



# The Driscoll Theory - Part 1

The Role of External Communicating Hydrocephalus, Mast Cell Disease and CCSVI as the Cause of POTS (Postural Orthostatic Tachycardia Syndrome) in Ehlers-Danlos Syndrome



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# **The Driscoll Theory: The Role of External Communicating Hydrocephalus, Mast Cell Disease and CCSVI as the Cause of POTS (Postural Orthostatic Tachycardia Syndrome) in Ehlers-Danlos Syndrome**

**External Communicating Hydrocephalus, often in conjunction with mast cell disorders and CCSVI (Chronic Cerebrovascular Venous Insufficiency), as a cause of POTS (Postural Orthostatic Tachycardia Syndrome), autonomic dysfunction, endocrine abnormalities, loss of cognitive function, fatigue, gastro-intestinal sensitivities (irritable bowel syndrome), and cranial nerve symptoms in Ehlers-Danlos Syndrome.**

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## About the Author

Dr. Diana Driscoll is both a patient (Ehlers-Danlos, POTS, dysautonomia, CCSVI and high intracranial pressure) and a doctor (therapeutic optometrist). Currently on professional disability and donating her body to science while still using it, she has reached out to others with similar conditions. Through collaboration, research and trial and error, she has found some answers and is now heading up clinical trials that may offer the much needed relief and answers that have eluded many for so long.

Dr. Driscoll graduated summa cum laude from The University of Texas and summa cum laude from the University Of Houston College Of Optometry. She received numerous awards for excellence in her field until struck down with an unusual virus she received while on a mission trip out of the country. This occurred after practicing in her field for over 20 years.

Both of her children also have Ehlers-Danlos Syndrome, as does one of their dogs!

Her passion (and admitted geekiness) is what drives her to find answers for a condition that can be life-changing, yet unfamiliar to most doctors.

She is conducting numerous clinical trials (you can locate these on [clinicaltrials.gov](http://clinicaltrials.gov)) and self-funds almost all of her work and research.

She lives in the Dallas/Fort Worth area with her wonderful husband (“heaven only knows why he is still with me”), two beautiful children, and two dogs. One of the dogs knows at least as much about Ehlers-Danlos as much of the medical community and is considering starting a Facebook page to spread the word.



External Communicating Hydrocephalus, often in conjunction with mast cell disorders and CCSVI (Chronic Cerebrovascular Venous Insufficiency), as a cause of POTS (Postural Orthostatic Tachycardia Syndrome), autonomic dysfunction, endocrine abnormalities, loss of cognitive function, fatigue and cranial nerve symptoms in Ehlers-Danlos Syndrome –  
“The Driscoll Theory”

## **Abstract:**

*The author explains how pilot studies indicate that External Communicating Hydrocephalus appears to be responsible for the autonomic symptoms (“POTS” – Postural Orthostatic Tachycardia Syndrome) found in 33-50% (or more) of the Classic, Hypermobile and Vascular Ehlers-Danlos Syndrome patient populations. Retrospective examination of head circumference growth in babies who were later diagnosed with EDS (Ehlers-Danlos Syndrome) and POTS, indicates such hydrocephalus is evident.*

*Furthermore, External Communicating Hydrocephalus, often in conjunction with CCSVI (chronic cerebrospinal venous insufficiency), is hypothesized as the cause of the constellation of cranial nerve signs and symptoms, endocrine abnormalities, personality changes, cognitive decline, extreme fatigue, left ventricular diastolic dysfunction and brain atrophy in the Ehlers-Danlos Syndrome patient population.*

*Finally, Mastocytosis (or mast cell disease) appears to be a common condition found in patients with EDS and POTS, potentially exacerbating brain fog, dementia, personality changes, and fatigue. Although it is presumed that mast cell disease is secondary to POTS, the potential for congenital mast cell disease causing POTS and hydrocephalus cannot yet be dismissed.*

