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“Cervico-Medullary Syndrome: Observations & Questions”

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Thanks a lot for having me here. It is always not just an honor, but a real pleasure to get together with so many stimulating minds, especially when meeting about this topic for which we all have such a passion.

Cervicomedullary syndrome is a term that we all agreed upon two years ago when we had the second-to-last CSF Research Colloquium. It was one of the parts of the consensus. Today I am just going to make some observations, in a very free style of presentation, with some questions at the end. I also apologize because I am sleep-deprived, I slept about five hours in the last three nights; so I apologize for any potential incoherent blabbering I'm going to have. I have no disclosures.

The definition of cervicomedullary syndrome (CMS) is a clinical entity caused by the involvement of the lower brainstem and the upper spinal cord. That is the agreement that we had reached— very generic. There are a number of different pathologies that may cause it; pathologies that clinically affect the area of the cervicomedullary junction. So, for our group, obviously, our focus is more on Chiari malformation and craniocervical instability-related disorders. Obviously, many other pathologies in the same area can cause a similar kind of syndrome and symptomatic presentation.

We see updates every once in a while from Dr. Ashley-Koch at Duke and, as we heard this morning, their lab has recently shown that there is actually a difference at the genetic marker level between the patients with Chiari alone, and the patients with Chiari and Ehlers-Danlos syndrome (EDS)— the former set of patients being very close to the genetic phenotype of people with Klippel-Feil.

Comment [KE1]: REFERENCE

Is this the correct paper for this reference?

Markunas CA, Lock E, Soldano K, Cope H, et al. Identification of Chiari Type I Malformation subtypes using whole genome expression profiles and cranial base morphometrics. *BMC Med Genomics.* 2014 June 25;7:39. doi: 10.1186/1755-8794-7-39.

So Chiari, EDS, Klippel-Feil: they appear to have a common mesenchymal ancestry. So the next logical question is, since we very often find mast cell activation disorder and mitochondrial disorder in these patients and their children as well: are they coming along with the ride? Is there a similar mesenchymal ancestry there, too?

Pathophysiologically, what greatly concerns our group is more or less a compression/distortion game. Obviously, if you have an ischemic lesion,

inflammatory lesion, intrinsic tumor in the same cervicomedullary junction, you are going to end up having similar presentations.

But of the compression and distortion that characterizes this class of pathology or group of pathologies, the first and most popular is that of the mass effect exerted by the tonsillar herniation from posterior towards anterior on the cervicomedullary junction. I introduce another complicating factor as there may also a component of neurovascular compression.

Neurovascular compression has been something that has been talked over and over regarding the seventh cranial nerve. I wonder if the eleventh cranial nerve, the ninth, the tenth can also be affected in the case of the problematic small posterior fossa and any bulky tonsils.

The tonsils also can be symmetric— sometimes they are symmetric. They are triangular, they are rounded; and obviously, their mass effect is heavily influenced by their shape and lack of asymmetry.

Anteriorly, there is a Grabb measurement and clivo-axial angle (CXA) to further quantify our pathologies. The Grabb measurement appears to quantify the anterior mass effect from these structures, while the CXA better describes the angular distortion that these structures are exerting on the nervous system. This distortion can be static, dynamic, or combined.

Tonsillar herniation is then another problem per se. Many people who are obviously not in this room since it is comprised of mainly experts will equate tonsillar herniation automatically with Chiari I malformation. This is often the mistake of a newbie. A neophyte finds tonsillar herniation, thinks it is a Chiari, tackles it as a Chiari, and then many of the neurosurgeons in this room pick up the pieces.

So, once again, tonsillar herniation can come from many different causes. These causes were qualified by an article from Dr. Milhorat in 2010 on which Dr. Kula was a coauthor. Tonsillar herniation can be described in a very pedestrian way, as resulting from four mechanisms: pushing, pulling, dangling, and squeezing. The squeeze represents the small posterior fossa of the typical Chiari I malformation.

Comment [KE2]: REFERENCE

Is this the correct Milhorat paper?

