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Research Article

The Complex Path to Intracranial Hypertension and CSF Leak in those with Hypermobility and Dysautonomia; The Theory of Spiky-Leaky Syndrome

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Abstract

We describe a clinical phenotype we have characterized and have been presenting over the past half-decade whereby the combination of a genetically vulnerable host and a chronic inflammatory state such as might occur from a chronic environmental toxic exposure leads to activation of mast cells and development of at least a localized hypermobility state including instability of anatomy in the craniofacio-cervical region. A cascade of events occurs from both the mast cell activation and unstable craniofacio-cervical structures that causes dysautonomia and hypopnea. These two phenomena lead to a large differential in daytime and nighttime blood carbon dioxide levels that cause an exaggerated increase in nighttime cerebral blood flow requiring rapid displacement of cerebrospinal fluid (CSF). The same unstable anatomy also prevents normal CSF and lymphatic drainage thereby causing an increase in intracranial pressure (the Spiky Phase). CSF pressure then pops-off through cranial nerve sheaths most notably through the olfactory nerve into sinus mucosa and into facial sinuses whereby it leaks out through the nose and ears, into facial tissue, or down the throat (the Leaky Phase). We call this Spiky-Leaky Syndrome and it may explain the vast collection of signs and symptoms co-segregating in these patients and also such other phenomena as cervical medullary syndrome, pseudotumor cerebri, idiopathic intracranial hypertension without papilledema, and occult tethered cord. Detailed data and theory are given as to why this has been difficult to detect to date as well as potential environmental toxins that may be responsible. Potential evaluations and therapies are posited

Keywords*: cerebrospinal fluid leak, mast cell activation syndrome, hypermobile Ehlers Danlos Syndrome, craniocervical instability, upper airway resistance syndrome, idiopathic intracranial hypertension without papilledema.*

Significance Statement: *We hypothesize that Spiky-Leaky Syndrome is an important but yet to be recognized or fully described phenomenon that might explain a variety of poorly understood neurological phenomena involving increased intracranial pressure and cerebral spinal fluid leaks and might be the end result of an environmental exposure.*

Abbreviations:

ADI: atlas-dens interval

ANS: Autonomic Nervous System

ASGP-R 1 and 2: asialo-glycoprotein receptors 1 and 2

AXA: atlas-axis angle

B2T: Beta-2-transferrin (asialo-transferrin)

BAI – basion-axial interval

BBB: blood-brain barrier

BDI: basion-dens interval

C0/C1/C2: atlantooccipital and atlantoaxial or first and second cervical joints

CAA: clivo-atlas angle

CANS: Childhood acute neuropsychiatric syndromes

CBAI: Chronic biotoxin-associated illness

CBCT: Cone-beam computerized tomography

CBF: cerebral blood flow

CCI: craniocervical instability

CCJ: craniocervical junction

CSF: cerebral spinal fluid

CN: cranial nerve

CN IX: Glossopharyngeal nerve

CN X: Vagus nerve

CN XI: Accessory nerve

CNS: central nervous system

CXA: clivo-axial angle

DAI: dens-axial interval

DMX: Digital-motion X-ray or videofluoroscopy

ETCO2: End-tidal carbon dioxide concentration

HBGAB: Harmful blue-green algae bloom

hEDS: Hypermobile Ehlers Danlos Syndrome

ICP: intracranial pressure

IH/IIH: intracranial hypertension, idiopathic intracranial hypertension

IIHWOP: Idiopathic intracranial hypertension without papilledema

IJV: internal jugular vein

IL2, IL3, IL4, IL5 IL6: interleukins, 2, 3, 4, 5, and 6

JVP: jugular venous pressure

LP: lumbar puncture

MCAS: mast cell activation syndrome

MCMRS: Mast Cell Mediatory Release Syndrome

ME/CSF: myalgic encephalomyelitis/chronic fatigue syndrome

NML: nasal mucosa lymphatics

OCD: obsessive-compulsive disorder

OMT: orofacial myofunctional therapy

ONSC: olfactory nerve sheath cuff

ONSCJ: olfactory nerve sheath cuff junction

OSA: obstructive sleep apnea

pCO2/pO2: partial pressure of carbon dioxide or oxygen

paCO2/paO2: partial pressure of carbon dioxide or oxygen in arterial blood

PANS: Pediatric acute neuropsychiatric syndrome

PET: patulous Eustachian tube

POTS: postural orthostatic tachycardia syndrome

QEESI: Quick Environmental Exposure and Sensitivity Inventory

SLS: Spiky-Leaky Syndrome

SIBO: small intestinal bacterial overgrowth

Tf/ asialo-Tf/ sialo-TF: transferrin, asialo-transferrin, sialo-transferrin

TILT: toxicant-induced loss of tolerance

TM: tympanic membrane

TMJ; temporomandibular joint

TNFα: Tumor Necrosis Factor alpha

TTTS: tonic tensor tympani syndrome

UARS: upper airway resistance syndrome

Terms Introduced in this Manuscript:

Carpal Tunnel Syndrome of the Neck

Eagle Space

Metabolic localized hypermobility/ hypermobile Ehlers Danlos syndrome

Occult CCI

Olfactory Nerve Sheath Cuff Junction

Pathologic cervical hypermobility

Pentad Super-syndrome

Pseudo-Eagle Syndrome

Pseudo-tethered cord

Spiky-Leaky Syndrome

The Zipper Model of Olfactory Nerve Sheath Cuff Junction

Wardly Phenomenon

Introduction

Over the past decade caring for pediatric and young adult patients with cardiac manifestations of a dysfunctional autonomic nervous system, otherwise known as dysautonomia, it became clear that most of these patients also had an underlying chronic inflammation and very often also had elements of connective tissue hypermobility. They often also had significant gastrointestinal dysmotility with abdominal pain and seem to also have a higher incidence of expressing autoimmunity. From that frequent association of those 5 entities arose the term "The Pentad Super-syndrome" (1) and these patients were being referred from the corresponding author's practice area daily. The symptoms of dysautonomia most commonly manifest as orthostatic intolerance with or without postural orthostatic tachycardia (POTS) and with or without myalgic encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) (2-4). Nearly all of these patients scored significantly high on the Afrin/Molderings/Weinstock Mast Cell Mediatory Release Syndrome (MCMRS) Inventory (5, 6), as well as the Quick Environmental Exposure and Sensitivity Inventory (QEESI) (7, 8), and met the clinical diagnosis of the condition known as mast cell activation syndrome (MCAS) while many had serum and urine markers consistent with this (9). About a third of these patients demonstrated joint hypermobility and other signs consistent with hypermobility syndrome or hypermobile Ehlers Danlos (hEDS) although few met the 2017 diagnostic criteria for hEDS which is consistent with the demographics of other large young dysautonomia populations (4, 10-12). This co-segregation of these particular entities is not unique to this author's practice and has been observed and described by many others outside of the literature and now recently in literature (13-15).

Further work with these patients revealed that a majority of these patients that demonstrated MCAS and hypermobility also displayed symptoms and findings consistent with cranial settling, cervical medullary syndrome, and craniocervical instability (CCI) (16-19). Often times the hypermobility was quite subtle with normal Beighton scores (20) and little other findings of hEDS but yet had complaints of temporomandibular joint (TMJ) dysfunction, physical exam findings consistent with cranial settling, and symptoms consistent with CCI and sometimes but not often with abnormal traditional craniocervical MRI measurements (18). For these patients, it is as if they have a localized hypermobility or hEDS within their craniocervical region at least early in the progression of their illness.

Of the subset of these Pentad patients with evidence of CCI, there is yet a smaller subset that also complains of headaches that are sometimes consistent with increased intracranial pressure and other times consistent with a CSF leak. They curiously describe that on the days they have a CSF leak-type headache they leak fluid

from their nose and ears and taste a salty metallic taste in the back of their throat. These are our Spiky-Leaky Syndrome (SLS) patients. From an unpublished review of a cohort of the patients from this population, 206 were found to have dysautonomia significant enough to interfere with daily function (Functional Grade III dysautonomia (1)), about 1/3rd have hypermobility (~70) and, of these, 30 were found to have at least major elements of SLS (Figure 1). From these data it might be considered that 1/3 of those with hEDS and 1 out of 7 patients with at least Grade III dysautonomia might be progressing towards SLS. The remainder might be at risk of developing SLS.

While SLS could be an unrecognized global phenomenon, alternatively, this may be a phenomenon unique to this author's geography where an 'epidemic' form of the Pentad is arising secondary to unique environmental exposure. It may very well be that SLS is uniquely a pathology of this particular environmental exposure. Our current suspicion is that those with genetic variants, the "canaries in the coal mine", that are exposed to mold, cyanobacteria, and their respective biotoxins, and perhaps any other toxins or stealth infections that chronically activate mast cells are at risk.

What became apparent with these patients is that geographic relationships between them seemed as significant as familial relationships. While many patients had a parent or one or more sibling with a "Pentad presentation", it was just as often that the corresponding author was seeing patients who are neighbors or classmates with each other. This prompted us to map the homes of where they first became ill and this revealed a strong geographical relationship. Many of these patients live in towns that bordered farmlands and the San Joaquin Delta and its canals. Indeed, many of the corresponding author's patients turn out to live in neighborhoods with several other patients. Within a half kilometer radius of one patient lives 10 other patients with The Pentad. Others have homes nearly adjacent to each other. This led to the realization that there was an environmental trigger behind much of this illness with mold, mold toxins, cyanotoxins from harmful blue-green algae blooms (HBGABs), products of coccidioides, industrial toxins such as herbicides and farm run-off, and products and consequences of the recent epidemic of California wildfires as candidate culprits making this perhaps a type of chronic biotoxin-associated illness (CBAI) (21). Exposure to stealth microorganisms and electric and magnetic fields (EMFs) has also been considered and not ruled out nor has the role of poor posture from excessive forward head tilt such as from excessive cell phone viewing. Exactly which of these or if there are multiple responsible is still under investigation. We are particularly compelled to consider cyanobacteria and their cyanotoxins from worsening HBGABs as a cause for many, but not all, of these patients and this is the subject of a separate theoretical paper.

In any case, the Pentad presentation and SLS are appearing to be common in the corresponding author's practice and in this geography. Since this original revelation of the SLS phenotype and theory and our first presentations at international conferences focusing on Ehlers Danlos syndrome, sleep disorders, airway physiology, and CSF Leak beginning in 2019, (1, 22-32), other geographic hotspots outside Northern California have been identified by these authors and other providers learning of this theory. These patients merit understanding and a solution to these yet undescribed phenomena.

Signs and Symptoms of Spiky-Leaky Syndrome

We have noted that the SLS population has some unique features that set them apart from other patients with dysautonomia syndromes. Their characteristics are enumerated in Table 1. The full Spiky-Leaky Syndrome phenomenon is laid out as a schematic sequence of events in a schematic as per Figure 2 which helps to place how such signs and symptoms fit into the full syndrome. The essential elements of the theory are laid out in a simpler schematic "The Roadmap to Spiky-Leaky Syndrome" for ease of understanding of theory (Figure 3). This is presented more visually as a summary in Figure 27.

Table 1: Signs and Symptoms of Spiky-Leaky Syndrome

1) Generally at the more ill end of spectrum with a Compass 31 score (271) and DQ score above 45 (DQ scoring is an unpublished scoring system of dysautonomia severitysimilar to Compass 31).
2) Usually with most components of "The Pentad"(1) but particularly a) Hypermobility and often meeting most criteria for hEDS commonly including instabilityof the temporomandibular joint and clinical evidence of cranial settling, CCI, vertebrobasilar insufficiency, any myofascial pain syndrome (253). b) Dysautonomia often with exaggerated swings in blood pressure both high & low c) Often with signs of chronic inflammation and criteria for MCAS and usually with high concentrations of CD117 positive mast cells on duodenal biopsy often leading to disruption of the upper gastrointestinal epithelium leading to signs of "leaky gut" (272, 273) and neuro-inflammation, perhaps with "leaky blood-brain-barrier", with neuropsychiatric symptoms of anxiety, obsessive-compulsive disorder, tics, and occasionally psychoses and autism (274-277). d. Often with evidence or suspicion of environmental exposure such as mold toxin exposure.
3) Extremely recalcitrant to therapies directed at these entities.

4) Often times there are others in the household that are ill in a similar manner with mother-daughter, sister-sister, sister-brother, brother-brother, identical twin, fraternal twin pairs common. Often times, younger household members present with CANS-likeor PANS-like syndromes (childhood acute neuropsychiatric syndromes and pediatric acute neuropsychiatric syndrome, respectively) and related disorders which are believed to have loss of blood brain barrier integrity and neuroinflammation as part of the pathophysiology (276, 278-284). These younger siblings may present with high anxiety, obsessive compulsive disorder, tics, and even autism while older siblings present with dysautonomia.
5) Have signs and symptoms that are consistent with BOTH intracranial hypertension (IH) AND CSF Leak a. Idiopathic Intracranial Hypertension (IIH) Symptoms: • Sometimes severe headaches upon waking in the morning, • pulsatile tinnitus • fullness and pressure in head b. CSF Leak Symptoms • Sometimes headache worse upon sitting up first thing in the morning • Sometimes worsens through the day
6) Have restless sleep with increased fight or flight response particularly when trying to lay flat. They may have signs of; • Upper Airway Resistance Syndrome (UARS) and occasionally frank obstructive sleep apnea (OSA) (124) • Bruxism • Short lingual frenulum and other causes of functional ankyloglossia (restricted tongue movement) (232, 240) • Preference to sleep elevated >10 degrees
7) Have a non-migraine headache that is often referred to as a feeling like a “bobble-head” or that the head “feels like a bowling ball”.
8) Pain in the throat of two kinds; • Aching pain in the back of the throat or base of tongue with a feeling of a mass (globus) • Sharp stabbing pains in the front of the throat made worse with head turns i.e. Eagle Syndrome-type pain
9) Fullness, tightness near cervical nodes (in Eagle Space) and frequent cervical lymphadenopathy
10) Pain and extreme hypersensitivity on the scalp consistent with occipital neuralgia
11) Extreme muscle tightness with spasms in the trapezius (beyond typical coathanger pain)
12) Ear/Hearing Issues; a. Pain in ear canals or middle ear b. Hyperacusis and/or phonophobia and/or autophony c. Tinnitus and/or vertigo
13) Showing signs of vertebrobasilar insufficiency from “cranial settling” causing vertebral artery compression at the craniocervical junction (CCJ); • Symptoms of brain fog, headache, fatigue, decreased vision relieved in the sitting position by upward cranial traction • History of sudden ‘drop attacks’ whereby the legs buckle with sudden core weakness while remaining fully conscious • History of narcolepsy and or cataplexy

14) Showing sometimes intermittent signs specific to lower brainstem injury or herniation oflow-lying cerebellar tonsils not distinguishable from those of Chiari Malformation;
   a) Pressure headache aggravated by Valsalva maneuvers
   b) Numbness, weakness, and tingling in arms and legs
   c) Loss of hand grip strength
   d) Swallowing difficulties
   e) Difficulty swallowing with gagging, choking, or swallowing
   f) Difficulty speaking or with hoarseness
   g) Problems with hand fine motor skills
   h) Quick downward eye movements (downbeat nystagmus) or gaze-evoked nystagmus, or nystagmus of skew (82-84)

15) Showing symptoms and signs sacral nerve dysfunction (signs of occult tethered cord)
   a) Irritable bladder and bowel, constipation
   b) Incontinence, difficulties initiating urination, incomplete voiding
   c) Ataxia

[The symptoms included in the points from 6 through 15 are consistent with cervical-medullary syndrome] *(16-18)*

16) Sleep study may be reported as normal but upon further review;
   a) Signs of Upper Airway Resistance Syndrome (UARS) (124)
   b) $TcCO_2$ is at least mildly elevated during a portion of sleep
   c) TcO_2 is sometimes depressed in 92% range

17) Funduscopic exams that reveal no papilledema

18) Head and Spine MRIs that reveal no CSF Leak and no evidence of Chiari
Re-read of MRI by hEDS Neurosurgeon may reveal signs of CCI (most commonly with measures of ADI, BAI, BDI, and DAI), CSF hypertension or hypotension
Upright Head MRI might identify Chiari or low-lying cerebellar tonsils

19) Cervical Spine CTs may be reported as normal but CT Angiograms with 3D reconstruction may reveal minor external compressions of internal jugular vein.

20) Urodynamic studies show evidence of intermittent neurogenic bladder

21) Daytime end-tidal CO_2 or transcutaneous CO_2 measurements showing CO_2 levels in low 30s (mmHg) indicative of chronic hyperventilation and sensation of borderline panic attack.

22) Patients often have a history of frequent diagnosis of chronic sinusitis, and abnormal turbinate anatomy. Those who have undergone septoplasty and turbinate reduction surgeries often worsen in these symptoms after surgery.

23) Patients who have undergone retractive orthodontic procedures often worsen with these symptoms afterward.

24) Assessment of fluid draining from nose is consistently negative for beta-2 transferrin.

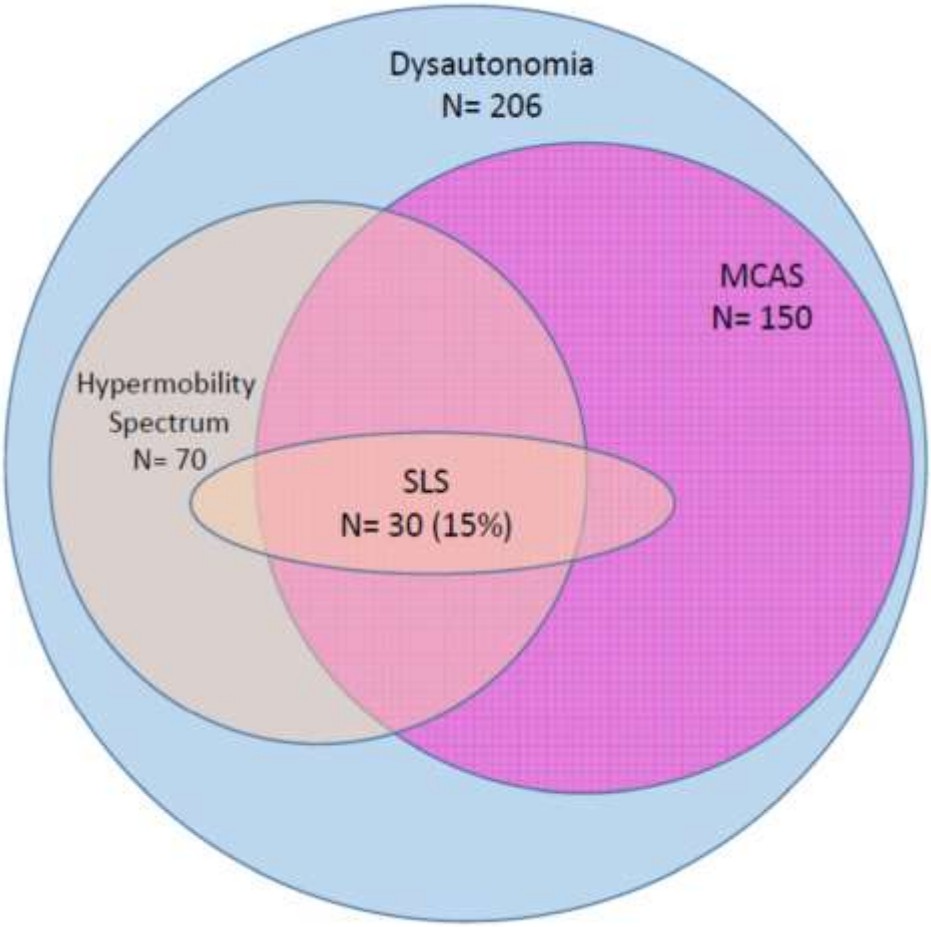


Figure 1: Overview Schematic of Spiky-Leaky Syndrome

Venn diagram of a population of 206 patients with autonomic dysfunction in corresponding author's practice. Of the 206 patients, 150 meet Consensus 2 criteria for MCAS (9), 70 showed evidence of hypermobility with at least one additional feature toward 2017 criteria for hypermobile Ehlers Danlos (10). Thirty (15%) had evidence of CCI and signs and symptoms consistent with IIH and/or CSF leak.