*Treatment for mast cell disease and mild hydrocephalus in EDS patients with POTS is resulting in consistently positive responses – encouraging the author to disseminate this information prior to the completion of all clinical trials. Treatment with Diamox and H1 and H2 inhibitors has shown to be effective in dramatically reducing symptoms in many of these potentially disabled patients.*

## INTRODUCTION

It is generally accepted that there are three major forms of hydrocephalus:

- Communicating Hydrocephalus: Cerebrospinal fluid (CSF) pressure and CSF volume increases due to poor absorption of CSF through the absorptive tissue (arachnoid villi and perhaps through lymph vessels).
- Non-Communicating Hydrocephalus: CSF flow is reduced or arrested due to a blockage between the ventricles.
- Normal Pressure Hydrocephalus: Usually found in seniors, ventricles enlarge and although lumbar punctures may indicate “normal CSF pressure” it has been found that surges in pressure do occur in these patients, usually at night time. <sup>(3)</sup>

In addition to the three forms listed above, the term “External Hydrocephalus” was coined to describe hydrocephalus that presents with an enlarged subarachnoid space and does not necessarily cause any change in the size of the ventricles. A research and literature review indicates that External Hydrocephalus, although not fully understood, has been considered to be a relatively benign condition, affecting babies and toddlers whose arachnoid villi have not yet fully matured (such maturation is assumed to occur at around 18 months).<sup>(4)</sup>

Indicative of the poor understanding of External Hydrocephalus are the numerous names used to identify this condition including: subdural effusion, hygroma, benign infantile hydrocephalus, pseudohydrocephalus-megalocephaly, benign subdural collections of infancy and extraventricular obstructive hydrocephalus.

“Hydrocephalus” involving the enlargement of baby’s heads is well recognized, as is “pseudo-tumor cerebri” involving an increase in CSF pressure sufficient to cause papilledema and potential vision loss, most frequently in young women. “Normal Pressure Hydrocephalus” (which we now understand involves intermittent spurts of increased CSF pressure) is recognizable in seniors.<sup>(3)</sup> It is the author’s opinion that little or no attention has been given to patients whose presentation represents a low level of increased CSF pressure which falls into the External

Communicating Hydrocephalus category, yet continues beyond childhood and may worsen with the effects of infection and age. Intuitively, we can understand how variable levels of abnormal CSF pressure, rather than falling into separate diagnoses based on the level of pressure, may instead involve a continuum of pressures, and related symptomology. To date, there has been no retrospective research evaluating young adults whose symptoms reflect relatively high CSF pressure, but whose medical history reflects what has been called “Benign External Hydrocephalus”.

The author hypothesizes that patients prone to poor CSF absorption, likely from birth (through abnormal arachnoid villi and also perhaps through compromised lymphatic and venous drainage) resulting in a “low-level” of high pressure over many years, may be prone to further damage to the outflow system later in life. When this damage to the CSF outflow system is triggered, it acts as the “last straw” in an already compromised CSF drainage system. The resulting signs and symptoms at this “tipping point” include autonomic dysfunction, endocrine abnormalities, chronic fatigue, cranial nerve symptoms and the seemingly unrelated constellation of neurological symptoms evident in 33-50% of Ehlers-Danlos patients (Classic, Hypermobile and Vascular Types).

### **Types of External Communicating Hydrocephalus:**

It is proposed that three types of External Communicating Hydrocephalus exist:

1. Congenital: the subarachnoid villi are immature (and perhaps never “mature” in Ehlers-Danlos patients, as these patients have faulty connective tissue). The faulty arachnoid villi may mature and heal when the patients are young, however it is the author’s belief that many Ehlers-Danlos patients never fully achieve proper CSF drainage, leaving a “low level of high pressure” on the brains of these patients. Indeed, research shows that Ehlers-Danlos patients typically present with low levels of anxiety, sometimes evident as O.C.D. (obsessive compulsive disorder) tendencies or over-achievement throughout their lives.<sup>(5) (6)</sup>