Milhorat TH, Nishikawa M, Kula RW, Dlugacz YD. Mechanisms of cerebellar tonsil herniation in patients with Chiari malformations as guide to clinical management. *Acta Neurochir (Wien).* 2010 Jul; 152(7): 1117–1127. Published online 2010 May 4. doi: 10.1007/s00701-010-0636-3

The complex Chiari is a kind of new concept. There is this brainstem sandwich, where there is tonsillar herniation from behind and there is anterior pathology, dynamic and/or static, from the front. There is a medullary kink. And all these things are contributing to a specific modulation of the syndrome. So if the Chiari I compression comes mostly from behind, the complex Chiari has an anterior and a posterior component, which brings along with it a different modulation of the syndrome.

One thing that every now and then I have to remind myself is that even if there is a gravity component on the skeleton, the reality is that the cerebellum is not really affected by gravity in the same way as the skeleton. Number one, the cerebellum is suspended inside the dura, inside the cerebrospinal fluid; so there is a sort of buoyancy and floating component. The other thing to recall is that the cerebellum is attached to the brainstem by three solid peduncles and where one goes, also the others tend to go.

Also in the complex Chiari there is sometimes an even, or uneven balance between the anterior and the posterior compression. Recently there was a controversy stirred up by Dr. Goel who went on to say that, in his opinion, the Chiari I malformation was secondary to anterior pathologies, which were distorting the brainstem downwards and backwards.

Comment [KE3]: REFERENCE

Is this the correct reference for the Goel article you are talking about here?

Goel A. Is atlantoaxial instability the cause of Chiari malformation? Outcome analysis of 65 patients treated by atlantoaxial fixation. *J Neurosurg: Spine*. Feb 2015. 22(2): 116-127. Published online November 21, 2014; DOI: 10.3171/2014.10.SPINE14176.

No one in this room marries that conclusion, but indeed there are some forces from anterior and posterior that tend to get the cervicomedullary junction in the middle, no matter how we want to represent it terminologically.

From a symptomatological standpoint, there are multiple symptoms because it is a busy area. There are a bunch of cables, bunch of centers; so, obviously, there is not going to be just one function that is affected. Anterior pathology alone is going to create selective compression— well, not “selective” but predominant compression on the anterior centers, while the posterior pathology is going to affect something different.

At last year’s Colloquium, we discussed comorbidities of Chiari I malformation beyond Chiari I and EDS. So besides postural orthostatic tachycardia syndrome (POTS), pseudotumor cerebri and tethered cord, many of

us have had patients present with mast cell activation disorder or even mitochondrial disorders. So all these issues are found in these patients, and it is unclear if they present as accidental partners in crime, or intentional partners in crime.

I am now going to breakdown a few clinical concerns not so much to reinvent the wheel and explain them again, but just to show how all these issues linked together by the cervicomedullary syndrome umbrella may sometimes be confusing since there are many contradictory or compounding factors.

Headaches can have a positional component; okay, so far so good. Cranial settling and craniocervical instability are easy to understand. We heard this morning from Dr. Luciano and Dr. Rowe about intracranial hypotension and POTS, respectively.

There is also the problem with over-shunting. Some of these patients have pseudotumor, they have accumulated hydrocephalus or they have a complication from cerebrospinal fluid leakages. Many of the surgeons have hardware that have been invented and designed for hydrocephalus, and when they place the shunt in some of these patients, the shunt is really struggling out of its own element. The correction that the shunt is seeking to make is not exactly the purpose for which it was intended, so very often these patients are over-shunted.

Now, when you have a patient with positional headaches with the unfortunate luck of having all these four elements: EDS, some leakage from former lumbar punctures, cranial settling, some POTS elements because they're dysautonomic, and maybe they also have a shunt or they are over-shunted—where exactly do we as neurosurgeons begin to fix this patient?

In relation to cerebrospinal fluid pressure, again we have been previously taught with MRIs showing us the anterior and posterior blockage. I remember the first MRI that I ever saw as a resident was an MRI coming from UCLA. We were all envying Dr. Batzdorf, who was playing with such a wonderful toy. Seeing that blockage not only was the epitome of the phrase “seeing is believing,” but it also provided a better understanding at a visceral level.

Now, it is known that people with Chiari I malformation have problems with flow. Some of them also have cerebrospinal fluid pressure problems that may persist in the aftermath of the decompression.

Some patients have hydrocephalus as a cause of the tonsillar herniation. So in retrospect, that is not a pure Chiari. However, in other cases, a patient can have a Chiari which is so tight that it is compressing the fourth ventricle as you would expect to see in hydrocephalus. So you do not necessarily know which is the chicken and which is the egg.