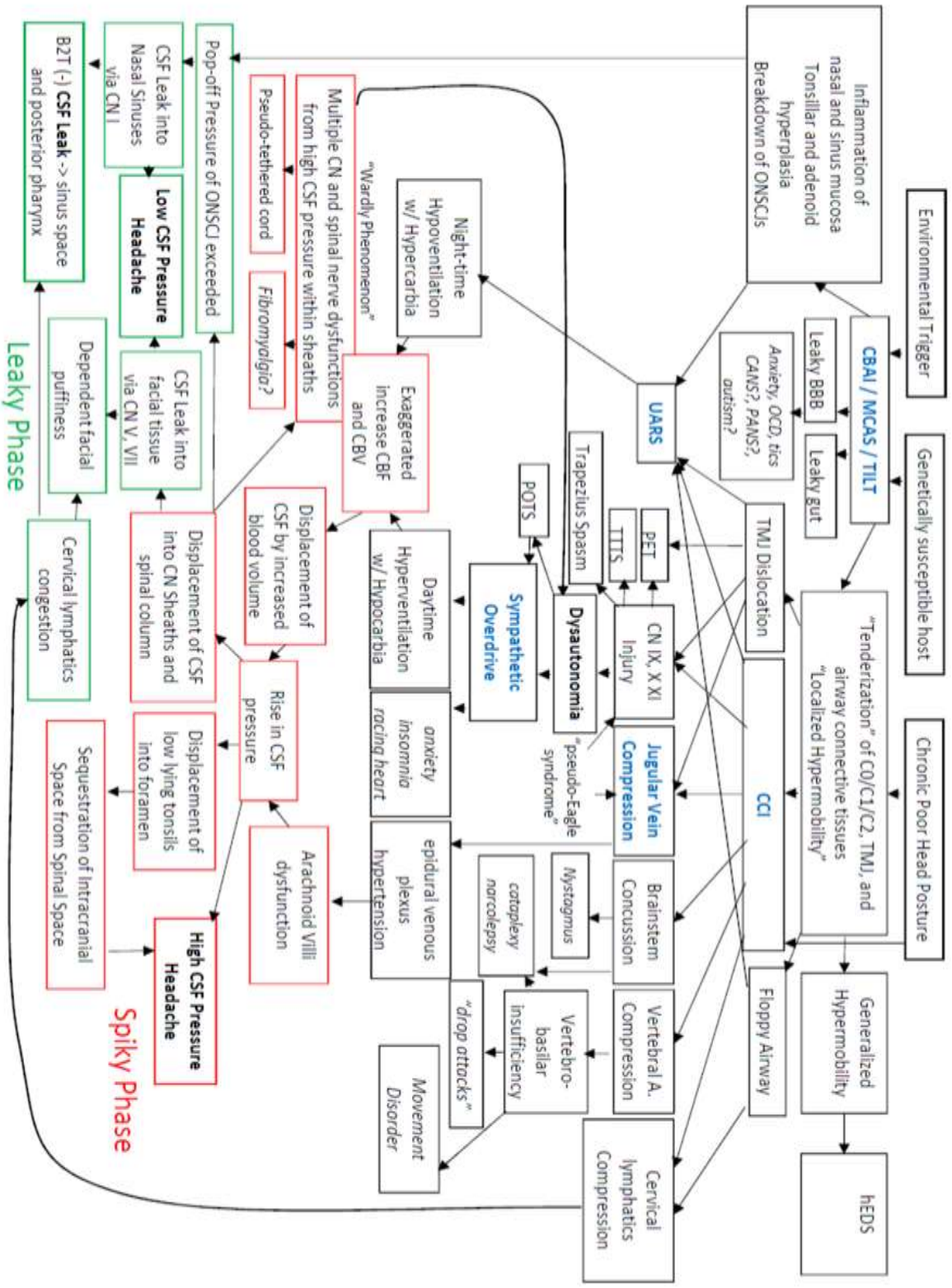


Figure 2: Overview Schematic of Spiky-Leaky Syndrome

This schematic shows the overall sequence of events that go together to create the full phenomenon. The blue text signifies key components that appear necessary to be present. For most patients it likely begins with a single or perhaps multiple triggers in a genetically vulnerable host that causes a chronic biotoxin-associated inflammation or illness (CBAI), which is most likely mast cell-mediated (MCAS), and mostly localized to the upper respiratory tissues. This may induce a phenomenon known as Toxicant-induced Loss of Tolerance (TILT)(265, 266) which further amplifies MCAS. In addition to likely causing loss of integrity of the BBB (274-277, 283) as well as the GI barrier with leaky gut (272, 273), mast cell activation likely "tenderizes" craniocervical connective tissue causing craniocervical instability (CCI). Chronic forward head posture for various reasons likely contributes. The leaky BBB may cause a host of neuropsychiatric conditions including anxiety, tics, OCD, and perhaps CANS (278), PANS syndrome (279, 284, 285), and autism (276, 281, 282, 286). Tenderization of the craniocervical connective tissues lead to 3 major phenomenon; upper airway resistance syndrome (UARS), sympathetic overdrive, and jugular venous compression. The sympathetic overdrive is a natural reflex to parasympathetic dysautonomia resulting from Vagus nerve injury, another consequence of CCI, and results in chronic hyperventilation driving down blood carbon dioxide as well as creating the symptoms of anxiety, insomnia and racing heart. The UARS, in contrast, causes a retention of carbon dioxide during sleep. The marked difference in daytime to nighttime blood carbon dioxide level causes a dramatic increase in nighttime cerebral blood flow (CBF) and thus blood volume. Displaced cerebral spinal fluid (CSF) cannot filter by normal means due to jugular and epidural venous backpressure on the arachnoid villi. Instead, CSF pressure rises and CSF displaces into cranial nerve (CN) sheaths (The Spiky Phase). Some patients also have herniation of low-lying cerebellar tonsils obstructing CSF displacement into the spinal column thus raising cerebral pressure further. CSF pressure rises causing intracranial hypertension (IH) until it pops off at the end of CN sheath cuffs most notably at the end of the olfactory nerve (The Leaky Phase). These concepts are discussed and referenced fully in the body of the paper.

BBB = blood-brain barrier, CBAI = chronic biotoxin-associated illness, C1/C2 = first and second cervical joints with occiput, CN IX, X, XI = glossopharyngeal, Vagus, spinal accessory cranial nerves, hEDS = hypermobile Ehlers Danlos syndrome. PET = patulous Eustachian tube, TMJ = temporomandibular joint, TTTS = tonic tensor tympani syndrome, OCD = obsessive compulsive disorder, CANS = childhood acute neuropsychiatric syndromes, PANS = pediatric acute neuropsychiatric syndrome, POTS = postural orthostatic tachycardia syndrome.

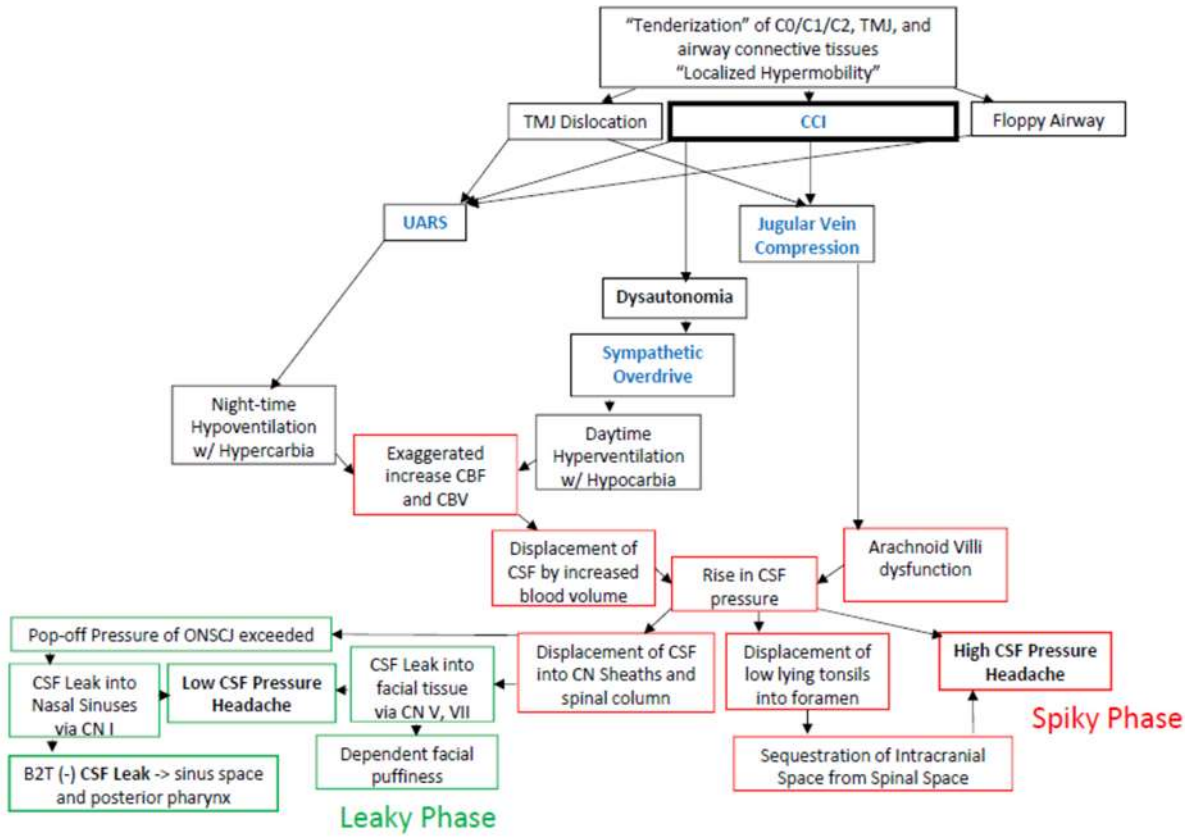


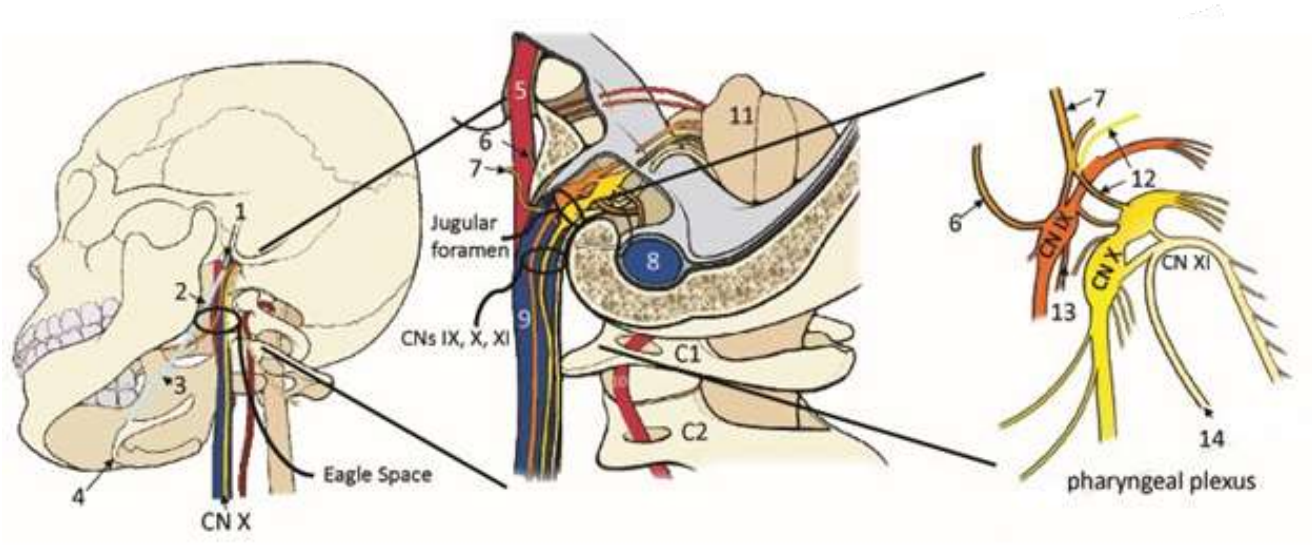
Figure 3: Simplified Schematic; The Roadmap to Spiky-Leaky Syndrome

The schematic of Figure 2 is pared down to the elements likely necessary for development of SLS. This ignores many of the important phenomena that explain many of the signs, symptoms, and syndromes within SLS but are not within the direct path to the spiking of intracranial pressure and leaking of CSF.

Anatomy of the Craniocervical Region Relevant to SLS

The division between the larger population that presents with combinations of dysautonomia, MCAS, and hypermobility, and the subpopulation of those well on their way to SLS appears to be with the onset of CCI. We have observed that the patients who have the potential for developing SLS, have a close temporal relationship of the onset of dysautonomia with a set of related cranial nerve dysfunctions, specifically those of the glossopharyngeal, vagus and accessory nerves (CNS IX, X, and XI). A very detailed discussion of the anatomy in this region is in order because we believe that many of signs and symptoms observed in our patients arise from injury in this region and, to our knowledge, it does not appear that a description of these specific injuries with resultant signs and symptoms has been described before in this context. An

understanding of the anatomy of this region also provides an explanation for many other signs and symptoms of SLS enumerated in Table 1.



a) ***b)*** ***c)***

Figure 4: Anatomy of the Eagle Space, Craniocervical Junction, and Pharyngeal Plexus

a) The nerve bundles of CN IX, X, and XI passing through the jugular foramen into the sub-cranial space (287) that begins the "Eagle Space". The Eagle Space is a name we devised to describe a critical area of the neck bordered posteriorly and medially by the spinal column, anteriorly by the posterior edge of the jaw [2], and laterally by the styloid process [1] and stylohyoid ligament [3] which attaches to the hyoid bone [4]. A true elongation of the styloid process causing sharp pains in the throat on head rotation is known as Eagle Syndrome (40, 41). This critical area is made smaller by hEDS-characteristics of TMJ subluxation, atlas slippage, and abnormal head positioning such that the same signs and symptoms are created with a normal styloid process length. We now term this collection of symptoms pseudo-Eagle syndrome given that the styloid process is not abnormally long in these patients.

b) The Craniocervical junction contains several important neurovascular structures. The nerves are described below. In addition the internal jugular vein [9] drains the sigmoid sinus [8] which, in turn, drains the sinuses responsible for draining CSF. The internal carotid [5] and vertebral arteries [10] supply cerebral blood flow. Cranial settling compresses the vertebral artery reducing cerebral blood flow. Cranial traction can relieve this along with symptoms of poor cerebral blood flow. Atlas (C1), Axis (C2), Medulla [11] (34).

c) *The pharyngeal nerve plexus of CNs IX & X. CN IX (glossopharyngeal nerve gives rise to the tympanic branch or Jacobson's nerve [6] responsible for sensory and parasympathetic innervating the inner and middle ear (287). CN IX is a sensory nerve for the muscles of the throat. Injury of CN IX can give symptoms of sharp pain in the throat indistinguishable from Eagle syndrome (40, 41). An afferent nerve to CN IX from the carotid sinus baroreceptor monitors blood pressure [13]. CN X (Vagus nerve) passes through this space where it gives rise to the auricular nerve [7]. Compression or injury of CN X leads to dysautonomia. A mix of nerves from CNs IX and X come together to form the pharyngeal plexus and branches of this send efferents [12] to the Eustachian tube and levator veli palentine muscle and [14] to the trapezius and sternocleidomastoid muscles. Injury of this plexus as it exits the jugular foramen explains the many middle and inner ear problems experienced by these patients. The CN XI is a motor nerve innervating the trapezius and sternocleidomastoid muscles. Its compression or injury at this level leads to tetany of these muscles (288).*

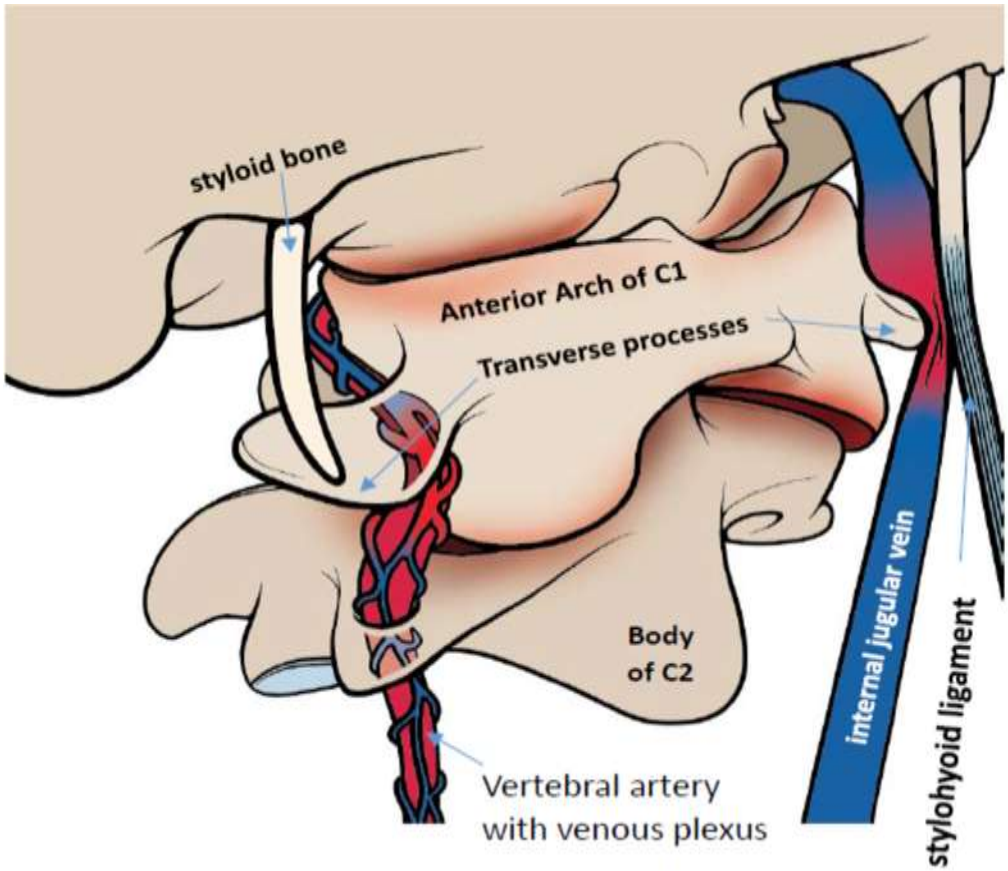


Figure 5 Craniocervical Instability with Vascular Compressions:

Anterolateral view of the C0-C1-C2 joints showing anterior slippage of C1 (atlas) relative to C2 (axis) causing the transverse process(es) of C1 to compress the internal jugular vein (uni- or bilaterally) into the styloid bone or stylohyoid ligament thereby obstructing venous return causing back-pressure on CSF drainage. Vertebral venous plexus drainage is also likely compromised. The vertebral arteries and venous plexus are also stretched and compressed (uni- or bilaterally) leading to vertebrobasilar insufficiency. The anterior slippage is thought to occur from various weakened ligaments responsible for stabilization in this region. This has been called 'jugular vein bone nutcracker' or Eagle Jugular Syndrome or Styloidogenic Jugular Venous Compression Syndrome (35, 92, 104, 105) (106).

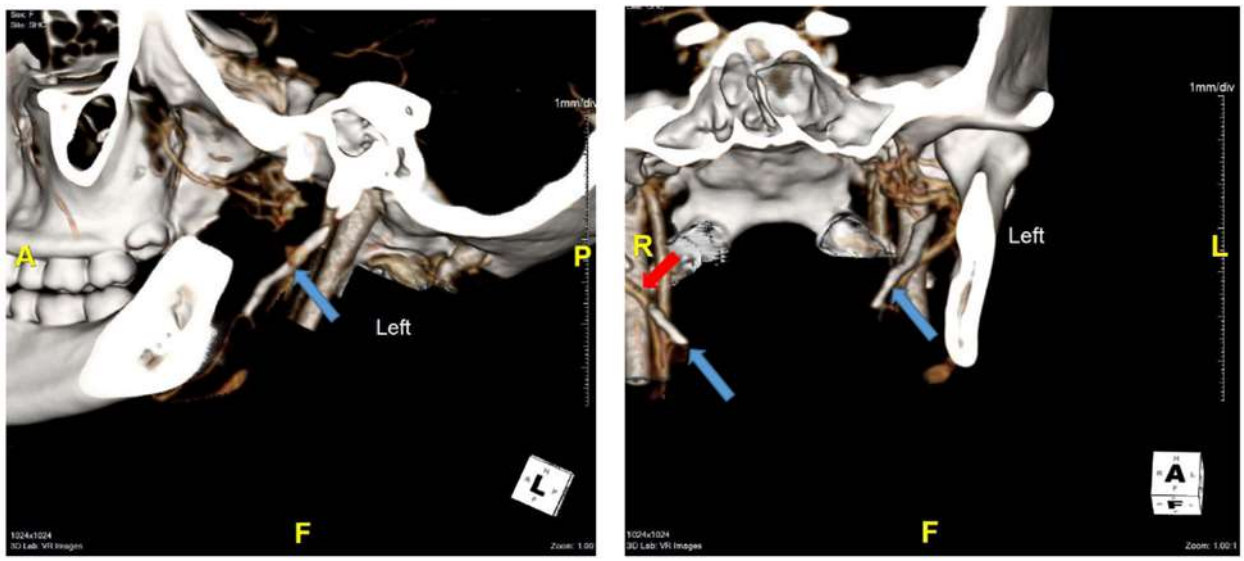


Figure 6 CT Angiogram with 3D Reconstruction of Eagle Space:

This reconstruction reveals calcification of the right and left stylohyoid ligaments (blue arrows) which might be confused with an elongated styloid bone (as was done on the radiology report of this patient). However, upon closer inspection of the right ligament, normal ligamentous tissue (red arrow) can be seen to be interposed between the styloid bone and calcified ligament.

