5. Dysautonomia – A co-morbidity or consequence of craniocervical instability and ventral brainstorm compression?

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Dysautonomia is a subject in which neurosurgeons have not dwelt. However, as craniocervical disorders have drawn more attention in recent years, especially in patients with connective tissue disorders, we're appreciating a greater number of problems are manifestations of dysautonomia, which beg the question as to causality or co-aggregation. And so I think Dr. Batzdorf asked me earlier to prepare a talk on the relationship between dysautonomia and brainstem disorders. In particular, does brainstem compression cause dysautonomia? (**Fig 1**)

From the outset, it is important to state that dysautonomia, or dysfunction of the autonomic nervous system, derives from all parts of the nervous system, so that the influence of the craniocervical junction should not be overestimated.

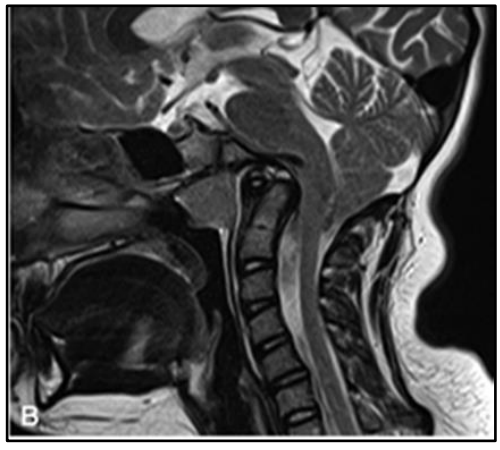

Figure 1 - Sagittal T2 weighted MRI demonstrating severe brainstem deformity as a result of a kyphotic clivo-axial angle.

It's a stratified, ubiquitous problem, and it's very complex. The autonomic nervous system was discovered in 1898 by Langley, who subsequently defined the three components: sympathetic, parasympathetic and enteric. Shortly later adrenaline was discovered, and it was then determined that adrenaline was actually a chemical mediator. Acetylcholine was then discovered, and over the last 50 years many more have been discovered -- peptidergic, glutamate, nitrous oxide and other compounds- that serve as mediators for the autonomic nervous system.

The standard doctrine shows the autonomic nervous system, as descending trunks. The sympathetics, descend through the intermediolateral cell column, exit through the spine from T1 to T12, and affect organs throughout the body. The craniosacral parasympathetic system, which exists in the cranial nerves and the sacral parasympathetic system, which governs the GI system from the splenic flexure down.

The sympathetic nervous intermediolateral cell column transmits through the spine as paired efferents rising and descending in the paravertebral spinal ganglia, the sympathetic trunks; and then as non-paired prevertebral ganglia in the celiac superior and inferior mesenteric ganglia. **(Fig 2)**

