Theory – Why Some EDS patients Have Anterior Brain Stem Symptoms, Chiari Symptoms, Endocrine Abnormalities and Various Seemingly Unrelated Neurologic Symptoms (with no imaging verification of retroflexed odontoid, clivus angle decrease upon upright posture or Chiari)

THE THEORY:

Note: This theory is the result of my Classic Ehlers-Danlos condition (the M.A.S.S. phenotype) and resulting autonomic dysfunction, that of my children’s and the hundreds of EDS patients I have been blessed to know and many who have contacted me concerning their condition. Contributions of knowledge by such experts as Dr. Fraser Henderson, Dr. Clair Francomano and Dr. Nazli McDonnell combined with a healthy dose of trial and error based on my own responses to various medications and potential treatments, and hundreds of hours of research have helped formulate this theory.

Most of the symptoms of brain stem and Chiari issues (see symptoms below) in many patients with Ehlers-Danlos Syndrome (EDS) should, theoretically, be the result of a crowded brain stem area, retroflexed odontoid and/or positional issues with their clivus angles; but for many EDS patients, there is no sign of such via imaging. Yet many patients notice the nausea, dizziness, orthostatic intolerance, sensitivity to light, noise and movement, difficulty in turning their heads, lightheadedness and/or fainting, blepharoclonus, tremulousness, tachycardia, blood pressure swings, digestive difficulties, endocrine abnormalities, fatigue, brain fog (or dementia), intolerance to temperature changes, the feeling of pressure in their heads, earaches and possible CSF rhinorrhea. Often, imaging indicates brain atrophy (especially cerebral), lumbar punctures are usually “normal” and entering pressures are usually “normal” and entering pressures are low or normal.

I believe that in EDS, patients exhibiting the symptoms and signs of anterior brainstem damage and Chiari symptoms (with other neurological manifestations), it is the fluid collecting in the cisterns surrounding the brain stem and pons that puts pressure on these areas causing the constellation of symptoms. In EDS patients, connective tissue is faulty, weak and more distensible (as is evident by commonly found dural ectasia located as high as the cervical region). Depending upon which cisterns contain the most fluid, and what position these patients are in at the time, the symptoms will vary accordingly. Likely, there is also fluid accumulation in the subarachnoid spaces and lower ventricles, especially in the supine position.

It is likely that the fluid pressure in the heads and necks of Ehlers-Danlos patients is higher than in the rest of the spine (which is why entering lumbar pressures in EDS patients don’t usually reflect the problem). I believe that the CSF outflow is sluggish, and getting “hung up” in the cisterns and cervical areas, using the easily distensible dura to allow the fluid to collect, as opposed to draining properly. This condition could come on gradually, as the dura stretches with time and cervical degeneration accelerates, but

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because viruses can trigger autonomic dysfunction at any age, I believe that the viral trigger can act as “the last straw” if you will, in an already compromised outflow system. I believe this is also the case in the development of POTS (postural orthostatic tachycardia syndrome) and blood pooling in the lower extremities which can begin abruptly, supporting a neurologic cause of venous failure more so than progressive venous weakness and stretching over time.

Additionally, I believe the ICP in affected Ehlers-Danlos patients is highest in the supine position (and is thus high when the patient is trying to sleep), due to the exaggeration of the sluggishness of venous outflow which occurs without the benefit of gravity, in concert with congenital malformations of the internal jugular veins (small, stenosed veins allowing bidirectional flow of blood, otherwise known as CCSVI), and arachnoid villi that are easily damaged by viral antibodies.

I propose that when EDS patients are exposed to certain viruses (and perhaps other triggers as well), antibodies cross the blood brain barrier (which is more permeable in EDS patients than that of normals due to its make up of faulty connective tissue) and damage the arachnoid villi (which may also be faulty), reducing the absorption of CSF and causing the CSF pressure to build. Some fluid will likely make it through the arachnoid villi and will drain via the lymphatic system and will attempt to drain through the venous structures. Any fluid that is still unable to “go anywhere” goes down the cisterns (after filling the subarachnoid spaces). Here is a picture of the location of the cisterns in relation to the brain stem.

The boundaries of the cisterns are made of dura, arachnoid and pia mater (which we know can stretch with EDS). When viewing the MRI’s of numerous symptomatic EDS patients, it becomes apparent that the cisterns often appear abnormally large and distended.
Another interesting point is that when many EDS patients lie on their backs or in the Fowler’s position, they are immediately more symptomatic with a sudden increase in heart palpitations and the feeling of suffocation. I propose this could this be the additional pressure on the brainstem translated from the cerebromedullary cistern, or the increase in venous blood volume in the brain secondary to bidirectional flow of malformed and stenosed veins (CCSVI), or most likely, the combination of the two. Neurosurgeons describe how even a “feather’s touch” on the brain stem can cause significant symptoms.