Eagle Syndrome, Pseudo-Eagle Syndrome and the Eagle Space

CNs IX, X, and XI exit together through the jugular foramen not far from the atlantooccipital joint (C0-C1) as shown in Figure 4b (33, 34). The jugular foramen also provides exit for the inferior petrosal dural venous sinus and the sigmoid dural venous sinus which drain cerebral blood flow and filtered cerebrospinal fluid (CSF) into the internal jugular vein. The 3 nerves together traverse away from the jugular foramen following

the course of the internal jugular vein and common carotid artery for a short distance. It is along this route that these nerves commingle and share nerve fibers to create the pharyngeal plexus (Figure 4c). This is a delicate region as all these structures (internal jugular vein, pharyngeal plexus, as well as the lymphatics that drain the sinus tissues and face) fit in a small space bordered by the structures of the airway medially, the spinal column postero-medially, the transverse processes of cervical bones posteriorly, the posterior border of the mandible and the hyoid bone anteriorly, and the styloid process and styloid ligament antero-laterally (Figure 4a). Therefore, if the mandible is dislocated backward and/or the cervical vertebrae are displaced anteriorly (Figure 5), then all of these structures can be compressed, injured, and create symptoms indistinguishable from the condition known as Eagle syndrome (35).

True Eagle syndrome or stylohyoid syndrome is an impingement of the glossopharyngeal nerve by an abnormally long styloid process which causes sudden intense sharp nerve-like pain in the jaw and the back of the throat and base of the tongue which can be triggered by swallowing, moving the jaw or turning the neck (36) (34, 37) (38). However, in the case of our SLS patients, the styloid process might be quite normal in length. Rather, the compromise is hypothesized to be with either the posterior displacement of the mandible and perhaps hyoid bone and/or anterior displacement of the atlas as discussed later (39-41). Therefore, we consider this pseudo-Eagle syndrome and we have coined the term Eagle Space for want of any other term not found in literature. We posit that the soft tissue compromise and injuries within the Eagle Space arising from repetitive motions of unstable adjacent joints leads to chronically waxing and waning degrees of multiple nerve, vascular and lymphatic dysfunctions and might be thought of as a "carpal tunnel syndrome of the neck". We can occasionally see the radiographic consequences of this chronic injury by the appearance of a calcification of the hyoid ligament which is often reported by the radiologist as elongated styloid bone consistent with Eagle syndrome. However, if analyzed closely, the osseous portions of the ligament might be separate from the styloid bone revealing their nature as being calcification (Figure 6).

Craniocervical Instability Injury to Pharyngeal Plexus

Of the adjacent joints that are unstable, perhaps instability of the craniocervical joints is most relevant in our patients. CCI is an instability of the atlantooccipital (C0-C1) and the atlantoaxial (C1-C2) joints by laxity of the ligaments responsible for stabilizing these structures. CCI is a common albeit likely underappreciated consequence of hypermobility syndrome and hEDS (18, 42) and this instability can injure many of these nearby structures together. The atlantoaxial joint is the most mobile joint of the human body. Its mechanical

properties are determined by ligamentous structures, most prominent of which are the transverse, alar, and accessory ligaments and anterior and posterior longitudinal ligaments (43, 44). Capsular and inter-spinous ligaments are important as well. The cervical spinal cord is protected within the spinal canal created by the arches of these cervical vertebrae. The cord is protected within a thecal sac which must adjust to this mobility. Therefore, it is not firmly attached to the spinal canal at this level. Instead, a variety of suspension ligaments, such as the Hofmann ligaments and myodural bridges, tether the thecal sac to the spinal canal and deep suboccipital musculature (42, 45-47). The spinal cord, in turn, is tethered to the thecal sac by the dentate ligaments and further tethered to the spinal canal below C2 by spinal nerve roots egressing through the intervertebral foramina (48, 49).

Injury in this region can happen in at least 3 major ways. Two of these, direct concussive injury to the brainstem and vertebrobasilar insufficiency, collectively termed cervical medullary syndrome, are discussed below. The third mechanism of injury in CCI is injury to the nearby nerves. The pharyngeal plexus, the occipital nerve, and spinal nerves C1 and C2 are at particular risk of injury arising from increased laxity of any and all of these connective tissues in those at risk for CCI. However, because of this uniquely flexible arrangement of these ligaments and bridges, the risk is not always apparent by standard radiographic procedures. Thus, CCI in these patients often remains elusive (42, 50).

This use of the term CCI deserves detailed consideration. Mao et al recently stated that the benign hypermobility of hEDS is often mistakenly classified as CCI (19). Their distinction seems to be in whether the craniocervical junction (CCJ) hypermobility causes transient neurologic symptoms versus a major risk of permanent deficits or death and most patients with hEDS do not risk death from their CCJ hypermobility (51). We posit that there is middle ground. Our experience is that patients with hEDS have significant neurologic symptoms that are essentially unrelenting if not permanent if left unmanaged even though there may not be a risk of death directly from CCI. A suitable analogy might be carpal tunnel syndrome of the wrist which is not life-threatening and not necessarily in need of urgent surgical correction but it is also not benign nor transient if left untreated. It is a serious medical issue causing major dysfunction and occupational limitation, pain, and is life-altering. It requires medical evaluation and appropriate treatment – even if not surgery. It also has little radiologic evidence at times. Applying this analogy to the neck, (carpal tunnel syndrome of the neck) and the dysfunction and limitation is an order magnitude greater. This middle ground might be better termed "pathologic cervical hypermobility" or "occult CCI" but CCI nonetheless. Therefore, we elect to retain this use of the term CCI in the patients we observe.

Localizing Injury of Pharyngeal Plexus

The specific location within the Eagle Space of nerve injury can be deduced by considering the following. Although pharyngeal plexus injury from CCI likely occurs near the jugular foramen, it is not likely immediately proximal to the foramen. The presentation we observe in our patients is distinctly different from nerve palsies or complete paralysis of these 3 nerves at the level of the jugular foramen, a condition known as Jugular Foramen Syndrome or Vernet's Syndrome (52, 53). Among other signs and symptoms, jugular foramen syndrome presents as paralysis of the laryngeal muscles leading to hoarseness and nasal pitch, loss of sensation to the posterior aspect of the tongue, reduced parotid secretions, loss of gag reflex, and weakness of the sternocleidomastoid and trapezius muscles (52). While many of the other signs and symptoms are observed, these particular signs are not observed in our patients. Furthermore, vocal cord paralysis associated with signs implicating injury also to CN IX may be regarded as a lesion seated in or above the jugular foramen (54). Since vocal cord paralysis or hoarseness, soft palate paralysis, and swallowing difficulties are not observed in our patients, we conclude the injury is distal to the branching of these fibers. With respect to the type of injury, rather than a complete palsy or paralysis, there is a neuralgia, or irritation, or stretch of these nerves; the difference being much the same analogy as paralysis of the hand versus the symptoms of carpal tunnel syndrome. Instead, we propose that pharyngeal plexus injury occurs at the level of the transverse processes of C1. We postulate that the atlas intermittently slips anteriorly causing its transverse processes to impinge on these nerves as well as compromise internal jugular vein and lymphatic flow by pressing them against the stylohyoid ligament within the Eagle Space (Figures 4 and 5).

Pharyngeal Plexus Injury Heralding onset of CCI

In our experience, Eagle syndrome-type symptoms are neither the earliest nor the most consistent symptoms suggesting pharyngeal plexus injury from CCI. Earlier and more consistent symptoms, but perhaps more easily confused with other etiologies, are those that can be traced back to injury of the individual cranial nerves of this nerve plexus. Injury to CN X causes dysautonomia. However, there are many causes of dysautonomia and its presence should not automatically raise suspicion for CCI. Suspicion for CCI should be raised when the onset of dysautonomia is accompanied temporally with the onset of many of the signs and symptoms indicating injury to CNs IX and XI.

CN IX injury within the pharyngeal plexus can manifest not only as Eagle syndrome-type symptoms but can also contribute to dysautonomia. There are afferent pathways of CN IX from the arterial baroreceptors in the carotid artery and of CN X from the aortic arch that relay information to the vasomotor center in the medulla (55). Injury to CN IX and/or X together within the pharyngeal plexus likely contributes to a presentation of dysautonomia with particularly wide and inappropriate variation in blood pressure by disrupting this control mechanism as well. Injury of both CNs together may very well be responsible for the phenomenon vagoglossopharyngeal neuralgia, whereby pain overflows from the CN IX distribution to include CN X and there is associated cardiogenic syncope (56, 57). We suspect some of the syncopal events our patients have are by this mechanism.

Accessory nerve (CN XI) injury within the pharyngeal plexus can manifest as trapezius muscle spasm and pain beyond the typical "coathanger pain" caused by poor blood flow to neck musculature in dysautonomia. The spinal component of the accessory nerve motor-innervates the sternocleidomastoid muscles and portions of the trapezius (58). The sternocleidomastoid muscles seem to be spared in our patients and so the proposed injury to CN XI seems to be distal to the bifurcation of the nerve to the sternocleidomastoids. Injury to the CN XI branch innervating the trapezius appears to lead to spasm and weakening of the trapezius muscles preferentially. The prominently knotty muscle spasms experienced by these patients may arise from injury to the nerve resulting in over-activation and spasm (analogous to carpal tunnel syndrome) or may be resulting in weakening of those portions of the trapezius innervated by it, while those portions of the muscle innervated by other sources are over-worked to compensate for the loss with secondary intense painful spasm (59-61). Further injury may result in partial paralysis of these muscles with resultant muscle wasting.

Another nerve injury that plays prominently is injury to the occipital nerve. The greater occipital nerve arises from the posterior ramus of the axis spinal nerve and travels cranially posterior to the transverse processes of the atlas. It picks up contributions from CN IX and X and so can be affected by injury to IX and X and by hypermobility of the altas, causing our patients with CCI to often have occipital neuralgia as well (62).

Evidence for Additional Neurologic Symptoms Caused by CCI

There are several other neurologic symptoms heralding the onset of CCI. Their temporal association with the development of other pharyngeal plexus injuries implicates these symptoms as part of pharyngeal plexus injury as well. With the onset of development of the signs and symptoms described above, many of these

patients describe symptoms of tinnitus, vertigo, phonophobia, hyperacusis, and ear canal pain. They can sometimes also complain of an unpleasant feeling of aural fullness, otalgia (middle ear pain), and autophony whereby one hears their own breathing (aerophony), heartbeat, and voice at an annoyingly high volume. The former set of symptoms are consistent with a condition known as tonic tensor tympani syndrome (TTTS) (63, 64). The latter set of symptoms are consistent with a condition known as patulous Eustachian tube (PET) (65).

TTTS occurs when the muscle most responsible for modulating the sensation of sound at the tympanic membrane, the tensor tympani, spasms. As part of the acoustic reflex, the tensor tympani tenses to protect the tympanic membrane (TM) and cochlear apparatus from acoustic, vibrational trauma precipitated by loud noises (66). Spasm of the tensor tympani is commonly believed to occur from injury to its nerve of innervation (mainly CN V3) from temporomandibular dysfunction or poor dental occlusion (67-69) or a direct effect on the muscle independent from its innervation due to exposure to loud sounds inducing acoustic shock or a nonspecific effect of anxiety (70, 71) (63). Therefore, traditionally, TTTS has not been considered to arise from pharyngeal plexus injury.

Patulous Eustachian tube is a physical disorder whereby the Eustachian tube, which is normally closed, remains intermittently open (72). PET has a relatively high prevalence in the healthy population and has many underlying causes, few of which are considered a neurologic dysfunction. PET is also typically not thought to arise from pharyngeal plexus injury. However, the physiology involved in both TTTS and PET may be influenced by the nerves of the pharyngeal plexus via the participation of these nerves in the tympanic plexus and we suggest this as a possible etiology given the constellation of symptoms manifested by our patients at the onset of CCI.

The tympanic plexus is formed from several nerves including CN IX and has additional communication with CN X (37). It is by these innervations that the tensor tympani muscle, considered mainly innervated by CN V3, is also innervated by the tympanic plexus (73). The tympanic membrane (TM) is innervated on the inner surface by the tympanic nerve which arises from CN IX just outside the foramen (74) and on outer surface by the auricular branch of CN X (66, 74). These nerves sense the movement of the TM and regulate tensor tympani tone. Furthermore, the Eustachian tube is innervated partly by the tympanic and pharyngeal plexi with parasympathetic branches from the tympanic nerve of CN IX playing a predominant role in Eustachian tube sensation and parasympathetic efferent action playing a major role in opening and closing this tube thereby controlling middle ear pressure and sound transmission. The pharyngeal plexus also innervates the levator veli palatini muscle which, in turn, is closely related in function to the tensor tympani muscle (68, 75-

77). From this complex set of innervations, it is plausible that injury to the pharyngeal plexus might produce the signs and symptoms of both TTTS and PET and this helps to explain why they are sometimes observed arising together in our population along with the other signs and symptoms of CCI. We suspect there is entirely another mechanism involved in this amplification, discussed in future sections as Wardly Phenomenon.

Evidence for CCI in SLS patients

Patients with CCI have signs and symptoms of cervical medullary syndrome (or cervicomedullary syndrome) including cranial settling (16-19). The symptoms of cranial settling likely result from compression of the vertebral artery leading to vertebrobasilar insufficiency and ischemia. This causes intermittent vertigo, paroxysmal dizziness, diplopia, confusion and altered consciousness, headache, dysphasia, incontinence, ataxia, weakness of the quadriceps muscles causing buckling of the knees where the legs give out (drop attack), episodes of narcolepsy or cataplexy, and sometimes loss of vision (35, 78-81). Some patients show downbeat nystagmus (82) or other forms of nystagmus indicating brainstem injury although this can also occur from compression of the brainstem by herniation of low lying cerebellar tonsils into the foramen (83, 84).

CCI has 3 vector components; vertical, horizontal and rotational instability. For the patients with the hypermobility syndromes, the most common and significant but least appreciated is vertical instability. Commonly, these patients get marked relief of symptoms (brain fog, headache, vision brightness, fatigue) simply by applying 20 pounds of upward traction on the head while in a seated position. On the other hand, the most over-rated vector is horizontal instability. During radiologic assessment, it is horizontal instability, or more accurately horizontal mobility, that is determined when calculating the commonly used measures for CCI, that of the clivo-axial angle, the clivo-atlas angle, and Grabb-Mapstone-Oaks measurement (16, 85, 86). Therefore, while these measurements might be abnormal in these patients, and indeed, such findings would be both specific to and sensitive for CCI in general, they are not sensitive for the vertical component of CCI. With standard static radiologic positioning, abnormal measures are not required nor even expected in patients with hypermobility syndromes. Indeed, attempts at detecting CCI radiographically have been historically frustrating. Milhorat and Bolognese proposed that better measurements are with and without traction measures of the basion-dens interval (BDI) and other similar intervals (Figure 7). Ideally, these are dynamic measures that require imaging without and with traction (12 to 20 pounds superiorly) (87). The BDI measure is traditionally used for craniocervical separation trauma (internal decapitation) which is essentially the opposite of the cranial settling in hypermobility patients. While these measurements are supportive, ultimately it is the

history consistent with cervical medullary syndrome/ cranial settling and response to cranial traction protocols that are most reliable in this diagnosis (Personal Communication with Paolo Bolognese). The use of videofluoroscopy, also known as Digital Motion X-Ray (DMX) has allowed some providers to detect CCI at various levels of the cervical vertebrae with a high degree of diagnostic accuracy (88, 89) (Figure 8). The advent of Cone Beam Computer Tomography (CBCT) may move radiologic detection of CCI further forward. The CBCT images in Figure 9 demonstrate the anterior displacement of the atlas with resultant posterior compression of the airway. This phenomenon may be an important contributor to the loss of airway discussed later.

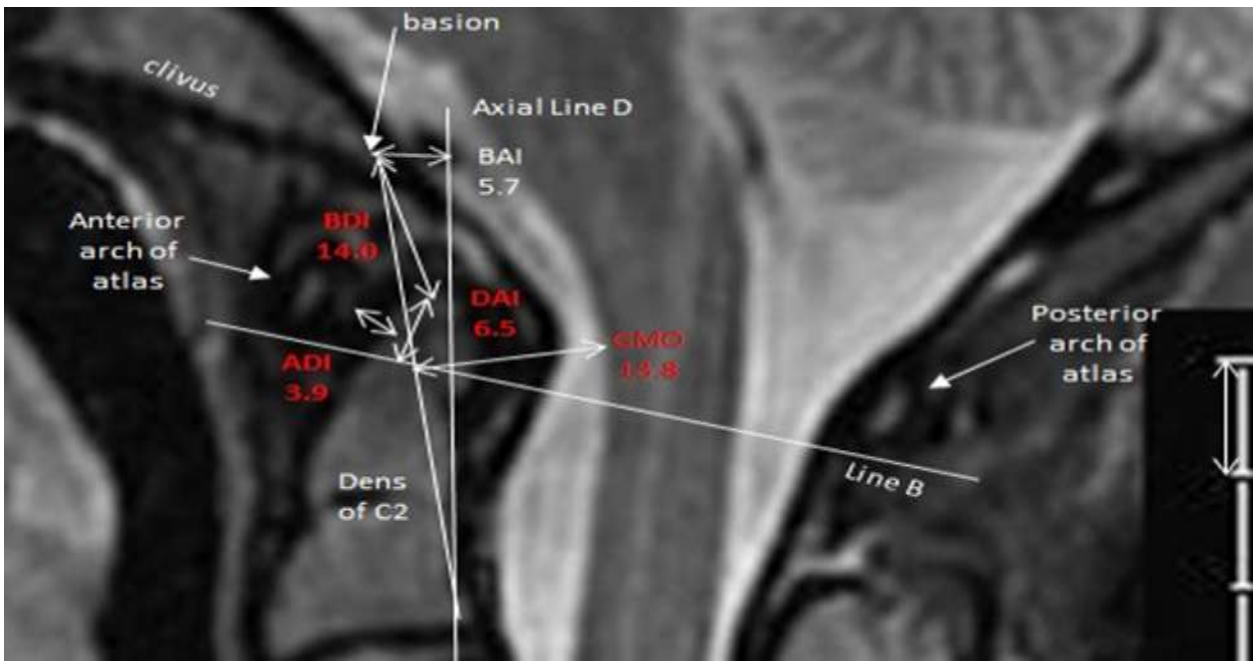


Figure 7: Abnormal CCJ Intervals

Mid-sagittal of 21 year old with full SLS. Axial Line D, the line along posterior surface of dens. Line B, that between lowest point of anterior arch of atlas and lowest point of posterior arch of atlas. Arrowheads identify the basion-axial interval (BAI = interval between the basion and Line D); the basion-dens interval (BDI = distance between the basion and top of dens); the interval between the dens and Line B (DAI), (ADI = distance between the posterior surface of the anterior arch of the atlas and dens), Grabb-Mapstone-Oakes Interval (GMO). The BAI is normal at 5.7 (Normal < 12 mm). The BDI is abnormal at 14.0 mm (7.7 +/- 1.6 mm), the ADI is abnormal at 3.9 (1.5 +/- 0.6 mm), the DAI is abnormal at 6.5 (12.3 +/- 2.2 mm), the GMO is abnormal at 13.8 (<=9 mm) (85-87).