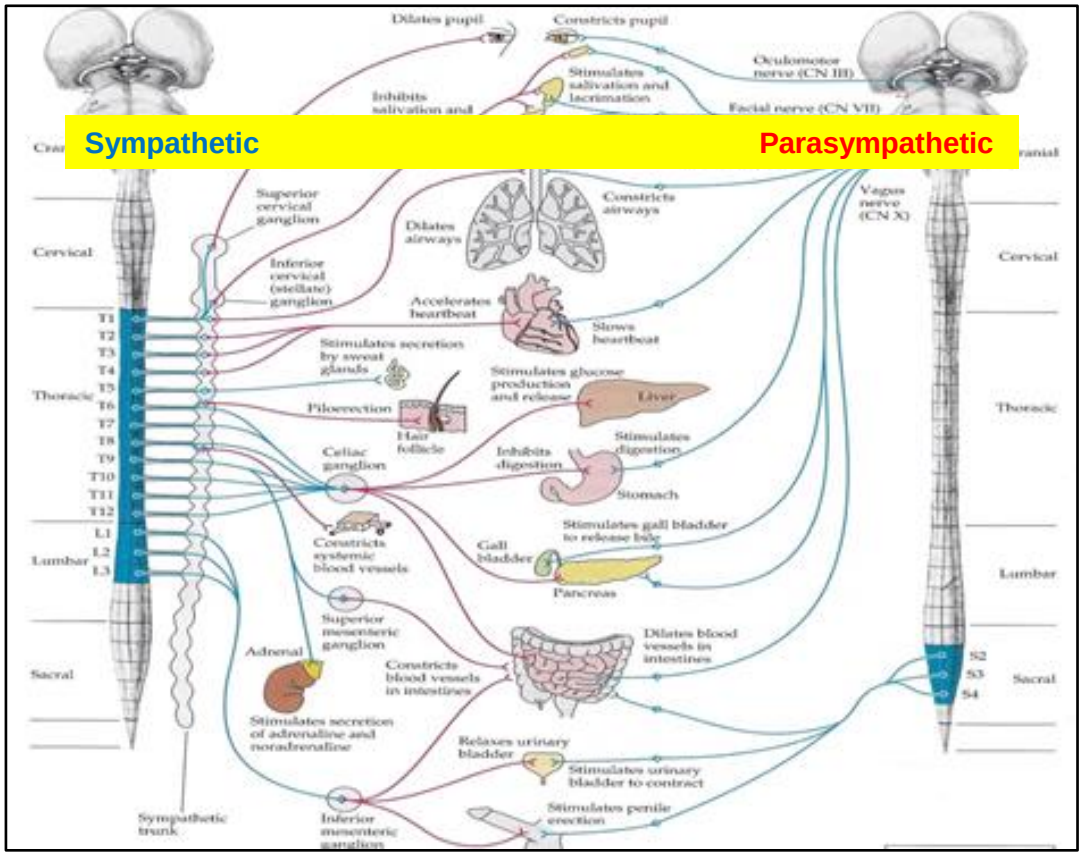

Figure 2 - The contribution of the sympathetic and the parasympathetic nervous system in the function of the organ systems of the body.

It is very important to recognize is that there are sensory fibers that ascend with the sympathetic system, and these sensory fibers are very important in terms of chronic pain syndromes. The craniosacral parasympathetic system: Cranial nerves III, VII, VIIII, and X and the sacral nuclei S2, 3, 4 in the dorsolateral cell column transmit postganglionic neurons that release acetylcholine, activating one of three known receptor subtypes, and very importantly, modulate other neurotransmitters.

So the autonomic control is very diverse, and I'm going to very briefly run through these or some of them. In the GI system cranial nerves V and VIIII stimulate the salivary glands. The vagus nerve stimulates gastric acid and pepsinogen secretion, secretion from the submucous plexus, secretory cells, the pancreatic acinar cells, and cholecystokinin to contract the bladder. Together with the sacral nerves, the vagus nerve modulates transmitters and peptides to control intrinsic muscles of the stomach and bowel. It's remarkable that the understanding of the autonomic nervous system, in terms of its function in the bowel is yet nascent. Generally speaking, however, the vagus nerve innervates down to the splenic flexure and the sacral parasympathetics from the splenic flexure down to the rectum, and may control peristalsis and motility; whereas, the sympathetic nerve maintains continence by contraction of the internal sphincter, and also serves to decrease the blood flow in the bowel.

The sympathetic nerves have other functions in the bowel that are not clearly characterized; so it's innervation of the bowel is more complex, and represents a balance of the sympathetics and parasympathetic nerves. The parasympathetics innervate the intrinsic muscles of the intestines – Auerbach's, Meissner's, and so on – seen on the right. (**Fig 3)**

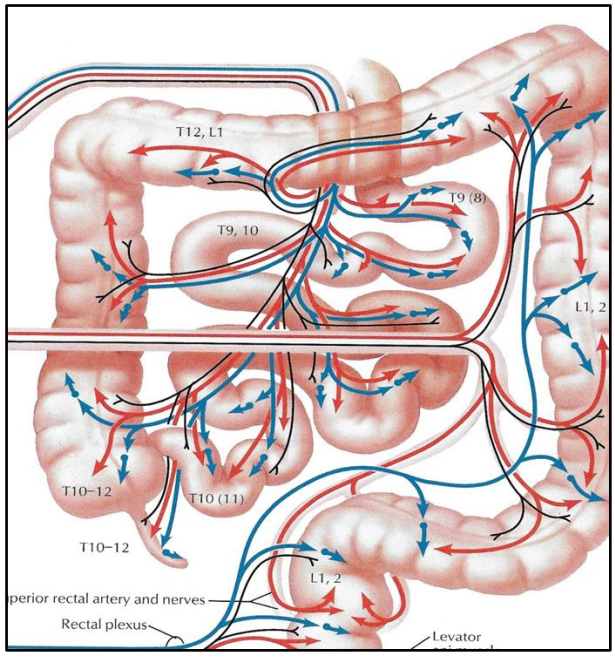

Figure 3 - The dual sympathetic (red) and parasympathetic (blue) innervation of the bowel. The Vagus innervates the bowel down to the splenic flexure, and the sacral plexus innervates from the splenic flexure down.

Blood pressure: The baroreceptor reflexes are all governed by the autonomic nervous system, which utilize the stretch-sensitive mechanoreceptors that maintain tonic activity in a split-second negative feedback loop to maintain blood pressure. These baroreceptors are located in the aortic arch, from which they travel in the vagus nerve; and, second, from the carotid artery they travel in the glossopharyngeal nerve to the Nucleus Solitarius and other parts of the brainstem. Thus an increased blood pressure causes increased firing at the nucleus solitarius, which excites – through glutamatergic neurons- the caudal ventrolateral thalamus, which elicit inhibitory GABAergic neurons (cf gamma-aminobutyric acid, the major inhibitory transmitter in the CNS), causing inhibition of the rostral ventrolateral thalamus. In turn, this inhibition results in decreased sympathetic activity in the preganglionic neurons of the intermedio-lateral tract of the spinal cord, and hence, through decreased sympathetic action, a decreased blood pressure. Increased blood pressure also stimulates the vagal nerve through reflex arcs to slow down cardiac pacemakers.