In even further patients, there may be a presence of pseudotumor along with minimal rounded herniation in the presence of a normal posterior fossa. A newbie will go into surgery and say, "That is a Chiari; do the decompression." He ends up with a proverbial egg on the face because there is a leak. The surgeon will then have the belated knowledge that the patient had 70 cm of water or CSF and then a bunch of other re-operations on his hands.

Comment [KE4]: Is this correct? Does it need to be clarified, medically?

Other times, the patient has a leakage after decompression, an aseptic meningitis; and as a late aftermath of that, besides the pseudomeningocele, there can be a development of this pseudotumor or cerebral-like syndrome, in which the pressures are not up to 70 or 80, but the are about in the 30s. This syndrome which did not exist before can make the patient cranky but it may be ameliorated by serial taps and/or shunting.

Regarding cerebrospinal fluid pressure, we have accumulated some other observations over the years. For instance, some of these patients have abnormal compliance. Some patients have decreased reabsorption; we will incidentally find an increased pattern in the cerebrospinal fluid spaces in T2 over the vertex by the arachnoid granulations. With EDS, similar to what Dr. Luciano was stressing this morning, we have found dural blebs, leaks, and cysts.

Comment [KE5]: Is this correct? Does it need to be clarified, medically?

There is also the roller coaster of a patient with pseudotumor and EDS. At the point when the pressure goes up, the abnormal compliance associated EDS creates all these blebs— the bleb can explode when the patient has an extra burst with a Valsalva, there is a minor leakage and the pressure goes down. The patient develops intracranial hypotension from the pseudotumor prior, and then

either Mother Nature or a neurosurgeon fixes the leak. The patient will wind up coming back over and over again for a pressure that is highly variable, up and down.

It is very difficult to handle at that point. Dr. *A* will encounter the patient when the pressure is up, and treat him one way; while Dr. *B* thinks that Dr. *A* is wrong because he measures the pressure much lower somewhere down the road.

In terms of blood pressure, we have seen the elements of POTS, EDS, the brainstem, the veins– I am not going repeat what Dr. Rowe has already elucidated– so I will forgo repeating this, other than pointing out the following.

First discovered by Dr. Milhorat in 1999, Chiari is frequently associated with arrhythmias, SVTs, and tachycardia, sinus tachycardia being the most frequent. And, obviously, when tachycardia goes out of control, it can have a direct effect on the blood pressure.

Then there is the frequently encountered problem with adrenal insufficiency. I once discovered this the hard way. Dr. Batzdorf and I once had a patient who was this big, gangly and tall guy who was about 6 feet eight— in retrospect, he probably had some Marfanoid features.

We gave him a small course of steroids after his surgery as was the standard practice—just a short course of steroids with Decadron, easy in/easy out. We began to notice, however, that the patient was really, really sick. So we hurried to get some imaging but found that there was no leakage, nothing obvious. We tried to check him for everything under the sun.

The local neurologist gave him a touch of steroids again because that is what most neurologists do– except Dr. Kula, who is much more particular than that. After two or three courses, all us geniuses finally figure out that the patient had adrenal insufficiency.

That case inspired me do a PubMed search, and I found an article coming out of Germany, which was describing the people with EDS had the selective vulnerability with their adrenal glands.

Comment [KE6]: REFERENCE NEEDED

I can't find this one because I don't have enough info about the paper. Do you remember the author's name, maybe?

After finding that article, I have seen probably 12 to 15 of my patients fit this description. In fact, the last patient is still in the hospital now with this. The last one had a very nice course. All of a sudden, she developed cerebral salt wasting after pedestal surgery and adrenal insufficiency. I made the referral calls for both issues. I called endocrine, and we put the patient in the ICU because the patient tanked their sodium all the way down to 119, practically overnight.

Comment [KE7]: Is this correct? Does it need to be clarified, medically?

It took three, maybe two and a half days for the endocrinologist of the hospital and for the intensive care specialist to actually accept my initial diagnosis. This is not because I am smarter, but simply because I happen to keep finding the same kind of predicament in these difficult patients, it's not very easy to make the call when the experience is there.