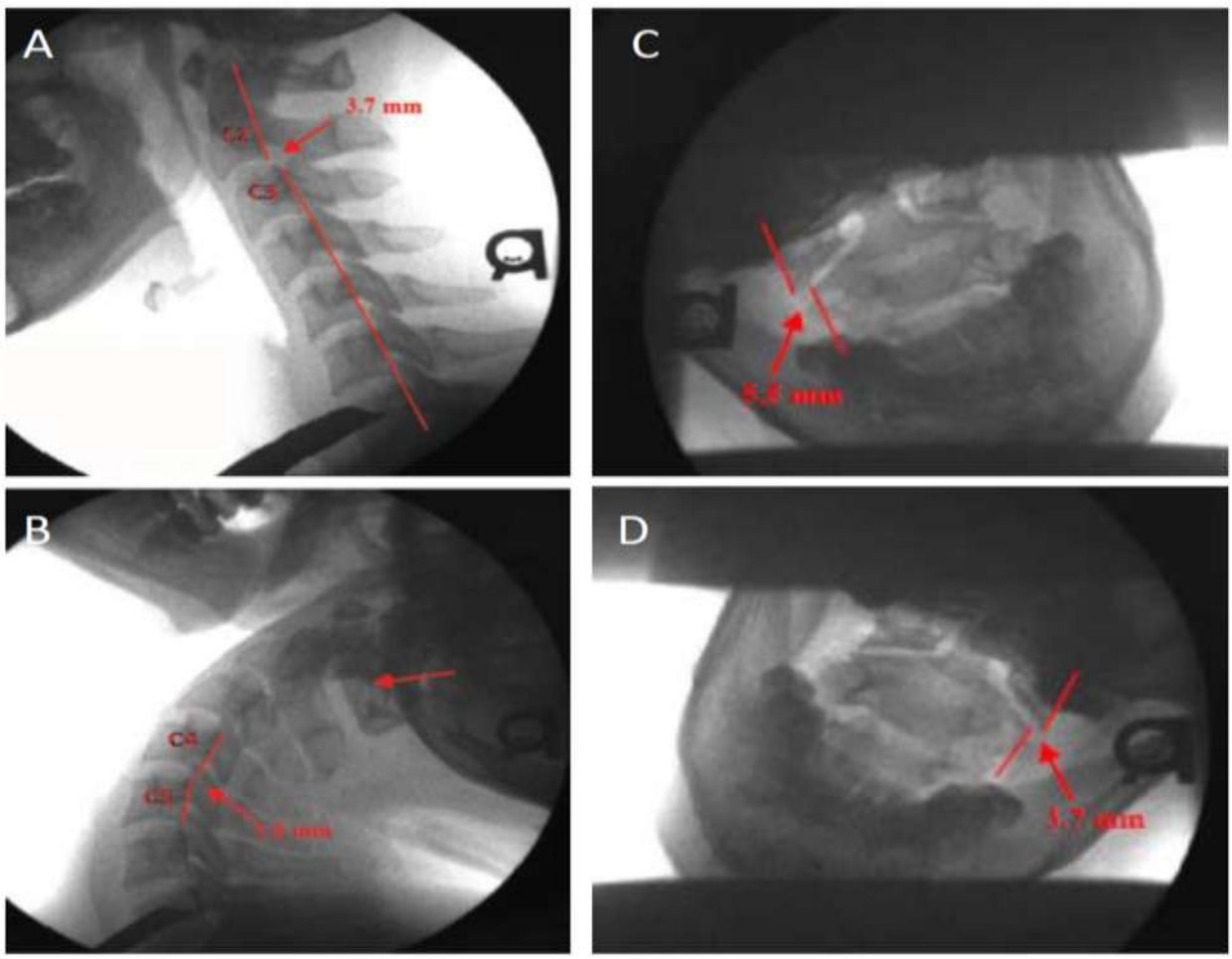


Figure 8: Digital Motion X-Ray (DMX) with CCI: Still images of DMX showing:

A) Lateral View Neutral Position showing anterior offset of C2 on C3 of 3.7 mm

B) Lateral Full Extension Position showing retrolisthesis of C4 on C5 by 2.8 mm

C) AP Open Mouth Left and D) Right showing abnormal lateral translation of C1 on C2 with bilateral overhang and asymmetric para-odontoid spaces. Images by R. Hauser (89)

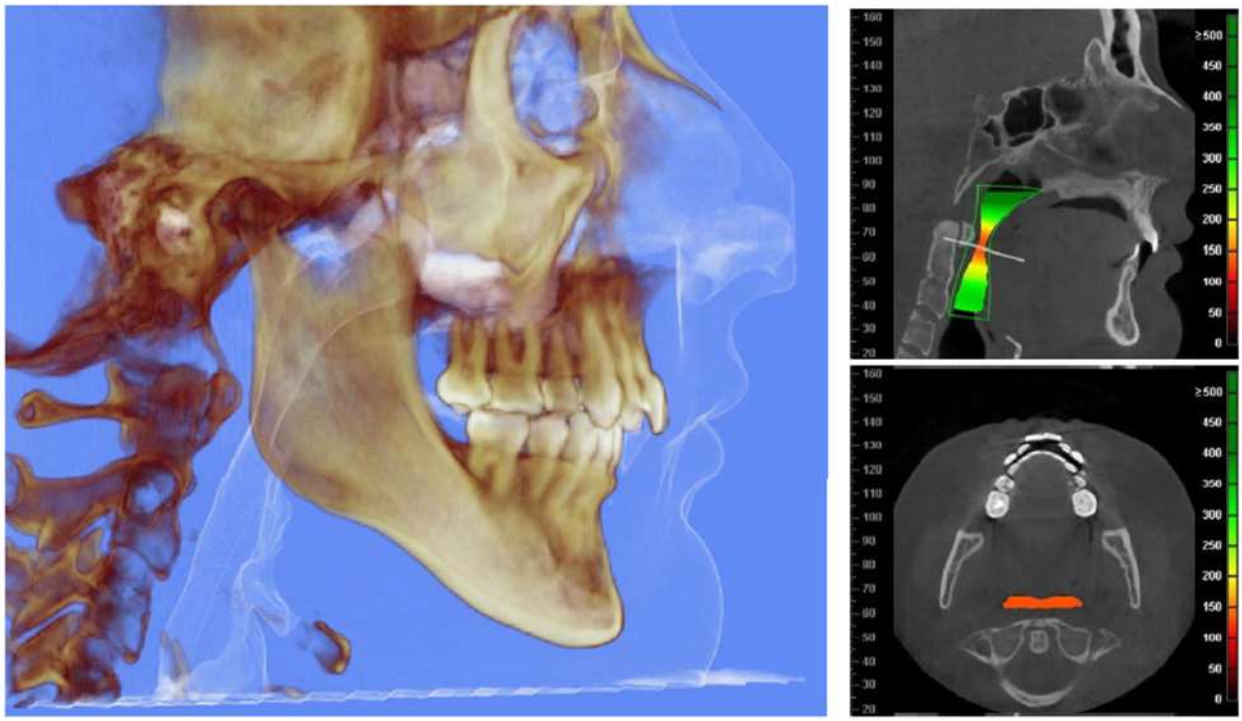


Figure 9: Cone Beam Computerized Tomography (CBCT) of CCI:

A) *Lateral view of both bone and soft tissue structures superimposed in 3D demonstrating anterior displacement of the atlas (C1) relative to the occiput and C2. The anterior arch of C1 appears to compress the posterior portion of the cervical airway. This is seen perhaps more dramatically in B) Lateral view with computer-generated analysis of airway cross-sectional size normalized to body size. Green is adequate cross-section for size while a shift toward red is inadequate. C) Short Axis view of airway at the level of C1 showing a very inadequate airway cross-section. CBCT is also very useful for showing compromised airways from many causes.*

Mechanisms that Lead to Intracranial Hypertension in SLS

Of the 30 patients we have been evaluating that have most elements of SLS, only three have had intracranial hypertension (IH) confirmed by lumbar puncture. However, the intermittent nature of the IH (often only when deeply asleep) and the presence of hypermobility syndrome or hEDS with fragile connective tissues with risk of chronic CSF leak following lumbar puncture has made pursuit of proof by lumbar puncture less desirable. Non-invasive techniques are being employed instead but these too must be selectively employed during times when IH is evident. One such patient demonstrated a significantly dilated optic nerve sheath by use of

retrobulbar optic nerve sheath diameter ultrasonography (90, 91). The clinical examination for evidence of IH is frustrated by the fact that most of these patients have no papilledema and the reason for this is discussed later. Therefore, IH has been deduced from the clinical picture and response to therapies such as acetazolamide. All patients demonstrated a positive short-term response to acetazolamide with a reduction in both low pressure and high pressure-type headaches as well as resolution of the clear drainage and facial puffiness characteristic of the leaky phase.

There are several phenomena which go into creating intermittent IH, any one of which might appear subtle or subclinical but when combined with the other phenomena, may become clinically important. Eagle Space crowding with jugular venous and cervical lymphatic compression, hyper-reactive vasodilatory response to elevated blood pCO2, hypopnea when sleeping, extent of sympathetic overdrive, tendency to herniate low-lying cerebellar tonsils, and ease of CSF leaking through cranial nerve sheaths or weak spots in cranial and spinal dura all likely contribute to the tendency and degree of IH although each one by themselves might not appear problematic.

Internal Jugular Venous Compression

The internal jugular vein (IJV) is found within the Eagle Space and this would also be predicted to be compressed by the same forces that impact the pharyngeal plexus (Figure 5). Compression of the IJV has very important ramifications for CSF drainage and pressure and even causes a decline in cerebral perfusion (92-94). Under normal conditions, the majority of CSF fluid is absorbed by the subarachnoid granules and delivered via cerebral glymphatics and lymphatics to the epidural sinuses and then to the IJV (95-97). Anything that increases the jugular venous pressure will inhibit normal CSF drainage and affect CSF pressure (94, 98). Pseudo-Eagle syndrome compression of the IJV would likely interfere with CSF drainage and would be predicted to worsen in a supine position and with sleep as discussed further below.

Eagle Space compression arising anteriorly might arise from a posterior subluxation or dislocation of the mandible at the TMJ joint particularly while in the supine position. TMJ subluxation and dislocation are common in those with hEDS (99-101). Moreover, CCJ pathology is much more common in those with TMJ dysfunction than those without. Of those with TMJ dysfunction, 77% were found to have functional limitations at C0-C1 compared to 20% of controls while 50% were found to have functional limitations at C1-C2

compared to 16% of controls (102). Thus, TMJ dysfunction coexists more commonly than not with CCJ disease in those with and without hEDS. Despite the high frequency of TMJ disease in this population, there is little documentation of direct IJV compression by mandibular dislocation in the medical literature suggesting this would be a less common cause of IJV compression. However, we suspect this is an under-appreciated cause of IJV compression. Some believe that any compression by mandibular position change likely is through the indirect effect to cause muscle spasms in the anterior and lateral neck (103).

Eagle Space compression arising posteriorly would be expected to happen from an unstable C1-C2 joint. The IJVs pass just anterior to the transverse processes of the atlas and just posteromedial to the stylohyoid ligaments or the styloid processes if they are excessively long as in true Eagle syndrome. Weak CCJ ligaments result in a counter-rotational misalignment or perhaps anterior slippage of C1 with C2 resulting in the transverse processes of the atlas compressing the IJVs likely against the stylohyoid ligament (35, 92, 104, 105) (Figures 5, 10 and 11). This has been called 'jugular vein bone nutcracker' or Eagle Jugular Syndrome (106) or Styloidogenic Jugular Venous Compression Syndrome (92). IJV compression can also happen in the setting of cervical spondylosis, a degenerative disease of the cervical spine (107). Thus, correction of IJV compression might be achieved by stabilization of C1 with C2 or, alternatively, bilateral stylohyoid ligament release or styloid process resection (92, 108, 109). Another alterative strategy is by stenting of the IJV as Liu and others have done (110).

Eagle Space compression arising laterally would be expected to happen from an excessively long or calcified styloid process as seen in this patient population. Other soft tissues such as excessive adipose and swollen lymph nodes (a consequence of lymphatic congestion in the Eagle Space) might also compress the jugular vein within and inferior to the Eagle space. Excision of such tissue might provide an additional remedy to relieve obstruction.

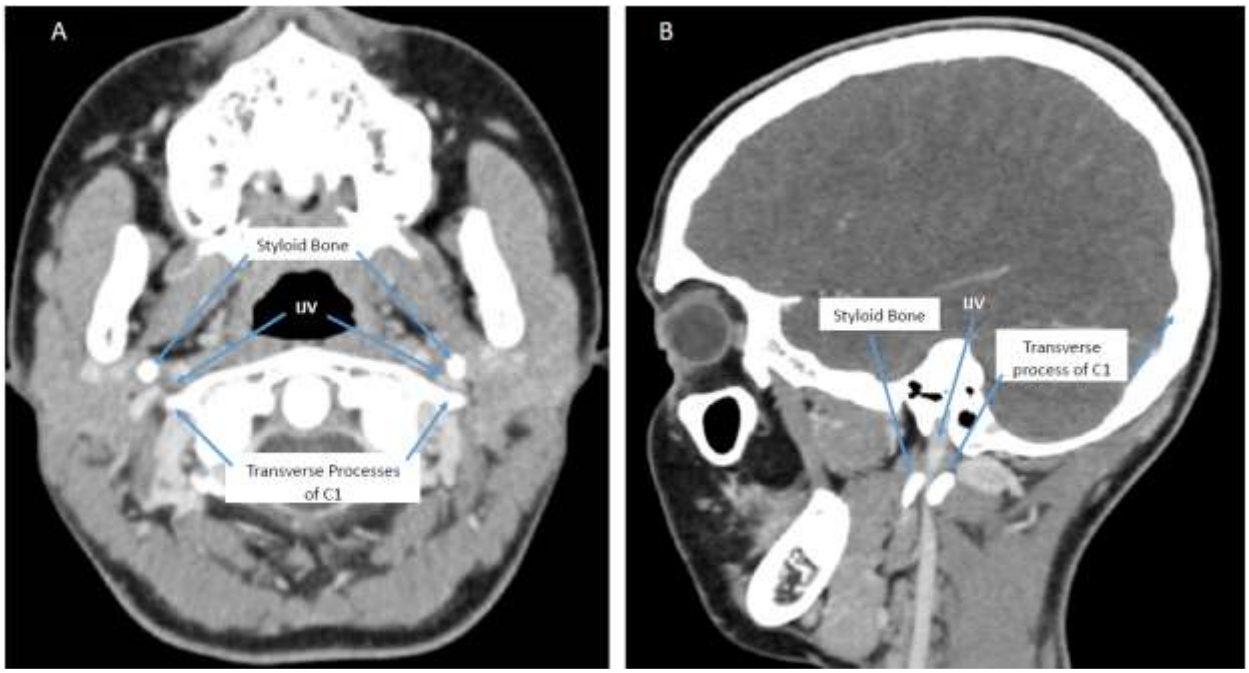


Figure 10: CT-Angiogram of Head and Cervical Spine

A: Axial view at level of C1 and styloid bone and B: left-sided sagittal section through left transverse process and styloid bone. These are images of a 15 year old female with a long history of exposure to mold including her current environment. She has evidence of MCAS with high CD117 count on duodenal biopsy and responsive to mast cell suppressing medications. She has little evidence of hEDS but strong evidence of CCI. Her most prominent presentations are drop attacks, narcolepsy and cataplexy consistent with vertebrobasilar insufficiency. She has dysautonomia with POTS with evidence of sympathetic overdrive. She has intermittent daily headaches that are better upon upright posture consistent with a high CSF pressure headache. Wardly phenomenon (discussed later) is not obvious but pseudo-tethered cord is. The CT shows compression of her left internal jugular vein (IJV) between her C1 transverse process and styloid and lateral displacement of her right IJV. Her Head and Cervical Spine MRI did not show obvious CCI.

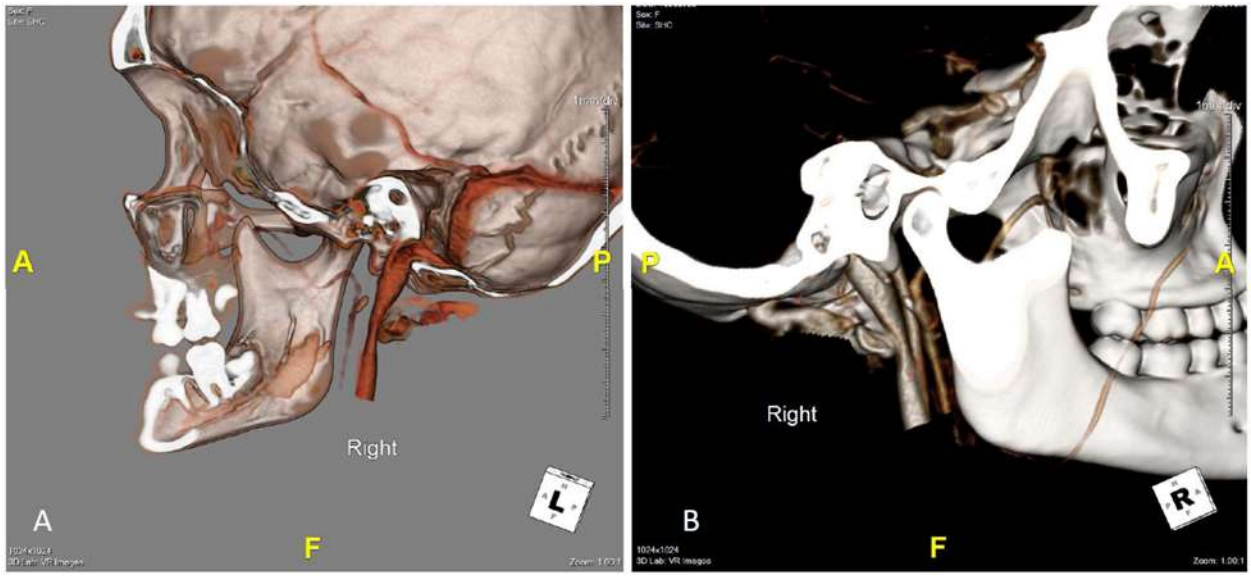


Figure 11: CT Angiogram with 3D Reconstruction Right Internal Jugular Vein:

This reconstruction demonstrates with two techniques the right internal jugular vein compressed by the transverse process of the atlas. A) from a left to right view and B) from a right to left view.

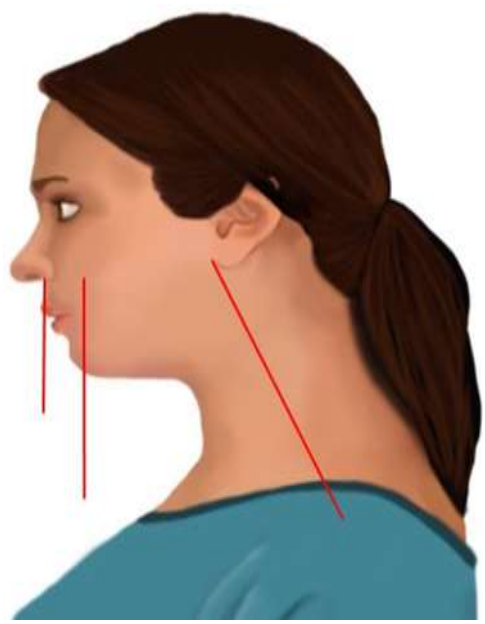


Figure 12: Eagle Space Compromise from Posture in hypermobility syndromes including hEDS

Lateral view of a patient with lax ligaments and small mandible that is retracted. The patient shows a typical sniffing position with the head extended forward. This opens the airway better for reducing airway resistance. In doing so, there is compromise to the Eagle Space with some compromise to jugular venous

return and compression of pharyngeal plexus, cervical lymphatics, and perhaps the carotid body.

Additional Factors Compromising Intracranial Venous Drainage

Although the IJVs, due to their caliber, are the dominant drainage channels in the craniocervical area, alternate channels are found in the vertebral vein and their principle affluents (111). Studies on the effects of posture on venous drainage reveal that the IJV system of drainage is much more important in the supine position but collapse upon upright posture while the vertebral venous system becomes dominant in the upright position (112, 113). Despite this collapse in the upright position, it has been determined that IJV compression in the upright position still results in retention of cerebral volume and so drainage by the IJV route remains important even in the upright position (113). This might have impact on study results when assessing venous drainage in any given patient. Anatomical variations in venous structures in the CCJ are also important to understand in such assessment (114). Given its even closer proximity to the cervical vertebrae, vertebral veins are also easily subjected to compressive forces in this condition and might also need attention when relieving venous hypertension.

To add to the problem, most patients with hypermobility or hEDS have lax back ligaments and tight and contracting fascia that cause them to have a pronounced craniocervical extension with forward leaning posture (Figure 12) (101, 115-117). Sleep disordered breathing from obstructed airway alone promotes a craniocervical extension and forward head position (118). This anatomic position likely helps open a small airway but also likely compresses the cervical soft tissue structures further in this area. The compression caused by this position would not be appreciated with radiologic studies if the patient is supine or asked to position upright for an upright study. Likewise, forward head tilt from excessive cell phone viewing is becoming an ever-increasing phenomenon and quite possibly adding additional mechanical stress.

Both pseudo-Eagle IJV compression and airway obstruction likely worsen in a supine position and these worsen further during deep sleep when oropharyngeal, temporomandibular, and cervical spine musculature maximally relaxes. The effect of this relaxation is likely exaggerated in these patients who have a ‘localized metabolic hypermobility or hEDS’ whereby the ligaments in the oral craniofacio-cervical region are lax with a resulting combination of muscle spasm caused by irritation from the instability and a compensatory increased tension of nearby musculature to help stabilize these joints (101, 115-117). This obstruction, along with a loss of airway muscle tone by the same mechanism, may explain our observation of so many of these patients

seemingly having great fear surrounding falling asleep and why many have found preference in sleeping at 45 to 60 degrees upright. This might also impact how radiologic imaging might fail to detect these pathologies in the conscious patient.

Finally, one additional cause of IJV compression is likely very important in this population and that is Wardly Phenomenon as discussed later.