It is important to recognize that these baroreceptors are mechano-receptors in which that the presence of a viscoelastic coupling may be altered in subjects, diagnosed with hypermobility disorders. The consequences of this viscoelastic coupling are threefold: first, they have a rate sensitivity -- wherein the rate change is more rapid with a high firing rate, the faster the firing the faster the rate change. Second, the effect of adaptation results in a firing rate may be rapid initially, and then tail off. And third, the effect of hysteresis, such that the firing rates are higher with pressure increasing. Knocking out the baroreceptors results in sustained hypertension.

Blood pressure is also controlled through control of the kidneys. This is a negative feedback loop, similar to that just described with the baroreceptors. Decreased blood pressure results in decreased firing in the nucleus solitarius, decreased stimulation of the caudal ventrolateral thalamus, and decreased inhibition of the rostral ventrolateral thalamus. This decreased inhibition results in increased stimulation of the intermedio-lateral cell column fibers, which are in turn mediated through the splanchnic nerve and the aorticorenal ganglia, and finally the endpoint on the beta-1 receptors of the juxtaglomerular

cells. These beta -1 receptors have the effect of increasing renin, hence sodium chloride retention, and increased blood pressure.

Conversely, increased blood pressure has the opposite effect, as well through the nucleus solitarius, decreasing antidiuretic hormone. Thus, increased blood pressure causes increased blood flow to the kidneys and increased glomerular filtration rate.

Autonomic control effect cardiac function: Most cardiac control is exerted through the intrinsic Starling mechanism. Through the Starling mechanism, cardiac output can increase from 5 to 13 liters per minute. However, input from the sympathetics and parasympathetics, can increase cardiac output to 20 liters per minute. Sympathetic input is mediated through the thoracic sympathetic ganglia, especially T6, T7 levels, via the coronary arteries, which affect the sinoatrial and atrioventricular nodes and the myocardium. Norepinephrine affects alpha-1 inotropes- the alpha-1 receptors, exerting an inotropic and chronotropic effects. The beta-1 receptors have an inotropic effect, stimulating the cyclic AMP-dependent phosphorylation of the calcium channels to increase the inotropes.

Parasympathetics of the vagus enter through the neural plexus of the AV groove, affecting the SA and AV nodes, increasing sarcolemmal K, hyperpolarizing the membrane, therefore making it less excitable with the result of a decreasing the heart rate.

The autonomic nervous system also affects the cerebral circulation, notwithstanding the intrinsic mechanisms to be governed by low pH, metabolic needs, and altered blood flow.

There is also an extrinsic mechanism, the sympathetic nerves, which enter via the carotid artery, affecting the forebrain structures, and via the vertebrobasilar arteries, affecting the hindbrain structures. In addition, the nucleus ceruleus, and locus ceruleus can cause brain effects, constricting arteries, but also having a trophic influence on circulation.

The parasympathetics, mediated through the superior salivatory nucleus, cranial nerve VII and the sphenopalatine ganglion, tend to relax the blood vessels. And they work by peptidergic transmitters- acetylcholine, nitrous oxide (NO), and vaso-intestinal peptide (VIP).

Autonomic control of the airways involves the nucleus ambiguous and vagus nerve. The vagus nerve interacts with three receptors in the lungs, including alpha delta fibers that are very sensitive to smoke, histamine, serotonin; and the C fibers that conduct pain. Afferent C fibers (Vagal) can be stimulated by any noxious stimulant causing reflex constriction, mucous gland secretion, vasodilation, increased vascular permeability, leaky vessels, and increased muco-ciliary activity. Adrenergic tone, on the other hand, is regulated by circulating epinephrine, involving the secondary utilization of nitric oxide. **(Fig 4)**

Psychological responses, mediated through the locus ceruleus, can increase epinephrine, and amongst other changes, causing increased cardiac output, inhibition of digestion. It can also trigger mast cell degranulation, and Maitland will be talking more about that. The sympathetic nerves also cause pupillary (mydriatic) responses, hyperhidrosis, Raynaud's-like phenomenon, altered flow to the skin, and the chronic regional pain syndromes.

The causes of dysautonomia are complex and stratified. Stratified, because there is often more than one cause of dysautonomia. Dysautonomia can arise from hereditary conditions, autoimmune injury, fibromyalgia, poisoning, injuries, trauma, hypermobility connective tissue disorders, degenerative conditions, brainstem conditions and mitochondrial disorders. Indeed, one of the six-question test to predict whether a subject has a mitochondrial disorder is "Do you have palpitations?".