2. Viral-induced: either a virus or viral antibodies cross the blood brain barrier (which is made of faulty, permeable connective tissue in the Ehlers-Danlos patient) and block or damage the susceptible arachnoid villi. This could occur at any age, and likely more easily with Ehlers-Danlos Syndrome than normals.
3. Combination of congenital and viral-induced: These patients usually show a form of megaloccephaly as they grow from birth to approximately 16 months (prior to the closing of the sutures of the skull). With the borderline ability to drain CSF fluid, these patients may be especially prone to further damage from viral antibodies. Indeed, studies have shown that high CSF pressure in-and-of itself is enough to damage arachnoid villi. <sup>(7)</sup> These patients, who already have a compromised CSF drainage system, cannot compensate for any further damage to their drainage system and thus become symptomatic almost immediately. (Note: the term “megaloccephaly” is sometimes reserved for head sizes in the top 2% of patients. In this use of the word, we are including those patients in the top 10% of head sizes whose head circumference increased markedly in the first 12-15 months of life.)



## **The Onset Of External Communicating Hydrocephalus In The Ehlers-Danlos Patient First Exhibiting Neurological Symptoms In Childhood Or Teenage Years:**

The author has observed in a small sample size of such patients, their MRI imaging indicates an excessive volume of CSF in the subarachnoid space above the brain, with little or no change in ventricle size.

Utilizing retrospective measurements of the patients' head circumferences (as a percent of normal in relation to their length and weight), megaloccephaly is quite apparent, with most of these children's head circumference approaching or exceeding the 95<sup>th</sup> percentile (while their weight and height does not).

Previous studies noted that many children with mild megaloccephaly show delayed motor development and some of them exhibited delayed speech development as well. <sup>(8)</sup> In some studies these children were treated with Diamox <sup>(4)</sup> and in other studies, they were merely observed <sup>(8)</sup>.

Because CT's at the age of 2 or 3 years appeared normal as did the neurological exams, it has been assumed that External Communicating Hydrocephalus is basically a benign condition.

One symptom of early onset hydrocephalus is delayed motor development. <sup>(8)</sup> Interestingly, EDS babies and toddlers usually exhibit delayed motor development and are often considered to be "floppy babies". This delayed motor development was presumed to be due loose ligaments and poor muscle tone <sup>(9)</sup>, however because babies who do not have Ehlers-Danlos Syndrome are also generally quite flexible, the author hypothesizes that it is the External Communicating Hydrocephalus that causes such developmental delay.

Elevated CSF pressure resulting in slowly evolving damage to the cerebellar area may also explain why Ehlers-Danlos patients typically show poor proprioception. <sup>(10)</sup>

It is the author's observation retrospectively (with a relatively small sample size) that the children studied went on to develop subtle neurological issues, such as "fits" (episodes of inconsolable crying and frustration), irritability, chronic headaches, loss of reflexes in the upper body and hyperreflexia in the lower body.

Low-level anxiety was often reported by the patient or caregiver, along with O.C.D. tendencies or the need to overachieve, even in children as young as kindergarten age.

Many of these children went on to demonstrate late-onset puberty and the anticipated delayed hormone profiles typical of puberty. It is the author's belief that the elevated pressure on the brain (hypothalamus and pituitary) is to blame for these abnormal endocrine panels. This could occur through translated pressure on the hypothalamus, directly on the pituitary, on the pituitary's blood supply, or on the neurological connection between the hypothalamus and the pituitary.

An insidious onset of autonomic dysfunction ("POTS") also occurs in many of these patients. Such dysfunction includes: orthostatic intolerance, dizziness, light-headedness, poor heat tolerance, poor digestion, tachycardia, heart palpitations, difficulty breathing, poor blood pressure regulation, tremulousness and nausea, among other symptoms.<sup>(1)</sup> Chronic headaches, migraine episodes and sleep disorders are also common and eventually these patients exhibit short-term memory loss and left ventricular diastolic dysfunction.<sup>(2)</sup>

## **The Onset Of External Communicating Hydrocephalus In The Ehlers-Danlos Patient First Exhibiting Neurological Symptoms In Adulthood:**

Ehlers-Danlos patients who first exhibit dramatic autonomic and other neurological symptoms in adulthood would not be expected to show the megaloccephaly apparent in the very young patients and indeed, in the author's sampling of patients, this is found to be the case.