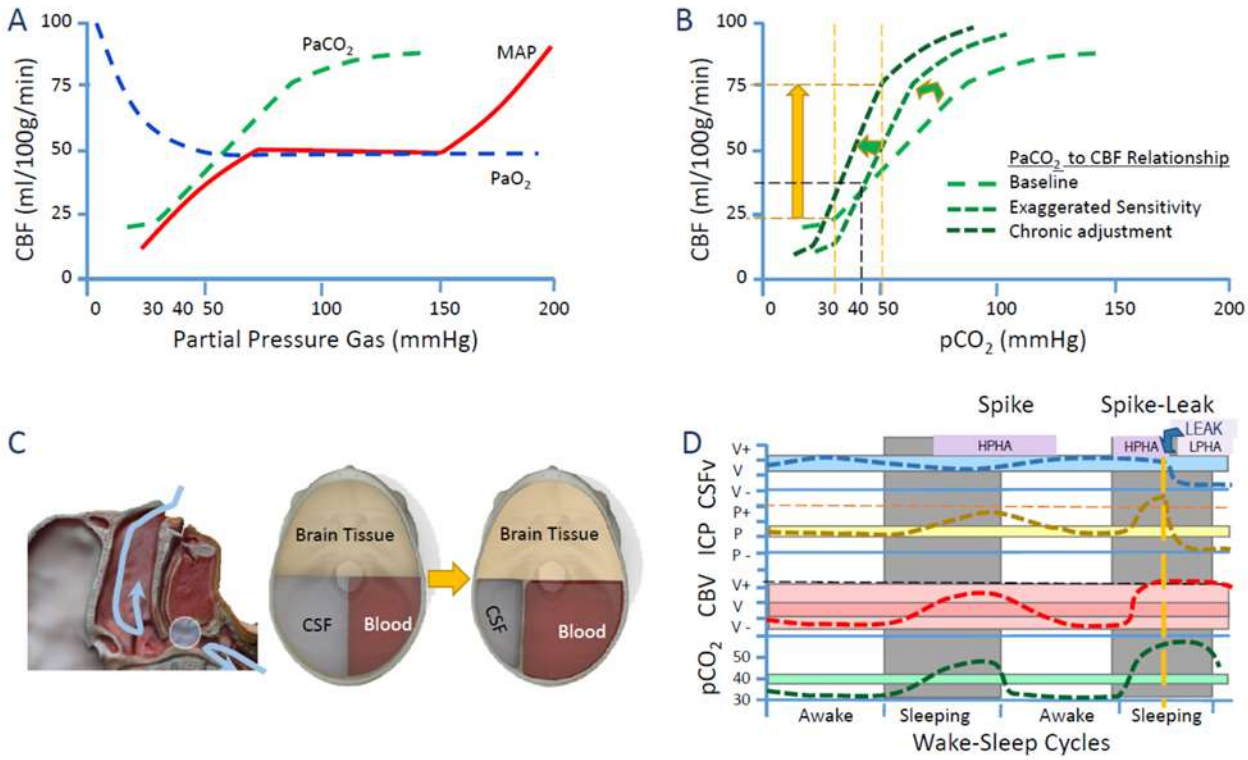


Figure 13: Determinants of CBF, CBF/pCO2 Relationships, & Hypopnea &The Monro- Kellie Doctrine:

A) Determinants of cerebral blood flow (CBF) include blood concentrations of O_2 (PaO_2) and CO_2($PaCO_2$) and arterial pressure (MAP). Of the 3 determinants, $PaCO_2$ has the greatest effect on CBF within physiologic and para-physiologic ranges.

B) Based on previous studies, the $PaCO_2$ curve is shifted to a steeper curve consistent with exaggerated sensitivity of CBF to changes in $PaCO_2$ and further shifted to the left from chronic daytime hypocarbia. This sets patients up for exaggerated blood flow response should airway compromise with hypopnea ensue. Image adapted from Taccone et al. (120).

C) The Monro-Kellie Doctrine: The combination of findings common in hypermobile patients leads to hypopnea (Upper Airway Resistance Syndrome (UARS) or frank obstructive sleep apnea (OSA)). The resultant hypercarbia causes a rapid increase in cerebral blood flow and, consequently, cerebral blood volume. The increased blood volume displaces CSF and causes an increase in ICP until equilibrium is achieved (119).

D) Graphs of pCO_2, Cerebral Blood Volume (CBV), Intracranial Pressure (ICP) and CSF Volume (CSFv) representing our hypotheses of how spikes and leaks occur in SLS patients. This graph is aligned over 2 wake-sleep cycles. The first cycle does not exceed the pop-off pressure threshold and the second exceeds the pop-off pressure threshold (dashed yellow line). Daytime hyperventilation with hypocarbia results in decreased CBF. ICP is maintained normal through enhanced production of CSF. Upon the first sleep cycle, hypopnea causes hypercarbia. CBF rapidly increases outside normal volume capacity. CSF is displaced to the extent it can "Windkessel" into reserve spaces such as cranial and spinal nerve sheaths. ICP increases while equilibrium is not yet attained (Spike). This results in a high pressure headache (HPHA). Upon arousal, hyperventilation resumes, CBV falls to below normal once again, ICP fall within normal. The HPHA lingers. Upon the second sleep cycle, the hypopnea/hypercarbia recur but this time CBV hits a critical volume (black dashed line) whereby the sum of CBV and CSFv fill all available reserve spaces including nerve sheaths. ICP increases abruptly further exceeding the pop-off pressure threshold. A CSF leak through the cuffs of cranial nerves ensues (Spike-Leak). This results in a low pressure headache (LPHA) and evidence of CSF leak.

Hypopnea and Upper Airway Resistance Syndrome

Intracranial pressure (ICP) is determined by the sum of the mass effects of the 3 major components within the fixed size of the cranium according to the Monro-Kellie Doctrine (119). With the brain tissue mass relatively fixed, pressure is thus mainly determined by the competition for space by CSF and blood (Figure 13c). Increases in blood volume into the brain must be compensated for by increased displacement and drainage of CSF. Cerebral blood volume is directly related to cerebral blood flow (CBF) and the most important determinant of CBF is the partial pressures of carbon dioxide and, to a lesser extent, particularly within physiologic ranges, oxygen in the blood. Hypoxia reduces CBF while hypercarbia increases CBF (120) (Figure 13a). This becomes extremely important during sleep in this population.

These patients tend to have at least subtle resistance to airflow when breathing at night and often have frank obstructive sleep apnea. This is due to many factors (121-124) including:

1) increased nasal mucosal thickening

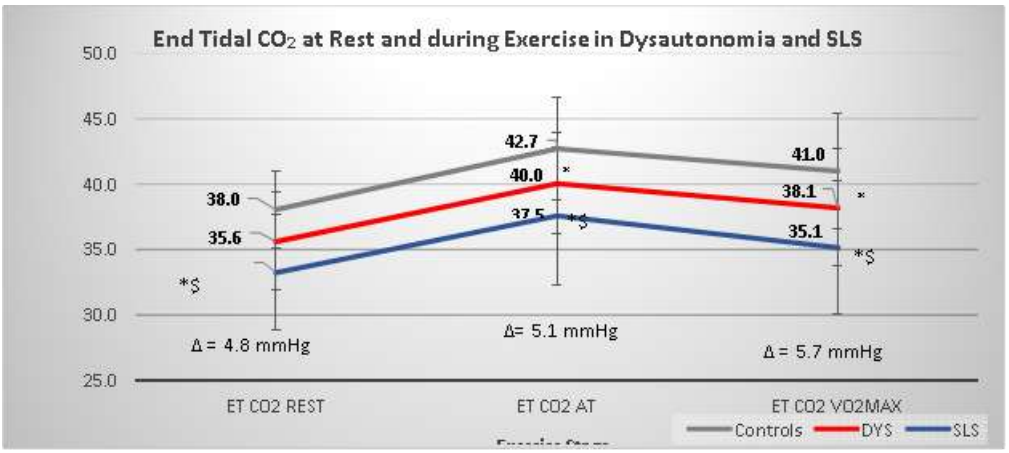
2) nasal septal deviation
3) restricted mobility of the tongue (functional ankyloglossia)
4) increased tonsillar and adenoid tissues
5) crowded dentition in a small mouth often made smaller by retractive orthodontia
6) a small mandible which often subluxes posteriorly particularly when supine
7) jaw clenching with activation of the superior pharyngeal constrictor muscle (101)
8) a normal size tongue that must fit in a small mouth and which often falls posteriorly from lax connective tissue
9) a cervical spine that is pushed anteriorly relative to the cranium (forward head posture) and
10) lax soft tissues in the neck and upper airway

We posit that our patient population with Pentad characteristics are particularly prone to these variations. MCAS may produce enlargement of lymphoid tissue as a result of inflammation. Lax ligaments and tissues in hEDS exacerbate many of these items. Nasal mucosal thickening may be from inflammation of any type, but there are other causes specific to SLS which will be discussed later. Some of these obstructions are compensated for by craniocervical extension with forward head position (118) which, as noted previously, may play a role to exacerbate the CCI.

All of these structural alterations lead to an unstable, narrow, inadequate upper airway and this leads to hypopnea. Airway inadequacy can manifest as frank obstructive sleep apnea (OSA) or by a more subtle upper airway resistance to flow while sleeping, a term called Upper Airway Resistance Syndrome (UARS) (124, 125). The resistance to airflow leads to subtle hypoxia and often not-so-subtle hypercapnia (126, 127) (Note on hypercarbia versus hypercapnia: though often used in medical literature interchangeably, in this paper we distinguish blood pCO_2 concentration from its surrogate breath carbon dioxide concentration as measured by end-tidal carbon dioxide concentration ($ETCO_2$) by use of "-carbia" for the former and "-capnia" for the latter (128-130)). While hypoxia causes decreased CBF, the mild hypoxia likely has little effect to oppose the counter effect of significant hypercarbia to cause vasodilation and increased CBF (131-133).

In a study in healthy adults, Grüne et al. has shown that acute changes in pCO_2 from 29 mmHg to 52 mmHg (over 60 minutes) can lead to a 2.3-fold increase (from 31 to 73 ml/100g/min) in cerebral blood flow (134). We postulate, and literature supports, that the relationship between blood pCO_2 (measured directly or by ET CO_2) and CBF is altered in our patients such that the CBF response to change in pCO_2 under conditions of chronic hypercarbia and hypocarbia is exaggerated (Figure 13b). The increase in CBF with hypercarbia is one

of the proposed mechanisms for how obstructive sleep apnea can increase ICP and lead to intracranial hypertension, a relationship that has been described but is not commonly known in medicine (135). We are not aware of any research on ICP in UARS, however one can deduce that the same relationship would be present given that hypercapnia and hypercarbia are present in UARS (126) as are significant intrathoracic pressure changes which would impact upon central venous pressure, another proposed mechanism for how OSA increases ICP (125, 135). Therefore we are stating that the presence of sleep disordered breathing in our patients is increasing their risk of having spikes of ICP (Figure 13d). We have investigated CO_2 levels in various states in our patients and present those results next.



Group	N	Female	Method: Bike	Age (years)	BMI
Controls	60	96.7%	91.7%	18.6 +/- 2.4	26.5 +/- 7.3
DYS	159	97.2%	89.9%	18.3 +/- 2.6	24.3 +/- 5.8
SLS	47	97.9%	85.1%	19.0 +/- 2.6	26.3 +/- 10.3

Figure 14 and Table 2 Study of end-tidal CO2 measurements at rest and during exercise.

*Groups are controlled for gender, method of exercise (bike versus treadmill), age, and BMI with no significant difference in these values by ANOVA. Controls = healthy patients, DYS = patients with diagnosis of clinically significant dysautonomia (with and without POTS) but without SLS, SLS = patients with Spiky-Leaky Syndrome, ET CO2 = End-tidal pCO_2 reported as mean +/- standard deviation in mmHg, Rest = 10 minutes of sitting and resting quietly, AT = at points of anaerobic threshold and maximum velocity of oxygen uptake (VO_2max) during metabolic exercise testing. Δ = difference between SLS and controls. * = $p < 0.0001$ versus controls, $ = $p < 0.0001$ versus DYS by MANOVA. Unpublished data from corresponding author's metabolic exercise laboratory.*

Exaggerated Blood Flow Response to Changes in PaCO2

The patients we discuss have dysfunction of the autonomic nervous system. We propose multiple reasons for the dysautonomia seen. First, there may be CCI or Eagle Space injury to CN IX and X within the pharyngeal plexus. Below we discuss Wardly Phenomenon which may be presumed to affect these same nerves. UARS per se appears to cause an autonomic dysfunction while sleeping (136) and UARS patients are also found to have orthostatic hypotension while awake (125). Patients with dysautonomia - dysfunction of the parasympathetic nervous system specifically, usually have a compensatory sympathetic overdrive that leads to chronic hyperventilation with resultant respiratory alkalosis (137-141). More recently, it has been shown that the hyperventilation is due to an alteration in carotid body function by hypercarbia and by the hypovolemia of POTS (142). We suspect that for some patients there is an underlying environmental exposure which may also be a significant contributing factor here as discussed later in the section on explaining an epidemic. Measurement of daytime end-tidal carbon dioxide reveals values often between 30 and 36 mmHg – well under the typical set point of 40 mmHg. This chronic hypocarbia with reduced cerebral blood flow, particularly in the upright position, has been demonstrated by several investigators (142-149).

We have demonstrated this in our own patient population by measuring ET CO_2 during rest and during 2 key points in exercise. Patients with clinically significant dysautonomia without evidence of SLS have an average pre-exercise resting ET CO_2 of 35.6 mmHg compared to controls having an average of 38.0 mmHg. Those with SLS findings have an average resting ET CO_2 of 33.2 mmHg. These findings are consistent with what Novak found in similar populations at rest and during tilt testing (149). What is interesting is that this relationship of a 5 to 6 mmHg lower ET CO_2 is maintained even during mid- and end-exercise which suggests that the body has adjusted to this hypocarbia and appears to see it as its new normal set-point (unpublished data, Figure 14, Table 2).

Altered cerebrovascular blood flow responses to changes in pCO_2 are not unique to SLS and have been demonstrated in various settings. Those with particularly symptomatic panic disorder have been found to have exaggerated decreases in CBF in response to hyperventilation with decreased pCO_2 (150). In contrast, studies on Andean men show impaired CBF response at sea level and altitude in those natives with and without chronic mountain sickness and headache (151). With respect to patients with sleep apnea, Fischer et al. demonstrated that middle cerebral artery velocity (a generally accepted surrogate for CBF) is lower in adults with chronic sleep apnea before, during and after sleep although their pCO_2 levels were higher under all tested conditions. An attempt at mathematical adjustment to control for pCO_2 differences resulted in significantly lower predicted

CBF under both sleep and awake conditions (152). Unlike in our dysautonomia patients, these patients demonstrated elevated pCO_2 while awake as well as during sleep. In contrast, using the same technique, Hill et al. found that children with sleep disordered breathing had higher middle cerebral artery velocity while awake than matched controls (153). In this study, flow velocities under sleep state were not measured nor was pCO_2 under any state. It is probably worth stating that studies that use middle cerebral artery flow velocity should be interpreted with caution particularly in conditions where pCO2 alters flow. Grüne et al. has demonstrated that, over a range of pCO2 levels from 29 to 52 mmHg, CBF increases 2.3-fold while middle cerebral artery velocity increases by only 67% (134). Other investigators have demonstrated that reactivity to pCO_2 is normal in the daytime but increased during sleep particularly during REM sleep (154) which cause particularly pronounced fluctuations in CBF in the early part of the morning creating greater risk from such fluctuations (155).

This chronic wake or daytime hypocarbia and/or the chronic sleep or nighttime hypercarbia may very well change the set-point for normal CBF at a lower pCO_2 level and therefore, even what might be considered a mild elevation in blood carbon dioxide levels at night, might lead to an exaggerated CBF response in those with dysautonomia. Evidence for a changed set-point for CBF in response to hypercarbia has been demonstrated previously (156) and perhaps over-shooting this set-point may explain the Hill et al. results (153) but we are not aware of any evidence for a change in set-point for chronic hyperventilation. However, we believe it stands to reason that a new set-point is established and hypersensitivity to hypercarbia explains our data thus far. It might be important to note that it has been known for a long time that between the pCO2 ranges of 37 and 19 mmHg, while CBF decreases from 45 to 25 mL/100g/min, cerebral oxygen extraction increases such that cerebral oxygen consumption remains unchanged (132, 133, 157). Thus, these dramatic changes in pCO2 with changes in CBF may not affect cerebral oxygenation but certainly may greatly affect volume fluxes of blood and CSF.

The result of this exaggerated rise in CO_2 from day to night presumably results in an exaggerated increase in cerebral blood volume that must be accommodated by an increased displacement and drainage of CSF. Before equilibrium can be achieved, intracranial hypertension results. As stated previously, drainage by the primary means via the subarachnoid granules is inhibited when increased jugular venous pressure from Pseudo-Eagle Syndrome is present. Thus, hypopnea in combination with Pseudo-Eagle Syndrome may result in an increase in intracranial pressure. This requires further study to confirm, but deductive reasoning predicts it.

It is our prediction that the evaluation of daytime end-tidal CO_2 compared with nighttime transcutaneous CO_2

is very helpful in predicting who is likely most at-risk for SLS. Figure 15 illustrates one example. The manipulation of daytime and nighttime pCO_2 by use of dysautonomia therapies, carbonic anhydrase inhibitors, and oral airway management are also studied this way and discussed here.

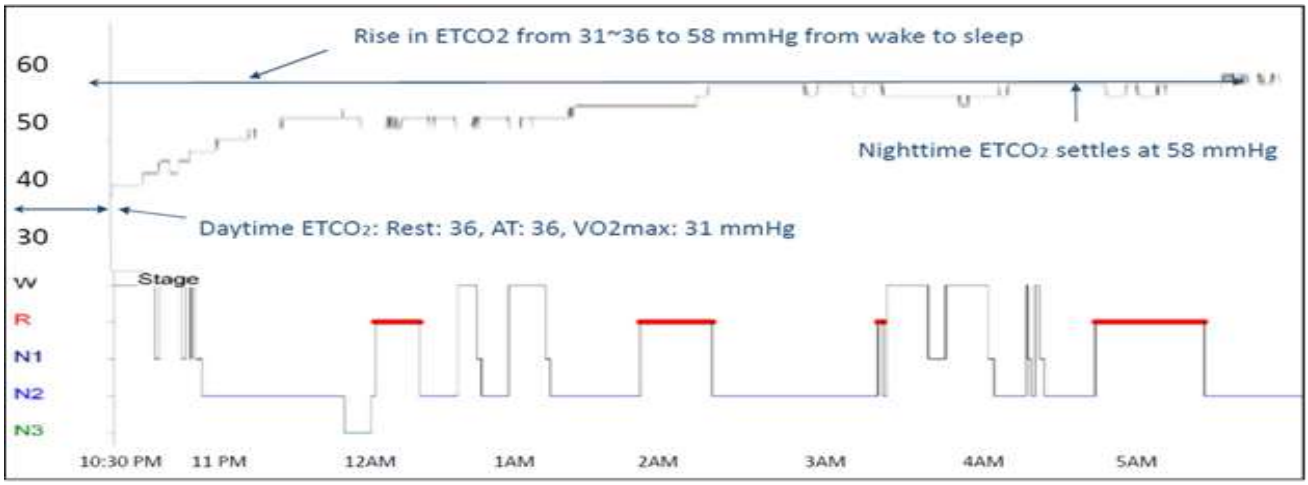


Figure 15 ETCO2 Measures while Awake and Sleeping; Awake Hypocapnia, Sleeping Hypercapnia, Spiky Phase (+), Leaky Phase (+) of SLS:

$ETCO_2$ data of 25 year old female with dysautonomia with mild sympathetic overdrive, and MCAS with severe brain fog, positional headaches. She is hypermobile but with little clinical evidence of hEDS although genetic analysis reveals that she has compound heterozygous variants for TNXB encoding for tenascin X protein as well as a variant in FNLN5 predicting a deleterious fibulin-5 protein. She denies Wardly Phenomenon but has intermittent sinus fullness and dependent facial edema on some mornings. She shows a modestly low daytime resting $ETCO_2$ that is 36 mmHg at rest but 31 mmHg at end exercise (normal at end exercise is 41 mmHg). She has a marked increase in $ETCO_2$ to 58 mmHg during REM and non-REM sleep.

What we deduce from these various studies of daytime resting and exercise metabolic testing with ET pCO_2 and sleep TC pCO_2 measures are the following;

1) Daytime Studies: Patients with dysautonomia have a lower resting ET pCO_2 level than healthy controls. Although ET pCO_2 levels rises though exercise, the relationship of pCO_2 compared to controls is maintained throughout exercise as if there is a new pCO_2 set-point that cannot be overcome even when falling behind on ventilation as typically seen during increasing exercise. This set-point is even lower for patients placed on acetazolamide or, to a lesser extent, on methazolamide.

2) Nighttime Studies: During sleep, the TC pCO_2 is seen to rise shortly after sleep is initiated and reaches a new plateau through the night. Based on limited data to date, it appears patients who tend to have a lower daytime ET pCO_2 tend to have a lower plateau at night. Once placed on acetazolamide, the ET pCO_2 is further lowered during the day and the nighttime TC pCO_2 is also lowered. So, while it might be assumed that the nighttime TC pCO_2 is entirely based on the severity of the upper airway obstruction, it appears that there is a set point for anyone sleeping to perhaps arouse and adjust so as to not exceed a certain level of pCO_2. That arousal level appears to be determined by the daytime set-point. The lower the set-point during the day, the lower it will be at night as well.

3) Change in pCO_2 from Day to Night: The magnitude of the rise in pCO2 from waking to sleep appears to contribute to the presence of SLS. However, the absolute magnitude of the rise doesn't necessarily determine the presence of SLS. We have studied patients where the magnitude of the rise is substantial but they demonstrate no evidence of SLS. Instead, modest rises in pCO_2 from day to night might lead to SLS if MCAS and/or hEDS is also present which changes the 'pop-off pressure' for leak as discussed later.