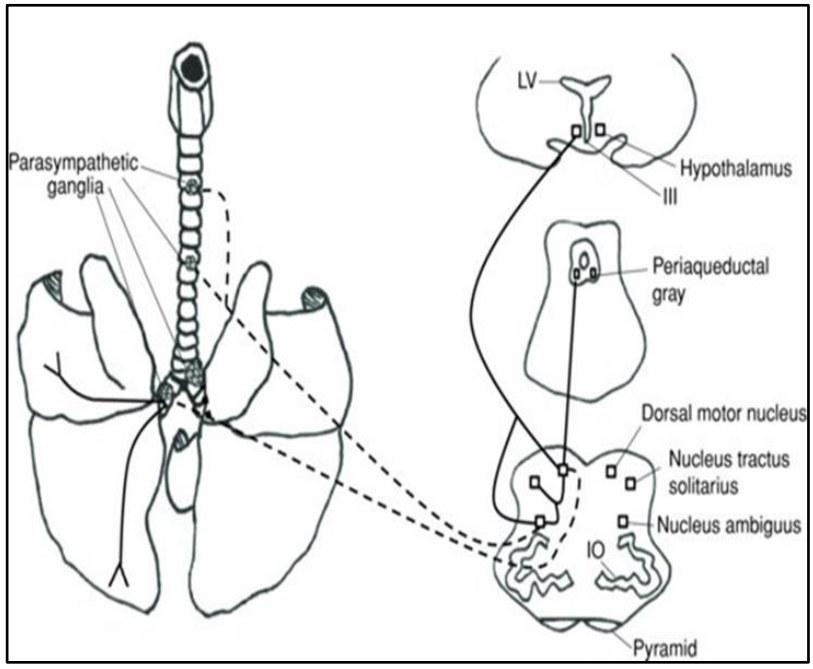

Figure 4 - The Nucleus ambiguus transmits Vagal efferents to M1 receptors in the parasympathetic ganglia of the airway wall. M3 receptors cause bronchoconstriction, and secretion by the mucosal glands through the mediator glutamate. AΔ delta fibers respond to smoke, histamine, serotonin. C fibers transmit painful stimuli.

Dysautonomia occurs commonly in children with developmental coordination disorders. Dysautonomia occurs not uncommonly in post-traumatic stress disorders. And is very common in subjects with ligamentous laxity syndromes, about which Dr. Rowe will be talking later today. **(Fig 5)**

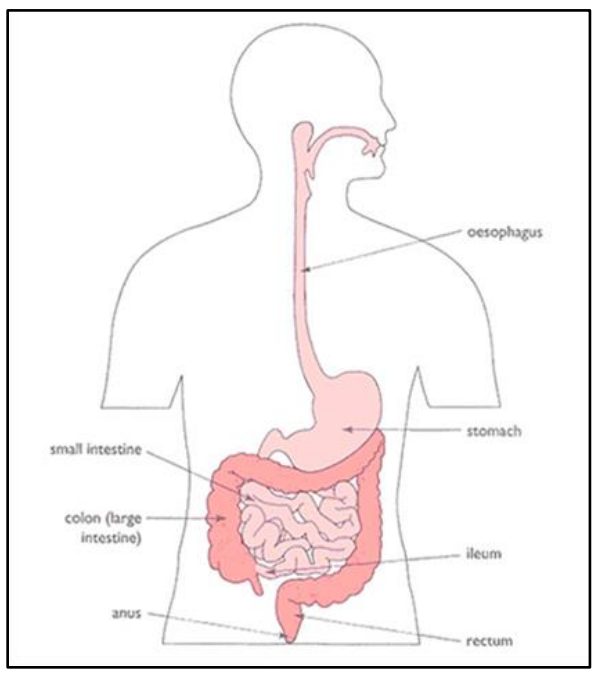

Figure 5 - Dysautonomia in the GI system results in dysphagia, gastric reflux, gastroparesis, malabsorption, bloating, constipation, irritable bowel syndrome, colitis and incontinence.

Dysautonomia may cause Syncope. The Framingham study showed that three percent of the population reported syncopal events, and a slightly higher percentage in women (3.5 percent of the women). This may be due to inappropriate activation of the cardio-inhibitory vasodepressor reflex or other causes of orthostatic hypotension, decreased cardiac output or increased resistance. Syncope is clearly a feature of hindbrain herniation with Syringomyelia and Arnold-Chiari malformation; and there have been many publications to that effect.[1,2,3] Sleep apnea, other breathing

disorders, and altered autonomic function are also clearly established as concomitants to brain stem deformity.[4,5,6,7,8,9,10] We showed, in ten patients with sleep apnea, that the apnea resolved after decompression of the brainstem by transoral odontoidectomy.[11] There is a great deal of literature that attributes the sleep apnea to basilar invagination.