Interestingly, these adults (upon detailed questioning) were able to remember symptomatic episodes earlier in their lives and most were found to have dealt with low levels of anxiety (exhibited by O.C.D. tendencies and overachievement in addition to free-floating anxiety). Many of these adults also experienced late-onset puberty, indicating these patients likely had a low level of External Communicating Hydrocephalus with either later onset, or lower CSF pressures than their early symptomatic cohorts.

MRI's of these patients also reveal large, CSF-filled subarachnoid spaces, with little or no enlargement of the ventricles. It is important to note in the vast majority of these MRI's, the subarachnoid space is enlarged above the brain, however very little, if any CSF is present just below the brain; this is most apparent under the frontal lobe. It can appear that the brains are "sinking", when in fact it is the author's contention that the turbulence and higher CSF pressure in the subarachnoid space above the brain is applying downward pressure on the brain, leading to the cascade of symptoms.

In some of these adult patients, it appears that skull anatomy plays a role. EDS adults with large heads (who have no records of their head circumferences in youth available), and a small skull base (a triangular shaped head, not totally dissimilar from that found in many patients with achondroplasia), may mean that the patients have small foramen and reduced ability to drain both CSF and venous blood. EDS patients have facial anatomical variations such as flat cheekbones, mid-face hypoplasia, narrow and high palates that may make them more prone to anatomically-caused poor CSF and/or venous blood drainage.

## **How Ehlers-Danlos Patients Develop External Communicating Hydrocephalus**

External Communicating Hydrocephalus could theoretically occur in patients with faulty connective tissue through either overproduction of CSF or poor drainage of CSF (or both). It is currently believed that the most likely escape route of CSF is through the arachnoid villi, although the possibility of drainage through the lymphatic system or accessory drainage routes through the foramen at the skull base cannot be completely ignored. Patients with Ehlers-Danlos Syndrome however, have faulty collagen (the varieties vary), making any of these routes potentially susceptible to abnormalities, and reduced CSF outflow. Thus, poor outflow may exist early in life, yet can also be exacerbated by damage to structurally unsound arachnoid villi by viral antibodies that can cross the (more permeable than normal) blood brain barrier. Unfortunately, this increase in CSF pressure can ironically cause further damage to the arachnoid villi leading to a vicious cycle for the patient.<sup>(7)</sup>

## **How External Communicating Hydrocephalus May Cause Autonomic Dysfunction**

When Ehlers-Danlos patients develop autonomic dysfunction, the symptoms usually include symptoms of Chiari 1 Malformation, a crowded brain stem, retroflexed odontoid with anterior brainstem damage and/or positional issues with their clivus angles; yet for many EDS patients there is no sign of any of these possibilities via imaging. <sup>(1)</sup>

Often, MRI's indicate an abnormally high volume of CSF in the subarachoid space above the brain in conjunction with brain atrophy or shrinkage (especially cerebral). Lumbar punctures are usually "normal" and entering pressures are usually low to normal.

It is the author's belief that in EDS patients exhibiting the signs and symptoms of anterior brainstem damage and/or Chiari type symptoms (with other neurological manifestations) it is the fluid collecting in the cisterns surrounding the brain stem and pons putting pressure on these areas that causes the constellation of symptoms. EDS patients have faulty connective tissue which is more distensible than that of normal patients and as such the dura is more prone to dural ectasias which commonly are 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, leading to symptoms that correspond to high pressure in these (and adjacent) areas of the brain.