4)

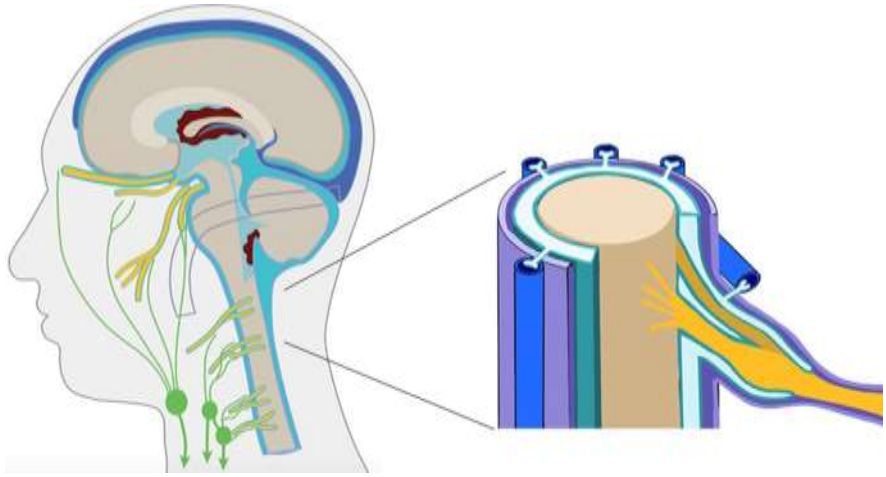


Figure 16: Cerebrospinal fluid (CSF) ''secretion-circulation absorption'' process.

(Left) CSF is mainly secreted by the choroid plexus and, to a lesser extent, by the interstitial compartment. It circulates rostro-caudally inside the ventricles and drains into the cerebello-medullary cistern (cisterna magna) through the median aperture (foramen of Magendie) of the fourth ventricle). CSF circulates in both cranial and spinal subarachnoid spaces. In the cranial subarachnoid space, CSF flows towards arachnoid villi in the wall of venous sinuses from which it is absorbed.

(Right) CSF absorption also occurs by spinal arachnoid villi and meningeal sheaths of spinal nerves. Spinal

arachnoid villi in contact with the epidural venous plexus and adjacent to spinal nerve roots.. Absorption surfaces are in the meningeal recess of spinal nerve roots. In addition, part of the CSF is absorbed by the olfactory mucosa and cranial nerve (optic, trigeminal, facial and vestibulocochlear nerves) sheaths and is drained by the lymphatic system. In the spinal subarachnoid space, the part of the CSF absorbed by the epidural venous plexus and spinal nerve sheaths enters the lymphatic system, while the remaining CSF circulates rostrally towards the cranial subarachnoid space. CSF communicates with interstitial fluid via Virchow-Robin perivascular spaces (55).

CSF Displacement into Cranial Nerve and Spinal Nerve Sheaths

The first result of the increased cerebral blood volume displacing CSF that cannot be absorbed by the arachnoid villa is that CSF is displaced in a Windkessel effect fashion (158, 159) into the sheaths of all the cranial nerves and spinal nerve sheaths (160, 161) (Figure 16). In other words, these sheaths act as a fluid capacitor. Reported among these are olfactory, trigeminal, facial, vestibulocochlear nerves, and, of course the optic nerve which is well-known for this given the end result is papilledema and imaging often reveals the fluid within sheaths. But, there is little report of the sheaths of CNs IX, X, and XI (vagus, glossopharyngeal and accessory) filling and yet their filling and compressive effect on the nerve axons particularly within the already tight space of the jugular foramen likely explains sudden worsening of symptoms associated with these nerves as described earlier following a Spiky-Leaky episode. Because important venous drainage of the inferior petrosal dural venous sinus and the sigmoid dural venous sinus also drain through this tight foramen, one might expect worsening backpressure on the arachnoid villi thereby interfering with proper CSF drainage. Once the cranial and spinal nerve sheaths fill, intracranial pressure would be predicted to rise even more so.

For CN II (optic nerve) the sheath fills and causes compression of the optic nerve which can lead to coning down of visual fields and loss of light intensity. This nerve sheath filling of course is a well-known phenomenon for the optic nerve and is a basic finding when evaluating intracranial hypertension by MRI and now can be detected by ultrasound techniques (90, 91). If it fills the entire sheath and into the back of the retina, papilledema forms. What is not typically recognized even by many neurologists, are the conditions of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) (2, 162, 163) and idiopathic intracranial hypertension without papilledema (IIHWOP) (164). In IIHWOP, there is no papilledema and the headache pattern can mimic that of migraine (165). In these cases, measuring opening lumbar pressure is likely to be the only way to confirm the diagnosis. Several studies have pointed out that there is overlap between the

symptoms of intracranial hypertension and ME/CSF, and have shown elevated ICPs or other signs of ICP in ME/CSF patients (164, 166). Other works have demonstrated overlap with the condition of fibromyalgia (160, 161) and both fibromyalgia and ME/CFS populations have been shown to experience relief of symptoms with CSF removal, even if the initial opening pressures were not considered significantly elevated (160, 166). If these conditions are just different manifestations of IIHWOP that is going unrecognized due to the absence of papilledema and the expectation by the physicians that papilledema must be present for IIH to be considered, then it becomes imperative to promote better understanding of the physiology of lymphatic drainage of CSF along the cranial nerves and why sometimes the optic nerve is spared. Our discussion on the olfactory nerve drainage might very well explain the phenomenon.

Wardly Phenomenon

The combined sum of these various cranial nerve impingements particularly occurring from increased CSF fluid pressure within nerve sheaths leading to corresponding cranial nerve dysfunctions has been proposed by Wardly to be responsible for the often multiple hyper-sensory symptoms seen in many patients with IIH: osmophobia, phonophobia, photophobia (167). Glossopharyngeal neuralgia and trigeminal neuralgia may also be included, as might any perturbation involving any of the cranial nerves, but the key is that usually more than one cranial nerve is involved, indicating a primary etiology of excess CSF pressure within the nerve sheaths. Therefore we will refer to this as the Wardly Phenomenon going forwards to encompass multiple cranial nerve involvement with both deficit and hypersensitivity symptoms caused by fluid and pressure overload of these nerves. Wardly Phenomenon is likely responsible for the amplification of the same neurologic symptoms described earlier caused by CCI. In this case, rather than being from external compression of the pharyngeal plexus, it is from the impingement of CNs IX, X, and XI within their sheaths within the Jugular foramen. Given the intra-sheath pressure under the influence of intracranial pressure as well as pulsatile arterial pressure, this might give rise to the fluctuating and pulsatile nature of these symptoms, for instance the fluctuating and pulsatile tinnitus known to be associated sometimes with IIH (168). Loss of nerve function (sensory, motor, autonomic) by the same mechanism was further described shortly after Wardly by Hulens et al. who extended the nerve dysfunction throughout the spinal cord as well and included the origin of the symptoms generalized fibromyalgia pain and symptoms of sacral nerve dysfunction including ataxia, poor balance, and bowel and bladder dysfunction (160) – symptoms that we suggest might be mistaken for occult tethered cord – in essence, what might be termed “pseudo-tethered cord”. In this paper by Hulens et al., the link was made that patients with hEDS were at higher risk for this phenomenon (160) which fits with the

known higher incidence of diagnoses of occult tethered cord in the hEDS population.

Note that Wardly Phenomenon of multiple cranial and spinal nerve dysfunctions from the compressive effects of high CSF pressure is the second mechanism of multiple nerve dysfunctions described in this paper in those with SLS, the first being the carpal tunnel-like injury of pseudo-Eagle syndrome. Yet third and fourth mechanisms of multiple cranial and spinal nerve dysfunction occurs in these patients when Chiari-like compressions and excessive nerve stretch arises from 'brain sag' following CSF leak in the "Leaky Phase" described next. Yet a 5th mechanism of multiple nerve dysfunction might exist from direct environmental toxin cytotoxicity as discussed in the final section.

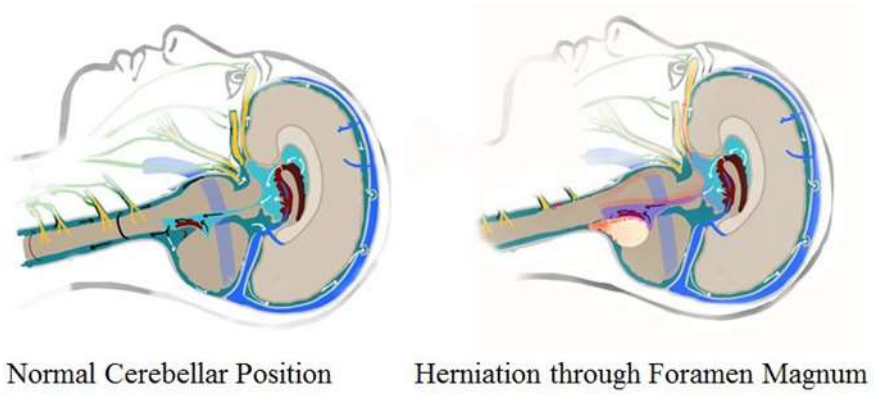


Figure 17: Supine Nighttime Intracranial Hypertension causing Herniation of Low-Lying Cerebellar Tonsils

Rising intracranial hypertension might result in cerebellar herniation, particularly those that are low-lying as is often the case in hEDS, at some point in the Spiky Phase process which would cause signs and symptoms of Chiari which might persist even after resolution of the herniation once pressure is relieved.

Herniation of Low-lying Cerebellar Tonsils in Intracranial Hypertension

Sometime during the peak of IH, some patients likely experience a herniation of the tonsils of the cerebellum into the foramen magnum (169) (Figure 17). This is more likely to occur in patients with low-lying tonsils which is more common in patients with hEDS (18, 87, 170). When that happens, not only would Chiari-like symptoms be predicted to arise but the pressure distribution of CSF across the intracranial space and spinal column is now blocked. This would predict an even greater rise in intracranial pressure. Indeed, in the supine

position, the majority of CSF compliance relieving excessive pressure exists in the spinal column (171). Even if the intracranial pressure decreases and the herniation subsequently resolves, these patients likely continue to have Chiari-like symptoms for some time after and complain of abnormal swallowing, speech or voice, tingling, numbness, weakness in extremities, weak handgrip and loss of fine motor skills for some time thereafter.

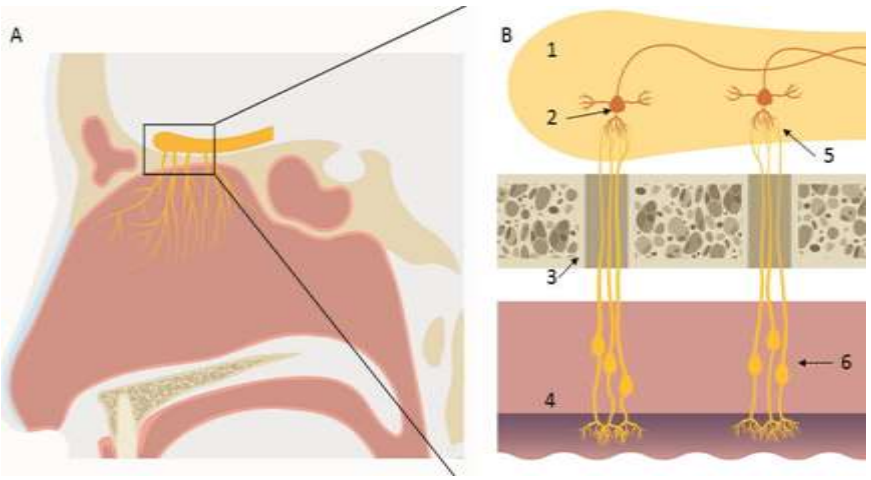


Figure 18: Human Olfactory System with Nasal Sinuses:

A) Views of the cribriform plate through which the olfactory receptor cells covered in tough dural nerve sheathes pass into nasal mucosa. The nasal septum intersects the cribriform plate inferiorly aligning with the crista galli.

B) Detailed Human olfactory system. 1: Olfactory bulb 2: Mitral cells 3: Bone (Cribriform plate) 4: Nasal mucosa and epithelium 5: Glomerulus 6: Olfactory receptor cells

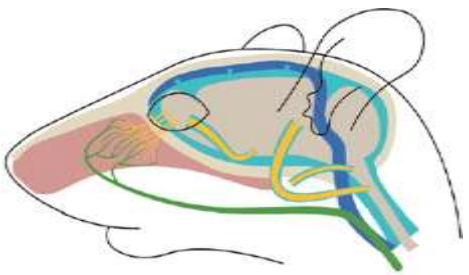


Figure 19: Figure 19: Rat CSF Circulation:

Diagram showing the routes of CSF drainage in the rat (modified from (181)). The olfactory pathway is the major route of CSF drainage from intracranial spaces with the arachnoid villi being less well-developed than in humans.

The Olfactory Nerve in Spiky-Leaky Syndrome

When the main pathway for CSF drainage into the venous system is blocked, it is apparent that alternative pathways for drainage must exist in the human body. As mentioned earlier, there is evidence to show that alternative pathways include drainage via CN sheaths to lymphatics at their end cuffs. One particular cranial nerve that is very important in such drainage in otherwise healthy humans but likely even more so in our SLS population is the olfactory nerve (172-176). Certainly, spontaneous CSF leaks have been known to occur through the cribriform plate, the ethmoid roof, and the sphenoid lateral pterygoid recesses in patients with IIH. However, these are large enough leaks that investigation reveals fluid positive for beta-2 transferrin and the site of injury can be identified and often surgically repaired (177). There is also a strong association between children with IIH and sinusitis although it has been assumed that the etiology of the IIH is secondary to the sinus infection and not that sinusitis is a consequence of IIH (178). There is also an association of non-allergic rhinitis with fibromyalgia and chronic fatigue syndrome (179). In this case, it has been suggested by Hulens et al. that higher pressure CSF draining into the olfactory lymphatics accumulates and saturates the nasal mucosa. Hulens et al. further postulates that the excess CSF leaks into the paranasal and nasal cavities causing rhinorrhea and sinusitis (160). Our hypothesis incorporates this mechanism as well.

The olfactory bulb sits above the cribriform plate of the base of the skull and sends sensory nerve fibers through the foramina within the plate directly into the nasal mucosa (Figure 18). These fibers are covered by a tough dural sheath and are cuffed at the end in such a way as to hold CSF under some pressure within them. Interdigitated with these sheathed sensory nerves are nasal mucosal lymphatics. It is quite likely that this relationship of the olfactory nerve sheath cuffs (ONSCs) with the nasal mucosal lymphatics (NML) provides an elegant junction, the olfactory nerve sheath cuff junction (ONSCJ) for which CSF has an evolutionarily-intended alternative drainage. Indeed, this route of flow has been worked out in detail in multiple animal models especially the rat (Figure 19) and it appears that the olfactory pathway is the main form of CSF drainage in this animal (173, 174, 176, 180-183) and in man (175). This pathway has been once again re-confirmed to be important in mammals (184).

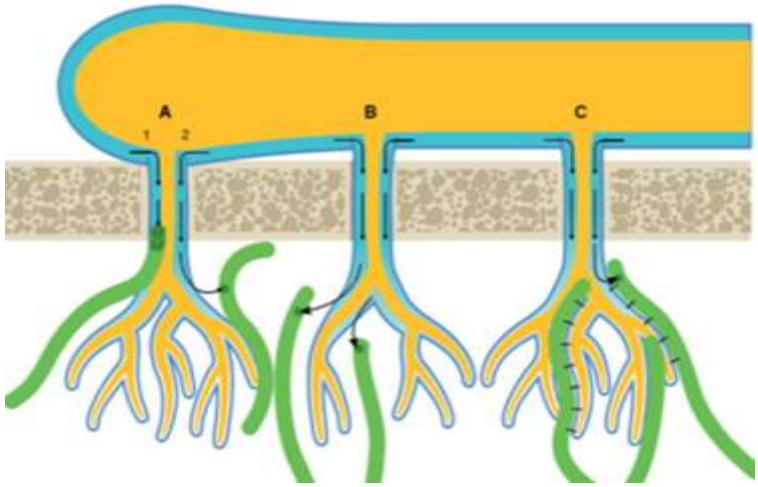


Figure 20: Three Theoretical Models for the Olfactory Nerve Sheath Cuff Junction:

*The diagram shows that distinct channels pass from the subarachnoid space (blue) through the cribriform plate within sheaths alongside olfactory nerves (yellow) to join lymphatics (green) in the nasal mucosa which are drained to the cervical lymph nodes (183). Three theoretical anatomical connections are proposed between the olfactory nerve and the nasal mucosal lymphatics. The first two have been proposed by Koh et al. (185) while we propose the third. In schematic A the lymphatics are connected directly with the CSF space such that the lymphatic vessels form a collar around the emerging olfactory nerve root with the lymphatic endothelium fusing to the perineural sheath of the nerve and the periosteum or dura associated with the cribriform plate. In effect, this lymphatic collar provides a 'seal' that ensures that little or no CSF enters the submucosal interstitium. In B, the lymphatics are not connected directly with the olfactory nerves or cribriform plate but are interspersed through the olfactory submucosa. In this proposal, CSF must convect first into the interstitium of the submucosa from which it is absorbed into blind-ending lymphatic vessels. (185). In C, we propose "**The Zipper Model**" whereby the lymphatic vessels are zippered tightly to the surface of the olfactory nerve sheath to facilitate transfer of CSF to the nasal lymphatics.*

The Olfactory Nerve Sheath Cuff and Junction

The olfactory nerve sheath ends in the olfactory nerve sheath cuff (ONSC) and aligns with the nasal mucosal lymphatics to form the olfactory nerve sheath cuff junction (ONSCJ). The ONSCJ has been postulated by others to be either 1) open at the end (Open Cuff Model) whereby the fluid drains freely into the sub-cribriform sinus mucosa and drained away by lymphatics interdigitated with the olfactory sensory nerves or they are 2)

closed at the end as a cul-de-sac (Closed Cuff Model) whereby CSF has direct access to the lymphatics through their direct fusion to the sheath (185) (Figures 20a and b). We propose a third model as per Figure 20c.

Our suspicion is that the ONSCJ is an elegant one-way valve interface between two connective tissues of the dural sheaths and lymphatic epithelia. These are likely to involve the same tight junction proteins that form other important connections allowing for tightly controlled fluid and nutrient passage such as that found in GI epithelium and in capillary beds including the blood brain barrier (186). These important tight junctions are made up of protein complexes called cadherins and integrins (187). We propose with our Zipper Model of ONSCJ that the OFNSC and the sinus lymphatics are "zipped together" with these same tight junctions. If this is the case, it would fit with the phenomena observed in other tissues with this patient population.

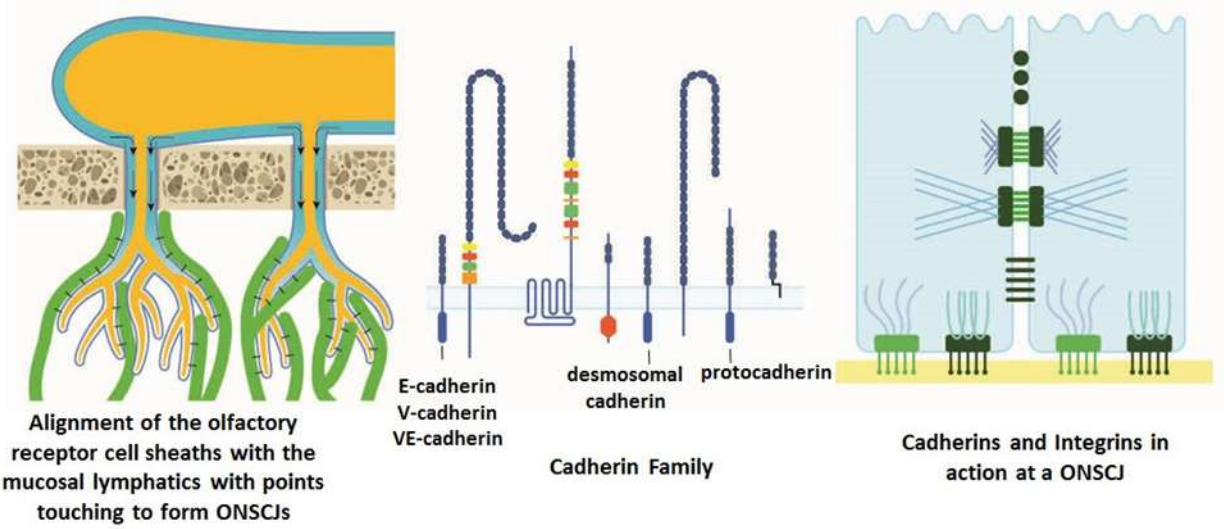


Figure 21: Olfactory Nerve Sheath Cuff Junction:

The Olfactory Nerve Sheath Cuff Junction (ONSCJ) is a theoretically-predicted delicate, sophisticated one-way valve that allows alternative drainage of CSF fluid under moderate pressure to transit from the olfactory nerve sheath to the nasal mucosal lymphatics which then drain into the jugular venous system (289). We further theorize that the lymphatics are "zippered" to the olfactory nerve sheaths by tight junctions similar to those in epithelial cells whereby cadherins form adherens junctions (290).