Dr. Rowe, who is probably the world expert on these issues, will be discussing orthostatic intolerance, postural orthostatic tachycardia syndrome, and neutrally - mediated hypotension. Notwithstanding a dearth of evidence, there also appears a significant connection between the autonomic nervous system and mast cell activation.

While dysautonomia has many parts, there appears to be a significant contribution from the brainstem nuclei near to the to the craniocervical junction. For instance, the dorsal motor nucleus of the vagus, the nucleus and tractus solitarius and the nucleus ambiguus. It would seem, theoretically, that deformity of the cervicomedullary junction might, by deformation of the brainstem, alter autonomic activity.

Symptoms of dysautonomia are certainly seen in the Chiari population. The complex Chiari malformations may be burdened with ventral brainstem compression from basilar invagination or odontoid pannus, or platybasia, atlanto-occipital assimilation, atlas assimilation, and craniocervical instability.

The figure shows a patient who suffers a chronic injury to the brainstem from the odontoid pressing into the ventral aspect of the brainstem. This results from backward and forward translation of the skull over the spine. **(Fig 6)**

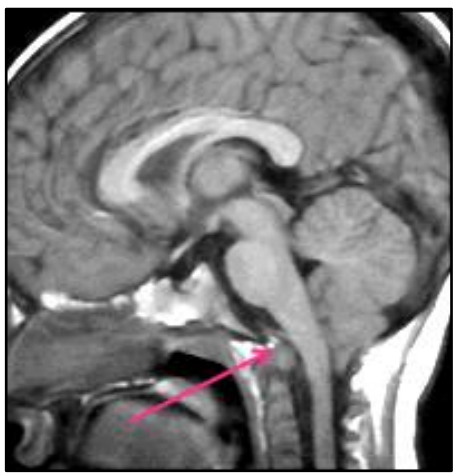

Figure 6 - The odontoid broaches Wackenheim's Line causing ventral brainstem compression. The Chiari malformation I causes some pressure behind the lower brainstem.

A generous sub occipital decompression OA Chiari malformation may relieve the compression posteriorly, but can exacerbate the craniocervical instability in a patient with a hypermobility connective tissue disorder, and thereby increase the degree of ventral brainstem compression.

Atlantoaxial instability may result in dysautonomia, manifesting as syncope. Atlantoaxial instability (AAI) is common in the connective tissue disorders, such as rheumatoid arthritis, systemic lupus; Down syndrome, ankylosing spondylitis, myxedema, and the skeletal dysplasia sand the hypermobility connective tissue disorders such as Ehlers-Danlos syndrome. (**Fig 7)**

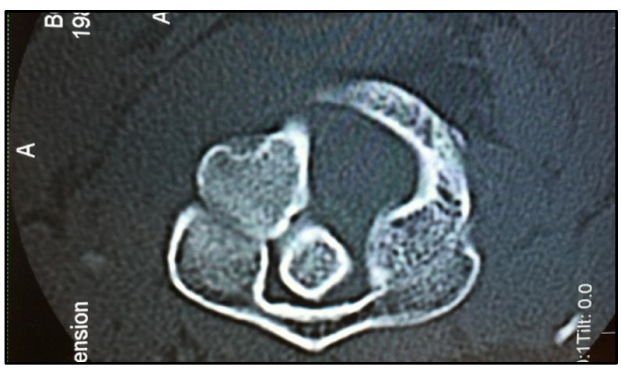

Figure 7 - This axial CT shows more than 44 degrees of rotation of C1 over C2, constituting pathological C1C2 rotary subluxation.

The association of dysautonomia with brainstem and upper spinal cord deformity begs the question as to the mechanism involved. How does deformation

of the neuraxis alter neurological function? The central nervous system is to some extent plastic, molding around any site of deformation.

However, the examination of cadaveric specimens of patients who died of basilar invagination, demonstrates the formation of axon retraction bulbs; and these are the pathological substrate of stretch myelopathy or deformity-induced injury.[12] **(Fig 8)**

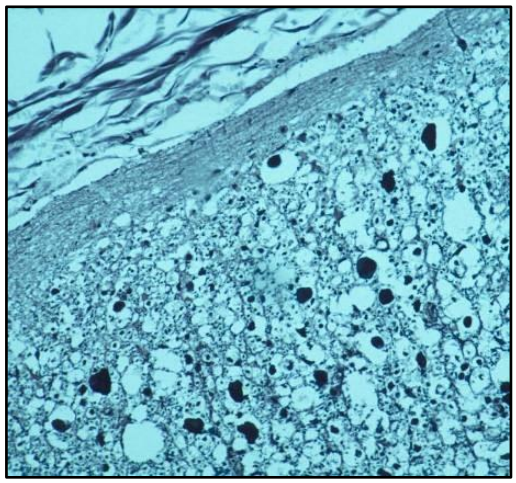

Figure 8 - The histological preparation shows the posterior tracts of the cervical cord of a cadaveric specimen of damaged spinal cord in the setting of basilar invagination: the silver staining shows axon retraction bulbs, which are thought to reflect stretch injury to the nerves.