The overly full cerebromedullary cistern (at the lowest portion of the brainstem, just above the foramen magnum) would put pressure on the same part of the brainstem that we would see affected by a retroflexed odontoid and/or Chiari – affecting the lower cranial nerves, brainstem and cerebellum. An overly full cerebromedullary cistern would act much like “milking the cow” of the brainstem, causing the constellations of symptoms as described by Ehlers-Danlos researchers in the attached article. (“Syndrome of occipitoatlantoaxial hypermobility, cranial settling, and Chiari malformation Type I in patients with hereditary disorders of connective tissue”)

When the third ventricle is full, the adjacent hypothalamic structures involved in autonomic function may be affected. A large number of EDS patients suffer from hypothalamic dysfunction.

When the lateral ventricles are full, the periventricular structures may be affected just enough to cause changes in personality. I hear from many EDS patients that they seem to have become bipolar – indeed some were actually medicated for bipolar disorder until they finally obtained a diagnosis of EDS.

The form of hydrocephalus as described above, with fluid accumulating in subarachnoid spaces, cisterns and lower ventricles could easily go undetected in MRI imaging. This is much like many cases of pseudo-tumor cerebri where the lateral ventricles do not always enlarge. Compression of the thecal sac of the brain stem could in fact hinder both CSF flow and blood flow, trapping CSF in the ventricles when the patient is vertical. Because the cisterns are more easily distended in the EDS patient, I propose the CSF fluid is also trapped in these cisterns upon upright posture, causing and/or exacerbating the orthostatic intolerance and autonomic dysfunction in these patients.

The increase in fluid retention in the skulls and cervical areas in EDS patients may also put direct pressure on (and cause irritation of) many cranial nerves. When the spinal accessory nerve is irritated, for example, patients may exhibit the classic neck and upper shoulder symptoms that can radiate down the arms and cause the fasciculations typically seen in the fingers. This common occipital headache radiating down the neck and shoulders (in the classic “angle-wing” pattern) of EDS patients is usually immediately reversible with the use of Diamox, supporting this theory.

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Many EDS patients appear to have “sinking brains” via MRI imaging. Could this be from the increased volume of CSF that would normally drain out of the brain, instead applying pressure to the brain and perhaps even inverting the normal CSF pressure gradient? Normally, pressure is highest in the ventricles and lowest above the brain where CSF is absorbed and exits through the venous system (primarily). If the CSF is not exiting, could the CSF pressure above the brain increase and thus be higher than the pressure inside the ventricles, resulting in pressure on, and ischemia of, the cranial nerves, and hippocampus and/or hypothalamus?

Supporting this supposition, many EDS patients have a constellation of cranial nerve symptoms, not to mention brain atrophy. Certainly, many patients’ images also show little or no CSF under the frontal lobes of the brain, which would result in irritation of CN2. EDS patients are more prone to developing glaucoma and macular degeneration than normals.

More support for this theory comes from the reversal of many symptoms with the use of Diamox in these patients. Patients who required cervical collars to maintain some functionality became comfortable without these collars, and became much more tolerant of jostling in the cervical area after the reduction of CSF from the use of Diamox. Additionally, researchers in POTS (and reports from POTS patients) report immediate improvement of symptoms with the use of abdominal binders for many of these patients (even though the use of surgical stockings provided no relief). These binders likely cause a small amount of lifting of the crowded brain stem area from the foramen magnum, reducing pressure on the cranial nerves, while allowing greater influx of oxygenated blood into the brain.

Dr. Zamboni’s theory that CCSVI (chronic cerebrospinal venous insufficiency) causes sluggish outflow of venous blood and this, perhaps in conjunction with iron accumulation on the brain due to poor CSF circulation, may be the cause of multiple sclerosis, may be especially pertinent to Ehlers-Danlos patients. Because EDS patients have both anatomical abnormalities of the skull (mid-face hypoplasia, narrow, high palates and small, sharply angled eustachian tubes, for example) and abnormal connective tissue (including dura) and vessels, they may be more likely to have anatomical variations of veins, including cervical veins. Indeed, researchers have noted that many more EDS patients go on to develop M.S. than in the normal population. The corollary has also been found to be true (“Ehlers-Danlos syndrome and multiple sclerosis: a possible association”). The M.S. population of patients contains approximately 10-11 times more EDS patients than what is found in the general population, according to this study.