Specifically, the disruption of these junctions might be by the same mechanisms leading to the disruption of similar tight junctions in other tissues in patients with hEDS and MCAS (188, 189) (Figure 21).

By any of the models proposed, the system works to drain CSF sufficiently so as to prevent the formation of

papilledema at the end of the nearby optic nerves. This mechanism of the ONSCJ may be able to explain why the optic nerves are spared in the condition of idiopathic intracranial hypertension without papilledema (IIHWOP) (190). We suggest that if pressure pops off in the nasal mucosa below the level required for optic nerve-end swelling to occur, papilledema will not form. Therefore, papilledema development is dependent upon the function of the ONSCJ. We demonstrate the fluid mechanics of this in a Fluid-Pressure Schematic in Figure 22.

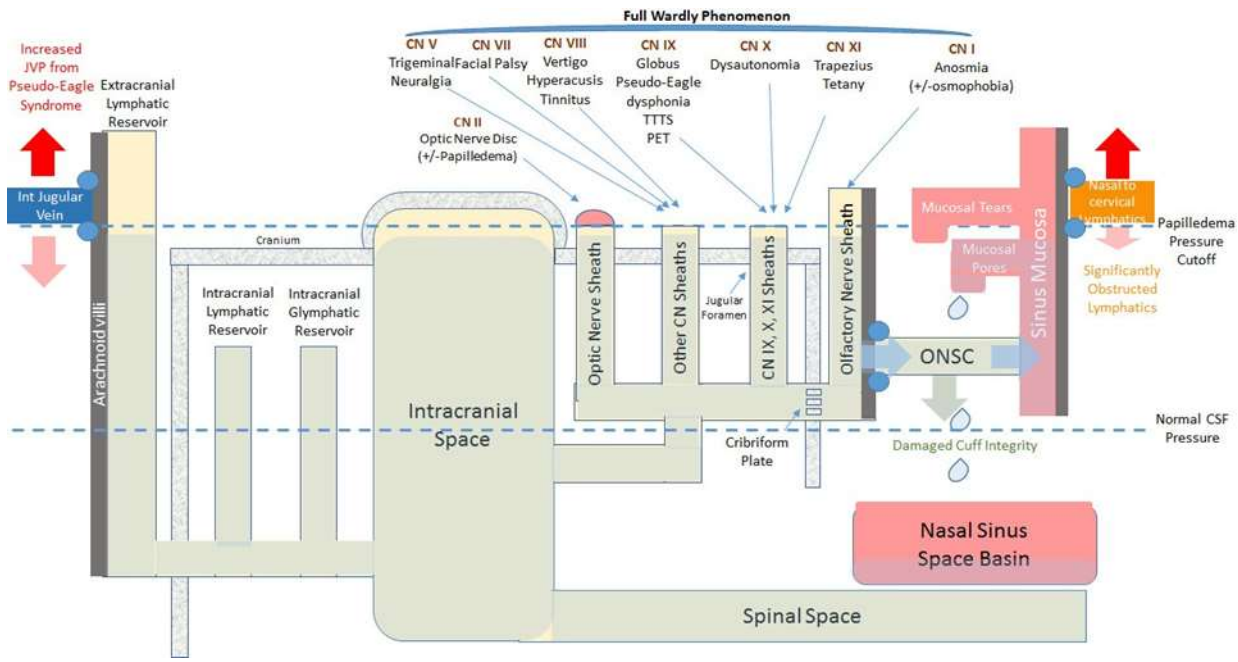


Figure 22: Significantly increased CSF pressure without papilledema and with onset of CSF leak:

Fluid-Pressure Schematic showing the components of the CSF fluid spaces and potential spaces important in Spiky Leaky Syndrome. In this schematic, there is CSF displacement by increased CBF from cerebral vasodilation in response to hypercarbia. Eagle Space compression of the IJV causes significantly elevated JVP causing CSF pressure to rise and displace into multiple CN and spinal nerve sheaths. As it displaces into the sheaths of CN I and II it hits a pop-off pressure at the alternate drainage route via ONSC. This may often occur before CSF fills the posterior retina which otherwise would have resulted in papilledema. This may be the mechanism behind IIHWOP. CSF drainage via ONSCs into nasal submucosa is then not successfully drained via lymphatics into the jugular vein because of the same Eagle Space compression. Thus, the nasal mucosa lymphatics fill with CSF (boggy sinuses) and begin to weep through pores into nasal sinus spaces leading to a CSF leak not detectable by conventional means.. ONSC; olfactory nerve sheath

cuff, JPV: jugular venous pressure, CLP: cervical lymphatic pressure.

Spiky-Leaky Syndrome, Hypermobility, and MCAS Connections

It seems odd to be describing such a phenomenon as spikes in intracranial pressure occurring during sleep followed by leaking of CSF from the nasal passages and ear canals. One might expect that this would be common in patients with both OSA and any jugular compression, and that this would be a well-known occurrence in the medical world. We strongly suspect that it will turn out to be a common phenomenon once this is recognized and it may very well explain the existence of IIHWOP as well as perhaps ME/CFS, certain subsets of dysautonomia, a subset of fibromyalgia, and some cases of occult tethered cord.

However, there is a proposed important caveat to this syndrome and that is that the ONSCJ may need to be compromised to make it leakier than intended in order to produce SLS. This is where the complications of hypermobility syndromes and MCAS come into play. Patients with hEDS often have underlying variations in connective tissue proteins (either genetically determined, or through post-processing of connective tissue proteins (191). Of the 206 patients in our recently analyzed series with Pentad findings, 120 underwent genetic analysis. Of these 120 patients, 3 have JUP variants and 10 have TNXB variants that are predicted to be pathologic by protein modelling. Of the 30 patients with suspected SLS, 25 have undergone whole exome and mitochondrial sequencing. Twenty of these have suspicious genetic variants. 11 have suspicious variant in genes of connective tissue (COL5A1 (x2), COL6A3, COL12A1, FBN1, FBN2, FBLN5, ADAMTS2, MYPN, FLG, and TNXB (x4). Indeed, 4 patients with suspected SLS have TNXB variants and 2 of these are compound heterozygous for TNXB variants. Five patients suspected of SLS have suspicious variants for autoinflammatory illness that might predict them being “obligate MCAS” patients. These variants include the common variant of TNFRSF1A causing TNFα receptor-associated periodic syndrome (TRAPS) (192, 193), a variant in IL10RA (encoding for the IL-10 receptor alpha chain) and a variant in MVK (encoding for mevalonate kinase) both belonging to the family of hereditary autoinflammatory syndromes otherwise known as inflammasomopathies (194-196), and PLCG2 which encodes for phospholipase C-gamma$_2$, a signaling molecule expressed in mast cells and other immune cells, variants of which cause Familial Cold Autoinflammatory Syndrome 3 (197). Three of these patients also have a variant in connective tissue as described above.

A few particular proteins of interest in these patients is plakoglobin encoded by JUP, tenascin-X encoded by

TNBX, and collagen type XII encoded by COL12A1. Plakoglobin is an important protein within or interacting with cadherin complexes and its alteration may make the cadherin weak and/or more susceptible to degradation by mast cell activity (198-200). Tenascin-X has multiple functions. One is structural whereby it holds together collagen fibrils, specifically type XII encoded by COL5A1, in such a way that it regulates the spacing and cohesiveness between collagen fibrils and other extracellular matrix components. It also anchors fibrils to cell surfaces. It also has a regulatory role in determining epithelial cell plasticity by localizing and delocalizing e-cadherins and actin within adheren junctions (201). It is compelling to consider whether the spacing of fibers making up connective tissue determines the ability of environmental toxins to penetrate tissues and which, in turn, may affect how mast cell behavior is able to alter that tissue.

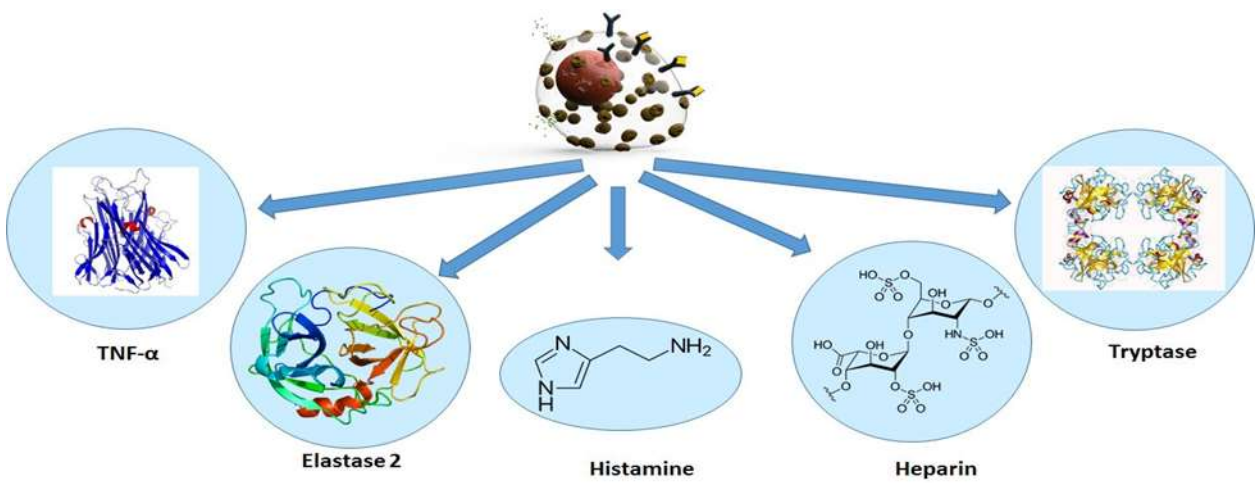


Figure 23: Better Known Factors Released by Mast Cells in Mast Cell Activation Syndrome

Patients with MCAS likely have compromise of the ONSCJ with or without a connective tissue disorder. Mast cells secrete many substances (Figure 23), but perhaps one of the most interesting ones is elastase-2 and that is because it selectively cleaves cadherin and integrins (123, 189, 202). Histamine has also been shown to promote degradation of connective tissue components (203). Alternatively, mast cells alter interleukins 4 and 5 (IL4, IL5), and tumor necrosis factor-alpha (TNFα) levels which have been shown to decrease expression of cadherins (204).

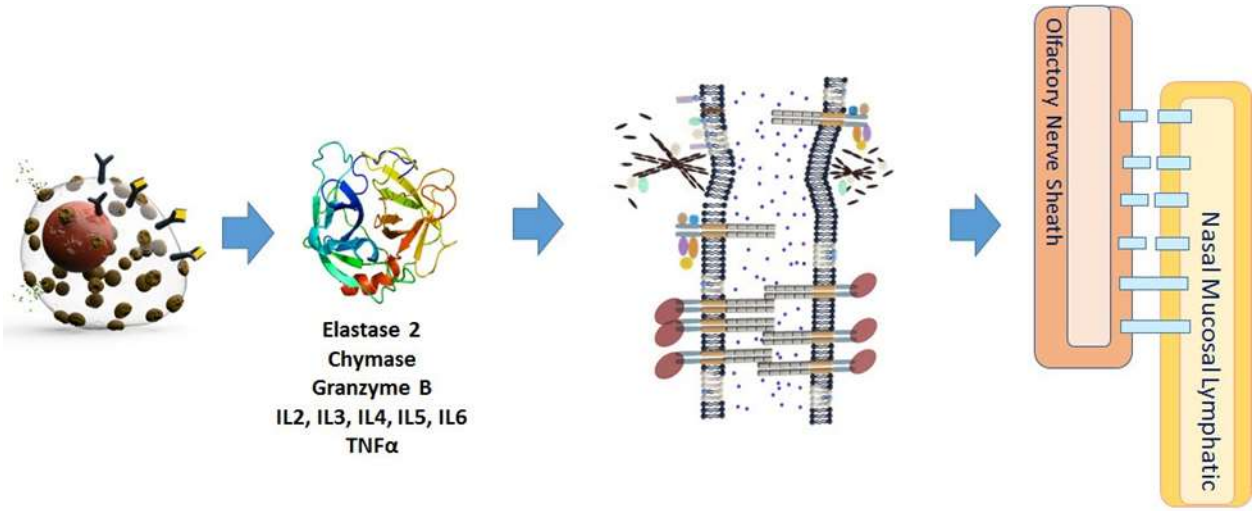


Figure 24: Destruction of the Olfactory Nerve Sheath Cuff Junction

The Hypermobility Syndromes Connection: The Olfactory Nerve Sheath Cuff Junction theoretically can be genetically compromised by variants in such genes as JUP encoding for plakoglobin, an important protein within the cadherin complex (291).

The MCAS Connection: Alternatively, or in addition, uncontrolled mast cell secretion of enzymes elastase-2, chymase and granzyme B and factors including interleukins 2 through 6, and TNFα directed specifically at cadherins and integrins may further disrupt ONSC integrity (188, 189, 204, 292).

We have observed the signs and symptoms of SLS to be prevalent in the hEDS/MCAS population. These details about the ONSCJ being subject to alterations by elastase-2 might explain why SLS would be more common in this population and perhaps less so in others (Figure 24). In any case, there is likely a threshold beyond which the ONSCJs open the floodgates and CSF drains into the nasal mucosa lymphatics (NMLs). There is probably a drainage capacity under which the drainage proceeds in an orderly fashion and CSF is successfully drained away to the cervical lymph nodes and beyond. However, there is may then be a breaking point in the system where CSF fluid pressure and flow cannot be drained away by the lymphatics to accommodate this route of CSF flow. CSF pressure and flow may exceed this drainage capacity and, at that point, either the cul-de-sacs rupture releasing CSF which overwhelms the lymphatics or the lymphatics themselves back up with CSF and finally rupture. The capacity is likely reduced by compression of cervical lymphatics by the same forces that compress the jugular vein (the displaced TMJ, cervical spine, lax ligaments in the Eagle Space, etc.). At this point, CSF simply leaks into the tissues of the nasal mucosa and bogs down

there. By whatever means, if drainage of the NMLs is not sufficient, then fluid might accumulate in the nasal mucosa and create the bogginess and fullness that patients often describe upon waking. Furthermore, should the fluid collection in the nasal mucosa progress, it is plausible that there is a point where the fluid weeps through mucosal pores or even ruptures into the sinus cavities themselves and this may be further facilitated by an MCAS-mediated breakdown of nasal sinus epithelium (205). The end result is the collection of CSF fluid in the sinus cavities and temporary intracranial hypotension.

In the morning, the patient has a bad headache while still lying in bed but arises to an even worse headache consistent with a CSF leak. A common complaint is that they then lean forward and then straighten up again, a salty clear fluid ejects from their nose and ear canals. Thus, the term, "The Spiky Leaky Syndrome" whereby patients have signs and symptoms of both increased ICP and decreased ICP with CSF leak. This mechanism possibly explains why it is notoriously difficult to find a suspected CSF leak when the MRI and myelogram fail to show it.

This mechanism may also explain the phenomenon of having either or alternating of both anosmia with extreme olfactory hypersensitivity. The anosmia may result when the olfactory nerve sheaths are under pressure filled with CSF and the hypersensitivity may occur due to injury of the ONSC and ONSCJ thereby inappropriately exposing olfactory sensory nerves. Both the loss of function and the hypersensitivity may fall under what we have termed Wardly Phenomenon because both are a result of this process of excess CSF drainage through the cranial nerves.

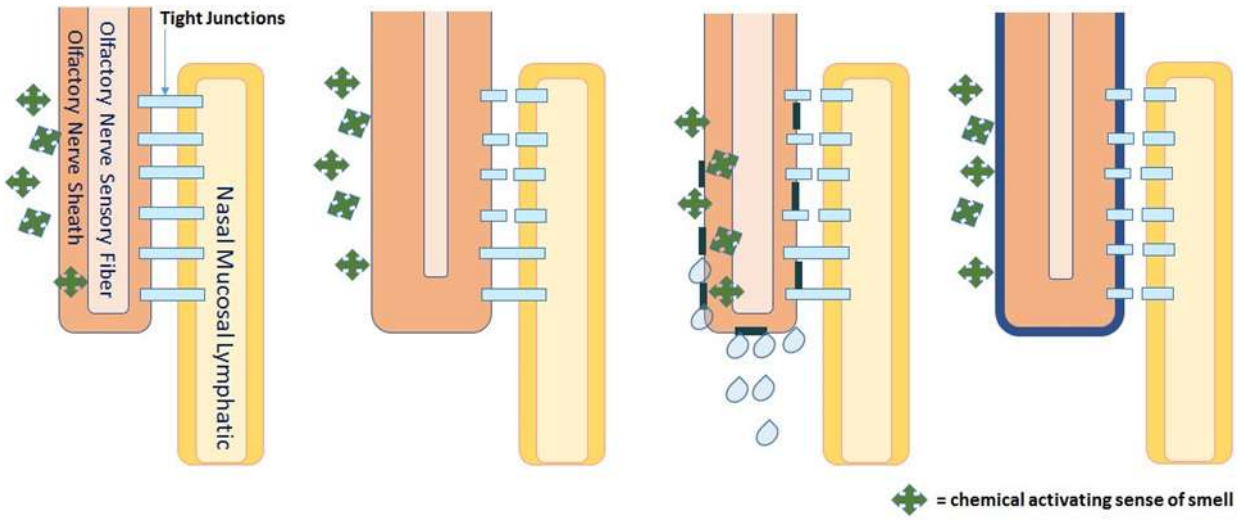


Figure 25: The four States of the Olfactory Nerve Cuff Junction:

1) *Normal Health with intact tight junctions allowing transfer of CSF to lymphatics at the appropriate 'pop-off' pressure*
2) *Partially impaired ONSCJ with elevated CSF pressure high within the ONSC causing ON compression with dysfunction and anosmia*
3) *Injured ONSC and ONSCJ allowing low pressure CSF leak and loss of protection leading to osmophobia.*
4) *Severely scarred ONSC and destroyed ONSCJ leading to lack of ability to 'pop-off' either by transfer or leak leading to chronic IIH*

It is likely that mixed states exist, notably 3 and 4, such that one has both IIH and osmophobia.

The Clinical States of the Olfactory Nerve Sheath Junction

In fact, there might be 4 clinical states important with this model of the ONSCJ (Figure 25). The first is the state of normal health whereby there is a normal set-point for the 'pop-off' pressure of CSF into the nasal lymphatics that is created by healthy tight junctions. The second state is where the tight junctions might be partially impaired and CSF pressure builds somewhat inappropriately causing compression of the olfactory sensory nerve fiber leading to its dysfunction and anosmia as chemicals cannot penetrate the CSF-filled sheaths under pressure.

The third is the state whereby the dura of the sheath is ruptured allowing CSF to leak out even under low pressure ICP conditions causing CSF-leak type symptoms and also allowing chemicals taken into the sinus mucosa to have excessive access to the olfactory sensory nerve causing hyper-sensation of the nerve with osmophobia and multiple chemical sensitivity syndrome (MCSS). This effect may be further accentuated by a similar breakdown at the nasal sinus epithelium as shown in animal models *in vivo* and in human model *in vitro* by Kortekaas Krohn et al (205). Genetic variation in hEDS and MCAS may create or worsen this state.

The fourth state occurs after a trauma event. The most concerning among these are complications from turbinate-reduction surgery with or without septorhinoplasty. Perhaps the procedures lead to scarring of the nasal mucosal in this region with destruction of the tight junctions which then prevents the transfer of CSF to lymphatics but also prevents the back-up 'pop-off' of sheath rupture into the mucosa. This inability to pop-off CSF pressure and volume by two backup means sets up the situation for a chronic elevation in ICP with

chronic headaches and other dysfunctions typical of high ICP. There might also be a combination of these 4 states in a given individual. Some patients who have had nasal surgeries may show a lack of ability to pop-off pressure yet have scarring in such a way that osmophobia predominates, manifesting in a combination of states 3 and 4.

How relevant is CCI and therefore SLS to hEDS?

Hypermobile EDS experts believe that CCI is a rare cause of dysautonomia (206), however, we suspect it is currently under-appreciated and deserves critical investigation and patients deserve attentive evaluation. Indeed, in a recent study, patients with chronic fatigue syndrome where 55% of the study population were found to be hypermobile, 80% were found to have obstruction of the cerebrospinal canal, 56% were found to have low-lying cerebellar tonsils obstructing the foramen magnum, 83% were found to have subtle MRI findings consistent with increased intracranial pressure, with 32% having findings of more severe intracranial hypertension (164). In the corresponding author's population of patients with dysautonomia, 15% demonstrate at least the spiky portion of SLS.

Assessment of Leaking Fluid

We as well as other clinicians who have recognized and suspected the fluid draining from nose and ears as being CSF have tried to collect and analyze the fluid to prove it so. To date, our attempts to analyze fluid discharges for evidence of CSF have been negative and, to my knowledge, so have these other clinicians. Analysis of CSF is now mostly by measuring for the presence of beta-2 transferrin (B2T) and this is what returns negative when my patients send their collected fluid to the lab. We have considered reasons why this might be.