Povlishok, Maxwell, and Jafari also showed that stretching neurons causes clumping of the neurofilaments- the architectural elements of the nerves- and of the microtubules- the pathways of micronutrients- resulting in the development of these axon retraction bulbs.[13] The same was shown by Saatman[14], who stretched optic nerves, and found the development of axon retraction bulbs that preceded further apoptotic changes. My colleague, Jennian Ford Geddes Montagu in Great Britain showed the presence of axon retraction bulbs in children with shaken baby syndrome.[15] (**Fig 9)**

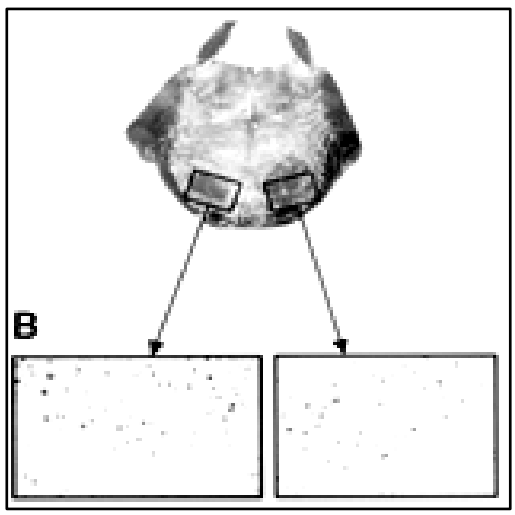

Figure 9 - An axial view through the lower pons with silver staining demonstrates the axon retraction bulbs, thought to result from a stretch deformation event.

Wolf showed that stretching nerves deforms the sodium channels, leading to an influx of sodium, depolarization of the voltage-gated calcium channels, and a pathological increase of calcium into the neurons.[16]

Arundine showed that stretching is an epigenetic stimulus, causing up-regulation of genetic expression, resulting in, for example, increased N-methyl-D-aspartate receptors. These neurons more sensitive, more vulnerable to free radical species, and nitrous oxides.[17] Thus deformative or stretch-induced injury is now becoming generally accepted as an important form of injury in the central nervous system.[18,19] We've certainly accepted the concept of stretch induced neural injury for many decades in the setting of tethered cord syndrome.

Thus stretch injury and deformation causes neural injury, spinal cord injury, and brainstem injury. But what evidence is there that this deformation alters autonomic nervous function? In a multi-disciplinary consensus statement in 2013, it was decided that the cervico-medullary syndrome occurs in association with craniocervical instability and basilar invagination.[20] Cervico-medullary syndrome is composed of many of the symptoms of which we discussed earlier in this presentation.

The importance of the kyphotic clivo-axial angle is being recognized by many authors. And in 2010 we published a work, performed mostly at Georgetown University Hospital, in which we correlated the predicted stresses induced by deformation of the brainstem due to a kyphotic clivo-axial angle. And we predicted these stresses using finite element analysis.[21]

In this study, a dynamic modeling that looked at aggregate strain and deformity and out-of-plane loading was used. It provided these axial images, which were color-coded for various levels of strain. So that orange strain is about 40 Newtons per square centimeter, a very, very high strain.

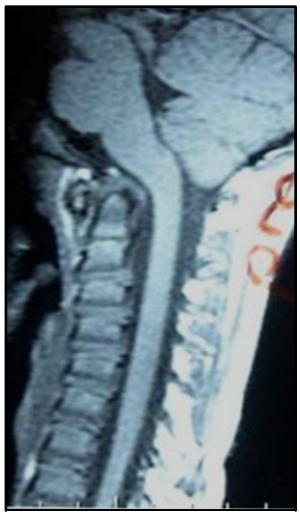

Figure 10a – mid sagittal T1 weighted MRI showing Chiari malformation, kyphotic clivo-axial angle with severe deformity of the brainstem in a young boy

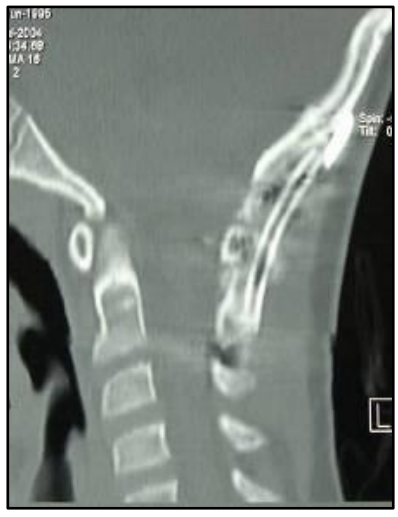

Figure 10b – postoperative, mid sagittal CT view showing correction of the clivo-axial angle and cranio-spinal alignment

