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

DePace NL, Acosta CR, DePace Jr. NL, Kaczmarski K, Goldis M, Colombo J.

Hypermobility/Ehlers-Danlos Syndrome (hEDS) 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. HEDS may be inherited, usually an autosomal dominant trait, however acquired cases occur frequently. To date there is no known cure for hEDS. 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 hEDS 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 effects 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.

Younger hEDS 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 hEDS 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 involved 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 hEDS 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-activity[1], also amplifies the pain response, especially in "Fibromyalgia-like" pain syndromes. Since the majority of hEDS 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 hEDS patients' resting P&S activity normalizes, as compared with that of the Normal subjects. However, the hEDS patients' resting S-activity remains high compared with resting P-activity.

hEDS is believed to not be life threatening, except for one form of EDS (the vascular form). However, based on these sample populations, hEDS 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 hEDS 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 (heat attack, stroke, heart failure, etc.). The higher mortality-risk is reflected in the CAN with SB > 2.5 condition in the hEDS patients starting around age 60, on average. 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 Sympatholytics or reducing stress, including Psychosocial stress. Overall, the P&S data are a better match to the natural history and progression of hEDS.

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, as measured as high-normal SB ($2.0 < SB < 3.0$). The persistent and prolonged stress on the more exposed and longer Parasympathetics (Vagal) nerves, including Oxidative Stress, 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 hEDS, 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 hEDS, only the ability to treat it to maintain P&S balance as much as possible as the systems 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 hEDS present, are often the result of P&S dysfunction. This goes hand in hand with the hEDS. Even the amplified and generalized pain and inflammatory responses (not only in the joints), anxiety, brain-fog, memory and cognitive difficulties, sleep difficulties, GI motility issues, may be secondary to P&S dysfunction caused by hEDS. 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, hEDs 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 hEDS 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 are 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 hEDS 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 hEDS and serve to exacerbate the symptoms of hEDS. 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 and Mast Cell Activation Syndrome (MCAS), and Small Fiber disorder.

PE may be a primary disorder caused by hEDS. It is well known that the Parasympathetics control and coordinate immune responses, including providing the "memory" for the immune system. Since hEDS 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 hEDS. 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.

As mentioned before, there is no genetic testing or lab testing that is diagnostic of hEDS. 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. This is just the beginning of a research effort that must include many more patients from many more sources as hEDS awareness continues to grow.