It is likely that the CSF fluid pressure in the heads and necks of Ehlers-Danlos patients is often higher than that found in the rest of the spine (which is why entering lumbar pressures in EDS patients don't usually reflect the problem, especially early in their symptomology). The author contends that the CSF outflow is sluggish due to:

- damaged arachnoid villi and inadequate lymph and venous drainage

- CSF 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.
- The CSF may continue to drain through the lymph and venous systems along the spine, resulting in lower pressures in the lumbar region than in the subarachnoid space above the brain.
- Ehlers-Danlos patients often show scoliosis and if cervical, this would further impede the flow and drainage of CSF.
- Because EDS patients are highly flexible, it is easy for them to bend their necks and end up in sleeping positions that could very easily further impede the CSF flow when the patient is supine.

This increased CSF pressure could come on gradually, as the dura stretches with time and cervical degeneration and scoliosis accelerates, however because viruses can trigger autonomic dysfunction at any age, the author contends that the viral trigger is sufficiently powerful to cause the dangerous increase in CSF pressure in an already poorly functioning or marginally functioning drainage system.

The author contends this accumulation of CSF in the cisterns around the brain stem is also the reason for 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.

The bottom line for these patients is that External Communicating Hydrocephalus in conjunction with weak connective tissue, overly full subarachnoid spaces and turbulent CSF flow in the subarachnoid space, applies direct pressure to the brain and brain stem. This (in possible conjunction with CCSVI – cerebrospinal venous insufficiency -- which limits venous outflow and often results in bidirectional flow of blood in the veins that should be draining blood from the brain), inhibits further CSF and venous drainage from the head. This cycle continues as the pressure in the cisterns (which is also part of the subarachnoid space) builds. The

increased pressure in the cerebromedullary cistern, for example, is likely the cause of the Chiari and anterior brainstem symptoms.

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 when venous or CSF 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. Many patients utilize caffeine and vasoconstrictors (such as Sudafed) to allow some oxygenated blood to enter the brain. Many patients learn to “self treat” their symptoms by increasing their blood pressure – a trade off which involves increased oxygen for the brain. Without sufficient blood pressure and tachycardia to overcome the pressure resistance, hypoxia leads to cognitive decline and short-term memory loss and an overall increase in symptoms.

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 <sup>(2)</sup>. There is early evidence suggesting affected EDS patients go on to develop congestive heart failure.

## **How External Communicating Hydrocephalus May Cause Endocrine Abnormalities**

Mildly increased intracranial pressure (ICP) over long periods of time 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. <sup>(5) (6)</sup>

The resulting hypothalamic dysfunction can also contribute to the abnormal endocrine profile of these patients. <sup>(14)</sup>

It has been observed in some Ehlers-Danlos patients (and incidentally in Multiple Sclerosis patients) that the third ventricle is full and perhaps somewhat enlarged. When the third ventricle applies pressure outward to the nearby brain tissue, the adjacent hypothalamic structures (and the thalamus) may be affected (either through direct pressure, or anoxia induced from high pressure). Pressure on the thalamus causing thalamic atrophy has been shown to be a cause of cognitive decline in Multiple Sclerosis. <sup>(11)</sup>



## **How External Communicating Hydrocephalus May Cause Cranial Nerve Signs and Symptoms**

As this cycle of increased pressure in the subarachnoid space above the brain and the subsequent turbulence of CSF continues, the subarachnoid space expands, applying direct pressure onto the brain. Initially, the brain will shift downwards, displacing some of the CSF located directly below the frontal lobe and cerebellum. This results in poor floatation of the brain and instead, the brain applies direct pressure to many of the cranial nerves and to the brainstem, resulting in a constellation of neurological symptoms that at first blush, seem unrelated. As the pressure continues, true brain atrophy can occur and CSF surrounding the sulci becomes more evident.

It is critical for us to learn if the pressure in the subarachnoid space above the brain may be higher than the pressure in the ventricles (the opposite of the typical presentation), and higher than that indicated with a lumbar puncture (LP). Numerous Ehlers-Danlos patients have a positive symptomatic response to Diamox, yet prior to taking this medication, their lumbar puncture results were almost inevitably measured as “normal” or even “low”. If the author’s hypothesis is correct, it may be critical to avoid LP’s in these patients, as the high pressure in the subarachnoid space above the brain could theoretically induce or exacerbate a Chiari presentation and/or symptoms. Decreasing the buoyancy of the brain through LP’s could indeed make recovery from this procedure difficult or impossible, unless the pressure in the subarachnoid space is reduced.