So here's an example, a nine-year-old boy who had repeated cardiorespiratory arrests, unable to breathe out, weekly trips to the emergency room, sleep apnea, dysphagia, many neurologic deficits, a clivo-axial angle of 115 degrees. The stresses before surgery were calculated by the finite element analysis and are extremely high in the upper medulla, posteriorly- in excess of 60 newtons per square centimeter. After surgery the stress is decreased to less than ten newtons, shown in deep blue. (**Fig 10a, 10b, 10c, and 10d)**

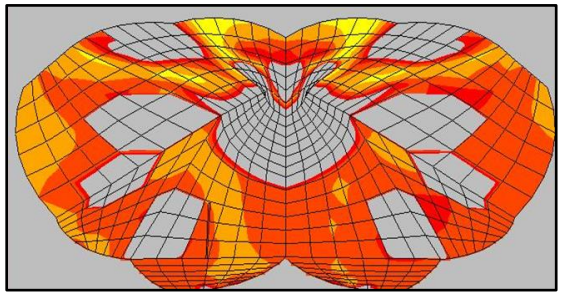

Figure 10c – finite element analysis showing a very high stresses in the lower brainstem pre-operatively.

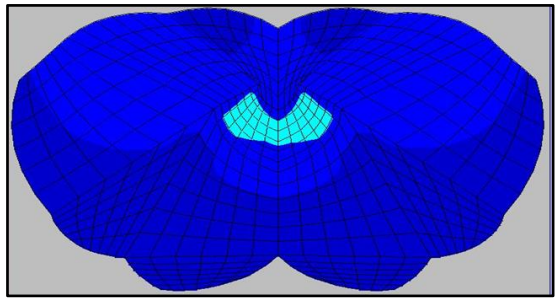

Figure 10d – normal stresses (0-5 Newtons) in the straightened cranio-cervical junction, post-operatively.

The improvement in stress after surgery correlated with the improvement in the clivo-axial angle, the resolution of the brainstem symptoms, improvement of Karnofsky and improvement of pain. This boy was playing sports, obtained his fly, and eventually earned a scholarship to study aerospace engineering. Examination of all ten of these children resulted in correlation of the predicted deformative stress in the brainstem with the clinical metrics. Correlation is not proof of causality. However, this data does suggest that removing the deformative stress from the brainstem improved the clinical performance. Examining the data on a more granular level, could specifically point toward the neural elements of the autonomic nervous system. For in-

stance, the nucleus solitaries, so important in the cardiac and carotid baroreceptor reflexes, exhibited very high strains before surgery and a significant decrease in strain after surgery. So that improvement in deformative stress correlated with the improvement in the many symptoms of brainstem. And these data were all statistically significant, despite the very small number of participants in the study of ten.[22]

In an unpublished study presented to the Army, adults with deformity of the brainstem and upper spinal cord were examined before and softer surgery. The calculated finite element analyses suggested the maximum predicted stress in the brainstem before surgery showed a statistically significant lessened after surgery to reduce and decompress the deformity. Thus mathematical predictions of stress, with finite element analysis, have demonstrated that straightening the brainstem and stabilized the craniocervical junction may decrease the calculated deformative stress of the CNS structures.

In another clinical study of 20 patients with hypermobility connective tissue disorders, we performed a reduction and fusion and stabilization for CCI and basilar invagination. The study is in preparation for publication. Some of the symptoms of dysautonomia were improved. These included fainting, swallowing. (**Fig 11)** Many symptoms were not reliably improved.

But of the patient symptoms pertaining to dysautonomia, there was improvement in only 33 percent of night awakenings, 20 percent of the sleep apnea, 38.5 % urinary frequency, 37% of Raynaud's–like symptoms (hands and feet turning cold in cold weather), 30% of gastro-esophageal reflux disorders (GERD) and 18% of irritable bowel syndrome.

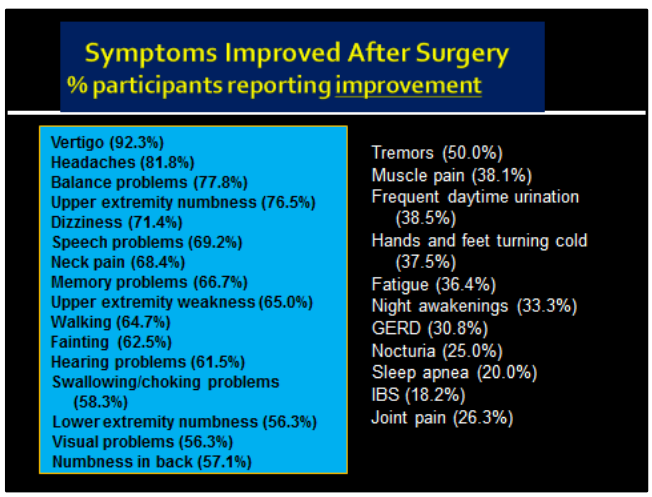

Figure 11 – Symptoms of dysautonomia following surgery

This data, therefore, suggests that all dysautonomia symptoms cannot be attributed to the brainstem. Another recent study suggests that in the population with hypermobility connective tissue the Ehlers-Danlos syndrome population that autonomic impairment is probably multifactorial, involving both the peripheral nerves and the sympathetic nerves.[23] The Ehlers Danlos syndrome population is reasonably representative of the hypermobility connective tissue population. In this population, patient subjects were found to have a higher resting sympathetic activity, but a decreased response to cardiovascular challenges, such as with Valsalva or tilt table or orthostatic response. For instance, the response to the tilt table shows a greater in blood pressure and a smaller, slower correction after the challenge. This suggests that there is impairment of vasoconstriction, and therefore of the sympathetic network.[24,25]

