variability (HRV), a standard measure of autonomic activity, is a mixed measure of P&S responses. Given that the P&S branches work synergistically and attempt to remain in balance, the total responses measured tend to look normal in younger patients. The Ewing Ratios (aka., Time Domain Ratios), taken from the Ewing challenges for this cohort, include the E/I ratio from the deep breathing challenge, the Valsalva Ratio from a 15 second Valsalva maneuver, and the 30:15 Ratio from an upright postural change challenge. These are qualitative, thresholded measures of P-activity (including the Valsalva Ratio). According to Vinik, Diabetic Autonomic Neuropathy (DAN, what we call Advanced Autonomic Dysfunction or AAD) is indicated when two of the three Time-Domain Ratios are below threshold. AAD or DAN indicate increased mortality risk. Also according to Vinik, Cardiovascular Autonomic Neuropathy (CAN) is indicated when all three are low. CAN indicates increased morbidity risk and is associated with a 50% increase in mortality over a two-year period. Subsequently, Vinik debunked the validity of the Valsalva and 30:15 Ratios, especially above the age of 55 yrs. This is highlighted in this population by the apparent increase (indicating a more normal response) in these two Ratios after the age of 65 yrs. Before adopting P&S Monitoring, Vinik considered only the E/I Ratio as a decent indicator of morbidity and mortality risk for Diabetics.

The other common, standard HRV measures are from spectral analysis, including the low frequency (LF) measure and the ratio of low to high frequency (LF/HF) measure. The LF measure is a mixed measure of P&S activity; however, it is assumed to be primarily a measure of Sympathetic activity. Although, the standards articles [4,5] state that the ratio of LF/HF is found to be a better measure of the change in Sympathetic activity with standing than LF alone. Perhaps the thinking is that HF (a mixed measure of Parasympathetic activity and noise, when the respiratory frequency is high enough; otherwise, it is just noise), assumed to measure Parasympathetic activity, will yield a more pure measure of Sympathetic activity from the ratio, LF/HF, by dividing out some of the Parasympathetic activity.

P&S Monitoring enables a direct measure of SW. Some of the symptoms of the typical EDSh patient are: 1) diffuse pain, especially in the shoulders, upper back, and inter-scapular area; 2) shortness of breath and palpitations; 3) inability to stand for long periods of time without lightheadedness or dizziness, often with a history of fainting or near-fainting, and oftentimes needing to lie down when trying to stand for periods of time; 4) extreme tiredness or persistent fatigue (that does not necessarily qualify as chronic fatigue syndrome); 5) sleep difficulties and difficulty getting going in the morning; 6) brain fog or memory and cognitive difficulties; 7) frequent headache or migraine; 8) edema of the legs, ankles, and feet; and 9) sensitivity to bright light or sound. All of these may be explained by poor cerebral perfusion due to Orthostatic dysfunction, caused or contributed to by SW.

The diffuse pain in areas above the heart may be a result of poor perfusion of any structure above the heart. Shortness of breath and palpitations may be a result of poor cardiac perfusion or poor cerebral perfusion leading to the brain releasing adrenaline to stimulate the heart, or both. Of course, lightheadedness is caused by poor cerebral perfusion, and so dizziness may be due to either or both central vestibular degradation due to poor cerebral perfusion or peripheral vestibular degradation due to poor perfusion above the heart. The inability to stand for long periods of time may be a combination of edema and associated pain in the lower extremities and lightheadedness.

The extreme tiredness or fatigue symptoms, which mimic depression-like symptoms is a direct result of poor cerebral perfusion. In fact, many patients also report bouts of anxiety-like symptoms with the feelings of fatigue and depression. This may be explained by the “adrenaline storms”. The sleep difficulties may be a result of abnormal changes in cerebral perfusion due to SW. For example, while upright (*e.g.*, sitting or standing all day) and due to SW, the brain is only marginally perfused and marginally functional (causing among the others the fatigue). As soon as a supine position is assumed, cerebral perfusion is restored (like falling down after fainting). Now the brain is fully perfused and fully functional. In fact, many patients report being more alert during this time (immediately after lying down in bed) than they were during the day. In effect, the patient’s day and night have been reversed. This leads to difficulty falling asleep, waking frequently during the night (more than twice even to go to the bathroom; the brain is still alert and active), or both. Ultimately, the poor sleep leads to the difficulty getting going in the morning, and compounds the fatigue (and any depression).

Of course, brain fog or memory and cognitive difficulties are a direct result of poor cerebral perfusion, as well as some types of headaches and migraines, and these may also involve sensitivity to bright light or sound. Also, edema of the lower extremities is an obvious result of OH due to SW. Relieving SW helps to relieve the orthostatic dysfunction, poor cardiac perfusion, and poor cerebral perfusion symptoms associated with SW, in the majority of the cases.

**CONCLUSION**

Sympathetic Withdrawal (SW) is a largely unrecognized autonomic disorder that is best measured by independent, simultaneous measures of the autonomic nervous system. SW is relatively easy to treat, once documented, requiring low dose pharmaceuticals and a natural antioxidant. SW in EDSh patients is often debilitating and simply treating the symptoms often exacerbates the case. Therapy durations are not short, lasting at least 9 months and perhaps up to 24 months depending on the duration and severity of the disorder. More research is needed to find a cure for 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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