It seems pretty clear from the literature and from technical characteristics of the various assays for B2T, a negative result is not an assay performance deficit or a sample stability issue. The standard electrophoresis – immunofixation test looks to be highly sensitive and specific and Quest Laboratory catalog reports that the sample is stable up to 7 days even at room temperature (207, 208). ARUP catalog reports samples are stable up to 14 days at ambient temperatures (209). There is a point of care immuno-chromatographic assay test being developed which may provide even greater sensitivity and specificity and provide quick, bedside results

(210).

A 1993 “analysis of sources of error” of B2T testing reveals that patient-related factors might alter sensitivity (211). Antibiotic-protein conjugates might form and this would change electrophoretic properties. Therefore, the possibility remains that perhaps as the glycoprotein is passing through the various anatomy including diffusing through sinus tissue, it conjugates with something else and this changes its characteristics.

Having considered these other possibilities, we favor the idea that this particularly unique type of CSF leak allows for the B2T to be scrubbed entirely from fluid as it leaves the CNS, travels through the olfactory nerve sheath by an evolutionarily intended secondary route. Consider that there is a big difference between free-flowing CSF that leaks from traumatic, fistulous, or surgical drainage that is easily identified with a B2T assay and CSF that must pass through a series of non-traumatic otherwise normal anatomy. This includes passing through cranial nerve sheaths, across tight junctions into nasal sinus lymphatics, and then forced by hydrostatic pressure into and through sinus mucosa. We believe this is where the difference might lie.

B2T has been well-studied (212). It is also known as asialo-transferrin. Regular standard transferrin (Tf) in circulating serum is normally glycosylated and so is a sialo-Tf. The loss of the terminal glycoprotein changing it from a sialo-glycoprotein to an asialo-glycoprotein appear to be a signal of an aging serum component tagged for removal. Sialo-Tf circulating in serum that become asialo-Tf is quickly removed by asialoglycoprotein receptors (ASGP-R), also known as “Ashwell-Morell receptors” that are in high concentration in the liver (213, 214). For example, platelets have sialo-glycoproteins on their surface. As they age, these glycoproteins are modified to asialo-glycoproteins and the platelets are then removed by these hepatic ASGP-R. It is believed that this is why beta-2-transferrin is not found outside the CSF, because it is immediately and very efficiently removed by these ASGP-R – mostly in the liver. On the other hand, Beta-2 transferrin, produced in the CNS is believed to only exist in CSF because there are no ASGP-R in the CNS to remove it. ASGP-R are in highest concentration in hepatic cells but are now identified in human intestinal epithelium, human renal proximal tubular epithelium, peripheral blood monocytes, as well as in rat thyroid, and testis and epididymis (215-219).

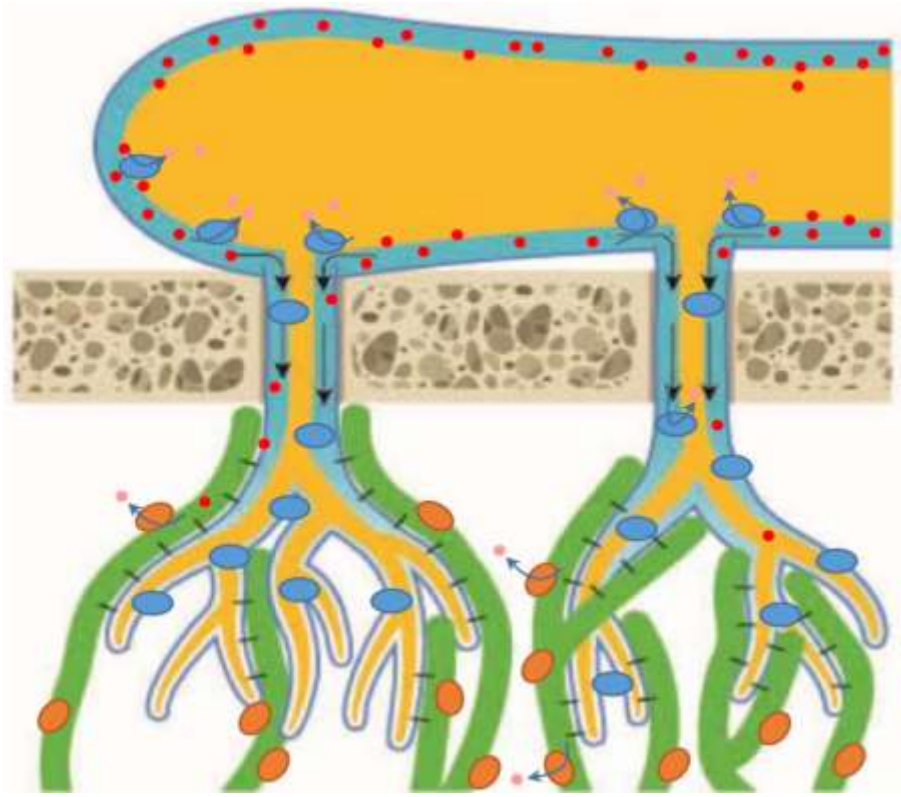


Figure 26: Scrubbing of beta-2 Transferrin at the Olfactory Nerve Sheath Cuff Junction:

Asialo-glycoprotein receptors ASGP-R (Ashwell-Morell receptors) quickly degrade beta-2 transferrin (B2T, asailo-tranferrin, red dots) to sialo-transferrin (pink dots). ASGP-R comes in two forms; ASGP-R1 (blue ovals) and ASGP-R2 (tan ovals). The olfactory tissue has the 5th highest expression of ASGP-R1 in the body while lymph tissue and nodes have the second highest expression of ASGP-R2 in the body (liver being first) (223-225, 227). Theoretically, the degradation results in leaked CSF being devoid of any detectable B2T.

RNA and Protein analysis informs us even more sensitively; There are two forms of ASGP-R 1 and 2 and these are coded by the genes ASGR1 and ASGR2 (220-222). ASGR1 protein expression has been detected in liver, stomach and gallbladder while ASGR2 protein expression has been detected in liver alone. However, tissue data for RNA expression obtained through Cap Analysis of Gene Expression (CAGE) generated by the FANTOM5 project as reported in The Human Protein Atlas lists the olfactory region as the 5th highest in ASGR1 RNA expression in the human body (223-226) while the lymph node as the second highest expression of ASGR2 RNA in the human body just after liver (223-225, 227).

Therefore, it is our contention that B2T is removed by ASGP-R1 in olfactory tissue and perhaps by local dendritic cells and monocytes and then further eradicated by ASGP-R2 in lymphatic tissue, and perhaps more B2T is cleared by monocytes that capture and endocytose any B2T attempting to leave the CNS by this route (Figure 26). Of course this removal is not possible in the context of a traumatic flood of tissue in the case of most standard CSF leaks which involve bony trauma or erosions. If our proposal is true, that a more subtle form of CSF leaking occurs from the olfactory nerve, then proof of this CSF leak route may require a novel radiographic approach or perhaps detection of some other marker specific to CSF which is not cleared by nasal and lymphatic tissue.

Consequences of This Theory and Hypothesis Testing

If Spiky-Leaky Syndrome is real, then:

- Studies to identify CCI would likely need to be designed to assess dynamic measures of BDI and BAI (with traction compared to without traction, supine compared to upright as examples) (87). These would likely be more fruitful compared to static single position imaging. The use of videofluoroscopy has allowed some providers to detect CCI with a high degree of diagnostic accuracy (88, 89) and Cone Beam Computerized Tomography appears promising. Additional elucidation of CCI might be accomplished by in vivo ultrasound imaging of the cervical spinal cord, C1 and C2 spinal nerve roots and subarachnoid space as described by Beland et al (42, 228).
- Studies to identify IIH or CSF leak of nearly any type during the awake state or in upright position are generally not helpful, including;
    - MRI supine or upright while awake
    - LP with opening pressure while awake or upright
    - Myelograms while awake or upright
    - Any CSF Leak evaluation not assessing leaks through CN cuffs and across cribriform plate
- Sleep studies that do not include certain measures are incomplete, including;
    - Failure to measure $TcCO_2$ (note that sleeping measures of ET CO2 are often unreliable (229))
    - Failure to identify mild hypoxia as abnormal

- Failure to test effect of BIPAP (not just CPAP. BIPAP allows for better CO_2 ventilation with hypopnea. CPAP might actually worsen CO_2 ventilation) (135)

- CSF Leak Patching will be useless and potentially harmful because these address spinal leaks and not leaks via the cranial nerves.
- Sinus surgery that disrupts sinus mucosa below cribriform plate may be harmful
- Orthodontic retractive procedures are harmful and to be avoided (230).

If Spiky-Leaky Syndrome is real, then:

- Sleep studies that include the following might be helpful in making such a diagnosis;
    - Continuous TcO2 and TcCO2 monitoring
    - Continuous intrathecal lumbar transduced pressure measurements
    - Continuous intracranial bolt transduced pressure measurements
    - FONAR MRI Cine Flow Studies http://www.fonar.com/csf-flow.htm
    - Contrast cisternograms
- Awake studies might be helpful in making such a diagnosis
    - Cervical MRI studies without and with head traction to assess CCI
    - Contrast-enhanced CT with Cone-Beam or multidetector scanner to assess CCJ
    - venous flow

If Spiky-Leaky Syndrome is real, then:

- Procedures to open airways are important (231-233)
    - CPAP likely to make situation worse (135, 234)
    - BIPAP may make situation better but not guaranteed

- Mandibular advancement devices, and most orthodontic devices that develop the mandible forwards might help but may also complicate the patient's airway in the long term by retracting the maxilla (230).
- Surgical maxillomandibular advancement may correct problem (234-237)
- Tongue retaining devices may help (238)
- Correction of restrictions in tongue mobility (functional ankyloglossia) via release of tongue ties (lingual frenectomy) may help (239-241)
- Orofacial myofunctional therapy (OMT) may be a very important therapy (232, 242-250) and this can be further assisted with oral devices (251) particularly non-removable or full-time functional appliances (252)

- Methods of opening Eagle Space are important
  - Correction and strengthening of TMJ is likely important and this can sometimes be accomplished by OMT (244, 253, 254)
  - Correction of CCI may be helpful depending on technique (109, 255)
  - Enhancement of head and neck lymphatic drainage
  - Stylohyoid ligament release might relieve internal jugular and lymphatic drainage (92, 108).
  - Stenting of the internal jugular vein and/or dural sinuses is another option although potentially fraught with stent complications (110, 256-258).
  - Removal of excess adipose and other soft tissues might be helpful
  - Attention to vertebral venous drainage system may also be important
- Methods of reducing CSF production, displacement and circulation are important
  - With regard to production, carbonic anhydrase inhibitors may be helpful at least in short term. Not only would they slow the production of CSF but perhaps more importantly they would keep blood pCO_2 levels lower regardless of ventilation state thereby reducing nighttime vasodilation (259-261).
  - With regard to displacement, methods of reducing hypercarbia at night and possibly hypocarbia (hyperventilation common in sympathetic overdrive or anxiety states) in the daytime. Strategies

such as biofeedback would be ineffective (given that 2 very powerful physiologic forces are working against the attempts at conscious manipulation, the first is the original sympathetic overdrive that caused the hyperventilation and the second is the blood pH which was corrected to normal via retention of acid by the kidneys) but sympathetic blockade as well as enhancement of parasympathetic activity would be helpful.

    - With regard to circulation, relieving the venous backpressure on arachnoid villi function is discussed above in methods to open the Eagle Space and JVP.

- Methods of early intervention would be ideal
- Avoidance or removal of environmental triggers
- Treatment of MCAS with anti-mast cell medications and supplements
- Potential treatment of hEDS both in onset (elastase 2 inhibitors? (262-264)), and with physical therapy of CCI directed at strengthening cervical ligaments and supporting muscles and fascia.
- Treatment of craniofacial issues in children early via tonsillectomy/ adenoidectomy, expansive orthodontia, and myofunctional therapy as discussed above.

Putting it All Together to Explain an Epidemic

Given the large numbers of patients we have in the corresponding author's clinic with what appears to be this syndrome, we are inclined to consider whether there is some sort of 'epidemic' that has arisen that underlies this issue. We also cannot help but take note of the potential relevance of patients very often also having a mast cell activation component in this disease which is often a phenomenon secondary to an environmental exposure. We also notice a geographical distribution and that often these patients have testing that is positive for mold and other environmental toxins. All of this raises suspicion about an underlying origin beginning with an environmental exposure producing an activation of mast cells. The initial triggering of mast cells by an environmental toxin seems to alter mast cells in a way that they become activated to many more triggers, some being common substances in foods, environment and drugs. This broadening of the triggers of mast cell activation is a phenomenon known as toxicant-induced loss of tolerance (TILT) and may explain why these patients seem to become sensitive to more and more substances over time and continue to react even when the original environmental toxin has been removed (265, 266). Chronic activation of mast cells causes a

breakdown of connective tissues in a particularly vulnerable host to create a ‘metabolic hypermobility syndrome’ or ‘metabolic hypermobile EDS’ patient. These patients go on to develop hypopnea, CCI, and Pseudo-Eagle syndrome which then progresses to the development of Spiky-Leaky Syndrome. In contemplation of such an environmental exposure, we have considered multiple potential etiologies relevant to this relatively newly encroached-upon farm and delta waters region and have left the details of such an exposure to another theoretical paper.

While our epidemiologic data compel us to believe there is an environmental driver, it is also possible that non-environmental triggers can initiate and perpetuate the chain of events that lead to SLS. Primary MCAS might certainly be enough to initiate and perpetuate an inflammatory state causing connective tissue breakdown. So too might conditions that active mast cells. Hypoxia alone may active mast cells (267). Psychological stress has been implicated as well (268, 269) and that may include the stress caused by not being able to breath adequately while sleeping, thus, hypopnea might activate mast cells driving the phenomena leading to SLS. UARS can also directly cause dysautonomia (136) making it a potential etiology driving SLS in multiple ways. This may explain cases of SLS when there is little evidence for any environmental exposure.

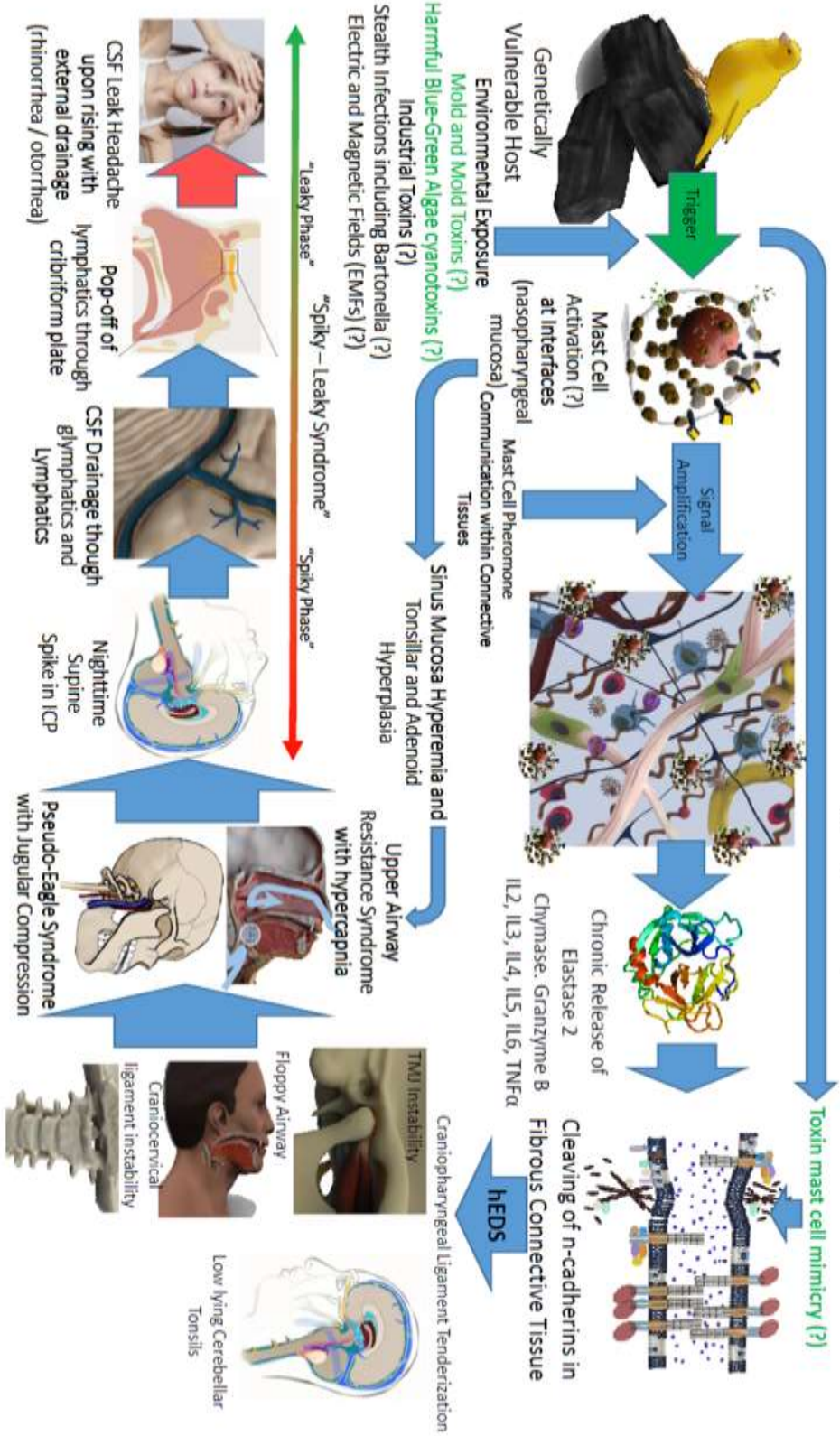


Figure 27: From Environmental Toxin to Spiky-Leak

Theoretically, a genetically-vulnerable host (the canary in the coal mine) with perhaps a connective tissue gene variant that makes the host more susceptible to permeation by environmental toxins or more susceptible to tissue breakdown, or more susceptible to activation of mast cells, has a chronic exposure to an environmental toxin such as a mold toxin or cyanotoxin which potentially activates mast cells. In doing so, mast cells release elastase-2 and potentially other proteases such as chymase and granzyme B as well as interleukins 2 through 6, and TNFα causing the destruction of connective tissue and creation of a "metabolic hypermobile Ehlers Danlos" patient. We also do not discount the possibility that certain toxins might mimic mast cell activation by downregulating cadherins directly (293). The individual is now prone to UARS, Pseudo-Eagle syndrome, CCI, and sensitivity to hypercarbia which becomes a set-up for Spiky-Leaky Syndrome. This provides an explanation for an epidemic of this phenomenon.

Conclusion:

In this paper we describe a set of theories that we believe are reasonable explanations in bulk and well-supported by the literature for the large population of patients we have been evaluating and managing. The sets of theories, summarized in Figure 27, are broken into 2 parts.

This theoretical paper focuses on the first part which is a set of theories that explains the wide range of neuro-cardiovascular, gastrointestinal, inflammatory, and musculoskeletal symptoms as well as disease progression these patients experience with particular attention to the development of CCI, hypopnea, dysautonomia, IIH, and CSF leak. We explain the well-described associations of MCAS and hypermobility syndromes as being particularly integral parts of the pathophysiology of what is fully Spiky-Leaky Syndrome. We conclude this part with predictions of various clinical states, with potential methods to test the hypotheses, and potential management strategies and treatment pitfalls.

A set of theories that explain why we believe there is a large population in our practice that have this condition is the subject of a separate theoretical paper. The geographical distribution and the associations of family members being affected (both genetic and environmental) as well as neighbors (environmental) raises the concern for a biotoxin-mediated process.

This is not to say that the SLS pathophysiology cannot occur independent of an environmental exposure. Indeed, psychological stress, hypoxia, airway limitation, and primary mast cell activation by themselves can

lead to dysautonomia and MCAS and so the chain of events can be perpetuated in anyone who has these conditions chronically. It is quite likely that some of our patients fall into this latter category. It is also likely that the environmental triggers are any number of substances and perhaps even multiple toxins affecting any given patient.

We present the two sets of theories together in 2 separate papers because it is hard to understand how SLS might have gone unnoticed until now, that perhaps it has taken an epidemic of such patients to put these pieces of the puzzle together and that epidemic requires some sort of explanation as well for the entire phenomenon to be better understood. Indeed, we are pleased to see a very recent description of what appears to be this patient population characterized in similar detail (270). In any event, these sets of theories provide a very large springboard for further investigation in many medical and bioenvironmental disciplines.

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Ethics Approval and Consent to Participate: Any original data presented in this manuscript was by chart review of corresponding author's practice and was exempted by an independent institutional review board (Ethical and Independent Review Services) due to its retrospective nature and informed consent was obtained as part of standard patient enrollment into the practice implicit to quality review of clinical practices.

Consent for Publication: No identifiable individual details, images or videos are included.

Availability of Data and Materials: The corresponding author has full access to all the data in the study and takes responsibility for its integrity and the data analysis. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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