Mildly increased ICP can cause hypothalamic dysfunction, exhibited as OCD tendencies, free-floating anxiety and/or the need to overachieve. These are typical presentations for EDS patients, yet no one has been able to discover why this is the case.

Many symptoms in the EDS patient with autonomic dysfunction (including short-term memory deficits and loss of executive function) may be attributable to decreased cerebral blood flow secondary to the resulting cerebrovascular resistance

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when venous outflow is inhibited. As we know, cerebral blood flow is equal to the cerebral perfusion pressure divided by the cerebrovascular resistance. This may be why vasoconstrictors and abdominal binders ease symptoms for many EDS patients.

This cerebrovascular resistance may also be the cause of the development of left ventricular diastolic dysfunction in many EDS patients. The heart is continually working against this venous pressure in attempt to get oxygenated blood into the brain. (“Echocardiographic Findings in Classical and Hypermobile Ehlers-Danlos Syndromes”).

Many EDS patients become plagued with endocrine abnormalities that fluctuate wildly. “Chronic fatigue” is also commonly exhibited by EDS patients and has been associated with low morning cortisol levels. Many EDS patients seem to get more energy in the evening, and will often be unable to sleep until the middle of the night. I believe the abnormal change in their CSF pressure is to blame.

Assuming Ehlers-Danlos patients have sluggish CSF outflow, they depend on gravity to help drain the fluid from their heads. This is likely because of the anatomical variations mentioned above. Additionally, CCSVI (chronic cerebrospinal venous insufficiency) and the often related bidirectional flow of blood in the veins, especially the internal jugular veins, make gravity and a vertical position even more critical for proper venous drainage and normal brain health. However, when asleep (or awake) in the supine position, the fluid does not drain well, and interferes with the normal cortisol production (either through increased pressure in the 3rd ventricle adjacent to the hypothalamus, direct pressure on the pituitary or on the pituitary’s blood supply). Thus, the patient’s cortisol level in the a.m. is abnormally low, but after the patient has become vertical allowing gravity and the normal “pumping action” of the sacral area to encourage CSF circulation and drainage, the cortisol level increases more than what is average in the evening, interfering with a normal sleep cycle. I believe the cortisol (and likely ACTH levels) may take on an inverted production curve at best, and may be low throughout both day and night, at worst.

This means that depending on what time of day cortisol levels are checked and how long the patient has been vertical, the patient’s cortisol may be within normal ranges, which can be deceiving. Typically, ACTH levels are also low for these patients and an ACTH stimulation test is certainly called for. Typically, we see some response of the adrenals (we usually look for a doubling of the cortisol levels), indicating that the problem may be in the hypothalamus (again, I would surmise from indirect pressure from the bulging 3rd ventricle).

As a part of the EDS patient’s profile, poor CSF and venous drainage may also be genetic. Certainly, if the patient is born with CCSVI, the sutures of the skull have not yet fused and the child has not yet developed collateral veins to assist in fluid drainage of their skulls, with even a low degree of high CSF pressure we should be able to demonstrate this with an evaluation of the child’s head circumference prior to the closure of the sutures of the skull. Indeed, in the handful of patients that have been able to

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provide this data, in the first 15 months of life, although the child’s length and weight stayed within a small range of percentages as compared with normals, their head circumference did not. Head circumference was found to increase from approximately the 40th percentile on the bell curve to above the 100th percentile. I believe this is due to congenitally high CSF pressure and possibly, congenital CCSVI (all patients tested for CCSVI were found to be positive for CCSVI, however not all patients were tested for CCSVI).

Finally, angioplasty for these CCSVI (with EDS) patients has not shown to be successful if the patient is not taking Diamox. I propose that unless the CSF can make it out of the brain, it won’t help the patients to have the veins opened. Once the CSF can exit the brain (with the use of Diamox) however, positive response to angioplasty has been noted. All of these patients have “viral-induced” autonomic dysfunction, thus much more research is needed in this area. At this stage, however, I would propose to all patients who have had little or no results from angioplasty, that a trial of Diamox may need to be considered.

Ehlers-Danlos patients may be excellent models for the evaluation of multiple sclerosis, chronic fatigue, fibromyalgia, and potentially other neurodegenerative diseases. Because of their poor connective tissue and abnormal vasculature, they may be more prone to developing these conditions, and more importantly, they may be able to provide answers for treatment.

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