Postural orthostatic hypotension (POTS) appears to occur in 74% of the EDS population, and represents the most disabling manifestation of dysautonomia in EDS. In contrast to the impaired sympathetic nervous system, and its failure to mount an adequate vasoconstriction response to hypotension, there appears to be normal parasympathetic regulation.

The level at which the sympathetic incompetence occurs has not been demonstrated. Peripheral neuropathy has been implicated, and is supported by the prevalence of sensory neuropathic symptoms in these same patients. However, quantitative sudomotor axon reflex testing (QSART), which measures the post-ganglionic cholinergic activity of the skin in terms of sweating, has shown that one third of patients with sympathetic nervous system dysfunction have normal QSART testing. Others have suggested that increased distensability of the vasculature allows for greater vascular pooling during the upright posture. The notion that this collagen laxity in the vasculature underlies the POTS is supported by the finding that skin hyper extensibility is the most important predictor of sympathetic dysfunction.[26]

In conclusion, dysautonomia is common, especially in the hypermobility connective tissue disorders. It is reasonable to posit that dysautonomia may arise centrally in the brainstem, or in the sympathetic tracts of the spinal cord (the intermediolateral cell columns), in the spinal ganglia or in the peripheral nervous system. Anatomically the autonomic nervous system is ubiquitous, and manifestations of its incompetence should reasonably be expected to result from diverse anatomical and physiological conditions. While there is abundant clinical evidence that dysautonomia is associated with basilar invagination and other conditions of deformation of the brainstem, it is almost certainly the result of changes in the spinal cord and peripheral nervous system.

Discussion following presentation

UNKNOWN 1: That list, Fraser, how many of the total patients that you saw – I just needed the denominator.

DR. HENDERSON: I had showed you two studies. The first study was ten; the second was 20.

UNKNOWN 1: That shows us we've got our work to do with the database and stuff. I think it's really, really important. And every patient is an individual. For that denominator every patient denominator is one. But it's very hard to predict which ones are going to get better and when they're going to get better.

DR. HENDERSON: Right.

UNKNOWN 2: Thank you Fraser. You are saying that the fact that dysautonomia does not always improve might reflect its multifactorial origin.

But couldn't it be that it's just damage that's been done, and it's a sign of irreversible changes? And then the question is on top of neurofilament breakdown due to stresses, it could also be that there are some neuro-inflammatory changes.

I don't know what the literature you cited on the retraction bulbs. Had they also looked at microbial changes in the tissue?

DR. HENDERSON: No, they did not discuss the microbial changes, number one. And I think it is very multifactorial and it's very difficult when you pose these questions to the patients. Many of these symptoms reoccur but with less frequency and with less

severity; but they're still present, suggesting that maybe there was some damage, it may take many years for that damage to repair itself. But we have to look beyond the craniocervical junction for all the answers.

UNKNOWN 3: Fraser, this is out of my own ignorance about the finite element analysis. When you showed that effect in the nucleus tractus solitarius intrinsic in the brainstem and showed the high stresses, was that stress due to movement of the head? Or could the stress be just from the pulsations and cardiac pulsations? How is it related to motion?

DR. HENDERSON: We used a finite element program that predicted the stresses created by placing the cervical spine in full flexion. The value represents the relative stress as compared to the spine and craniocervical junction in the neutral position. The calculations did not take into account the smaller stresses, such as from pulsations.

UNKNOWN 4: Fraser, some 20-plus years ago the great physicist Roger Penrose wrote a wonderful book called "The Emperor's New Mind". And he takes all of us biologists to task for ignoring transient changes in membrane physiology related to stress.

And I think, only a comment, that as this proceeds, it's going to be very important to discover what's dynamic, and what's fixed, what's injury, and what is not, because I've always thought Dr. Penrose's criticism was well deserved, and very little has been done since he made it.

UNKONWN 5: Another possible variable complicating the Dysautonomia in general, is that many of these patients are hormonal imbalance. Hormones and the autonomic nervous system have a close regulation. The other thing is that maybe these patients are on medications that somehow do modulate function of the autonomic nervous system in general, and at least may affect other organ systems - for example, bronchospasm or vascular spasm of the heart.

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