It may also be in the patient’s best interest to lower the CSF pressure in the subarachnoid space with Diamox before contemplating Chiari surgery. If the pressure in the subarachnoid space above the brain is indeed higher than that below the brain, traditional Chiari surgery may exacerbate the patient’s symptoms. The same may be said of the traditional ventriculoperitoneal brain shunt.

## **How Patient Position Plays a Critical Role in Presentation**

**When the patient is upright**, maximal drainage of the venous blood and CSF is possible. If the patient has CCSVI and venous regurgitation of blood (especially in the internal jugular veins), gravity assists in drainage of venous blood and bidirectionality of flow is at its minimum in this position. However, gravity works against the perfusion of arterial blood into the brain. This is especially significant if the arterial perfusion is working against venous or CSF congestion and if the patient has postural orthostatic tachycardia syndrome (POTS), meaning blood tends to pool in the lower extremities. The patient becomes symptomatic due to poor arterial perfusion, and as the pressure on the top of the brain pushes the brain down, the cranial nerve symptoms increase.

**When the patient becomes supine**, arterial blood more easily enters the brain as it is no longer working against gravity, nor is it pooling in the lower extremities. However, the CSF and venous blood once again do not drain well and the ICP increases. When the patient is initially supine, the brain lifts off of the cranial nerves. However, over time the ICP (in the subarachnoid space above the brain) continues to increase because the CSF and venous blood once again does not drain well in the supine position resulting in an increase of symptoms of brain and brain stem compression. The patient again becomes symptomatic and if asleep, is often awakened by a burst of tachycardia accompanied by a feeling of suffocation.

It is the author's presumption that constant movement of the brain up and down, combined with the continual change in pressure on the delicate brain tissue results in cerebral edema causing additional symptoms. It is for these reasons that we hear from these patients that they must lie down, but not for long; they must be vertical, but not for long; and they don't feel completely well in any position. Fortunately, Diamox reduces cerebral edema in addition to reducing CSF production and ICP.

**Why CCSVI may be part of the picture** – drainage of CSF and venous blood must be accomplished within all areas of the skull and spine to maintain normal CSF levels and proper cerebral perfusion pressure. This includes the exit of CSF

through the arachnoid villi (and lymphatic system as applicable) as well as the exit of blood and CSF through the venous structure after exiting the brain.

It is the author's contention that if MRI results indicate an abundance of CSF in the subarachnoid space (or any enlargement of the third ventricle is noted) then symptomatic patients who qualify should undergo a trial of Diamox to see if reduced CSF production, the mild diuretic effects of Diamox and the reduction of any existing brain ischemia causes an improvement in symptoms. It is the author's experience with about a dozen Ehlers-Danlos patients and their physicians that initiating a trial with Diamox results in the obvious reduction of symptoms overnight.

If the patient either doesn't respond to Diamox or achieves a partial reduction of symptoms, then an fMRI should be encouraged to look for CCSVI (chronic cerebrospinal venous insufficiency) and angioplasty should be considered if the fMRI indicates venous blockage or bidirectionality of venous blood flow.

It is the author's recommendation that patients who had no positive results, or fleetingly positive results from CCSVI also undergo a trial with Diamox. Because most of these patients can relate the onset of their symptoms with a "trigger" (viral infection being a common cause), it is the author's suspicion that poor drainage of CSF may be a larger contributing factor to the symptomology of these patients than stenosed internal jugular and azygous veins. Ideally both venous drainage and cerebrospinal flow should be maximized.

The majority of patients in this "family" of disorders complain of the same disabling fatigue, weakness, cognition problems, aphasia, gastro-intestinal difficulties and numerous cranial nerve symptoms. Depression and a bipolar presentation are not uncommon and can often be linked to the "trigger" that began the cascade of symptoms.

It is the author's hypothesis that External Communicating Hydrocephalus applies pressure to many brain structures, including the hypothalamus, thalamus (generally affecting all cranial nerve functions excepting CN1 – olfactory), frontal cortex and cerebellum. This pressure translates to the brainstem area. If the patient's CSF pressure is highest in the supine position and causes the

hypothalamus and thalamus to shut down the cortisol and ACTH production at night time, it would explain the disabling morning fatigue found in most of these patients. The thalamus controls wakefulness, sleep regulation, arousal and all senses, excepting the olfactory sense. The thalamus also involves some motor functions which can lead to tremor when damaged. To learn if this is indeed part of the problem, patients could have their cortisol and ACTH levels checked in the hospital overnight (without waking the patient or asking them to sit up). Once the patient is vertical, CSF and venous drainage increases. By the time the patient gets dressed and arrives at the lab or doctor's office, the cortisol production may already have increased to the acceptable range.

## **The Role of Inflammation, Mast Cell Disease and Blood Vessel Permeability**

Most symptomatic patients blame a “trigger” as a cause of their increase or onset of symptoms. Many times this trigger is presumed to be a viral infection.

Because signs and symptoms after the triggering event result in increased inflammation, this trigger may begin the cascade of problems via the release of inflammatory components. Mast cells contain cytokines, histamine, chemokines, prostaglandins, heparin, neutral proteases and acid hydrolases, whose release is a likely trigger for increased inflammation.

Mastocytosis, a commonly found condition in this patient population, can also cause disabling fatigue, labile emotions, brain fog and/or dementia, suicide ideation and numerous other bodily changes as explained below (depending upon the site(s) of mast cell infection).<sup>(15)</sup>

We see in Ehlers-Danlos and Multiple Sclerosis patients that their vessels are “leakier” and weaker – more prone to varicosities and collapse. We also see the development of telangiectasia and collateral vessels (which likely develop in an attempt to circumvent the inadequate veins). We also see the “leaky gut” and rather sudden onset of gluten intolerance, persistent diarrhea, and GI issues that result in the patients being tested for celiac disease (with negative results). Many Ehlers-Danlos patients exhibiting POTS (especially if hyperadrenergic) have systemic and/or cutaneous mastocytosis. It is presumed that the mastocytosis is secondary to the primary condition of EDS.<sup>(12)</sup> EDS or MS patients who continue to experience brain fog and extreme fatigue (especially with cutaneous signs of mastocytosis) may do well with H1 and H2 blockers and may need the addition of Cromolyn Sodium and/or Proton Pump Inhibitors. This is indeed resulting in positive results for most POTS patients with EDS.

Interestingly, the author has also located a patient with cutis laxa who also has idiopathic anaphylaxis. It is the author’s contention that the two conditions are related, likely through the same mechanism that EDS/POTS is related to mastocytosis.

It is the author's belief that the inflammatory component triggering these symptoms includes the chemicals released by mast cells: cytokines, histamine, chemokines, prostaglandins, heparin, neutral proteases and acid hydrolases.<sup>(13)</sup> It is critical to treat these conditions in this patient population as early as possible. Many of these patients, treated or not, continue to experience increased disability.

Reducing CSF pressure must be instituted as soon as possible, as evidence suggests that early treatment may allow damaged arachnoid villi to repair themselves.

If CSF pressure is not to blame for the patient's symptoms and CCSVI is found, angioplasty should be considered. Mastocytosis must be controlled prior to the procedure, however, as angioplasty may trigger a mast cell reaction in these patients. (It is the author's recommendation that all patients should be screened for EDS via the Beighton scale prior to angioplasty. Certainly, patients with the vascular form of EDS should not undergo venous angioplasty).

It is the author's belief that early treatment of hydrocephalus, CCSVI and Mastocytosis may avoid the cascade of symptoms that plague Ehlers-Danlos Syndrome Patients suffering from POTS.

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