Today we did not dive into it in great detail, so I will mention hormones in passing. Chiari psuedotumor can be associated with empty sella. It is not necessarily a direct association, but rather, they can cause the empty sella since they increase the cerebrospinal fluid pressure; the convexity, the domelike appearance of the skull concentrates the pressure waves towards the base of the skull and there is a flattened effect on the sella. Sometimes, and this is not in all patients, we see hormonal dysfunctions follow.

The most common hormonal change we have found in these patients (by doing labs) was hypothyroidism. This type of hypothyroidism tended not to share the most telltale, classical signs that the endocrinologist would feel required to check off, but it was, in some selective cases, reacting well to supplementary therapy.

Then the second hormonal issue we find fairly often tends to be problems concerning LH and FSH. Besides their regular menses, which also complicate their headaches, some of these patients are frankly unable to conceive. Interestingly, within six months after surgery, many of them are actually able to conceive without any help.

The third problem we found concerned the adrenal hormone. Again, it was my ignorance that I did not know that EDS patients were more vulnerable for that kind of insult. I do not know what the mechanism is.

Then there are problems with behavior and cognition. Chiari “personality” is something that we have all experienced in our practice, but have never published. We are all familiar with patients who understandably— usually after years and years of being misdiagnosed or not listened to— develop this sort of sense of borderline paranoia, hyper-attention to minimal things because they really do not know how to distinguish the proverbial forest from the tree in terms of their condition. So the patients will pay close attention to these floaters in their eyes with the same intensity they would to weakness in their lower extremities. Because of this, the patients develop this kind of persistence and militancy in promoting their own clinical case or the clinical case of their fellow patients.

Brain fog is something that is described by patients; it is a terminology mostly used by the patient population. In more scientific terms, “brain fog” is expressed as the inability to multitask, inability to focus on specific tasks like mathematical problems and difficulty in retaining short-term memory.

Dr. Milhorat and I were discussing this phenomenon for a long period of time— we discussed it a lot, actually. We would say, “Okay, is this coming from CSF pressure, or is it faulty wiring?” Unfortunately, we really never discovered the answer.

Two or three years ago, I came across a very nice article with excellent pictures— the pictures struck me more than the writing. The article came out of India and used functional MRIs showing a probable wiring problem in people with Chiari I malformation who had these kind of cognitive issues. The case numbers presented were very small, however, so perhaps the most outstanding part of the article were the pictures.

Depression is very frequently found in these patients. But, once again, for someone who is generally treated poorly by the medical community and diagnosed late, reactive depression is probably the best-suited explanation for these symptoms. ADD/ADHD is probably different because it is much higher than in the standard population.

Comment [KE8]: REFERENCE

Is this the correct reference?

Kumar M, Rathore RKS, Srivastava A, Yadav SK, et al. Correlation of Diffusion Tensor Imaging Metrics with Neurocognitive Function in Chiari I Malformation. *World Neurosurgery*. July-August 2011; 76(1-2): 189-194. Doi: http://dx.doi.org/10.1016/j.wneu.2011.02.022

And then there is the problem with autistic spectrum. I know where Dr. Henderson stands on this issue. Our position has been a little bit different after the initial enthusiasm. Our revised position being that Chiari I malformation was just a compounding factor of autistic clinical presentation.

For instance, if an autistic child gets pneumonia, the autistic symptoms worsen; when the pneumonia remedies, the autistic symptoms get better, too. A severely autistic child with symptomatic Chiari with headache behavior is, obviously, not going to say to you, "I have a suboccipital headache that is exacerbated by a Valsalva." However, if you do have a severely autistic child who also has symptomatic Chiari with headache behavior, removing the Chiari just removes one compounding thorn from that child's diagnosis. At that point, it does not rectify the autistic symptoms, but can provide higher functioning in that patient and allow that patient to be better managed long-term.

About half of us in this room were in Sydney for Dr. Stoodley's 2013 meeting on syringomyelia. And I remember a boat ride back from the meeting site towards our hotel with Mr. Flint from the United Kingdom; and we're comparing notes about the different personalities associated with people who had Chiari and people who had Chiari and syringomyelia. We were wondering aloud whether or not there was something different at the mechanical or pathophysiological level to explain those personalities.

We began noticing that people with Chiari, alone were having all these kind of ultra attentive, almost neurotic personalities, while the people with Chiari and syringomyelia, especially those patients that were the most sick, had this very stoic attitude. These patients were not neurotic at all. It was as if the two sub-populations were like two entirely different groups of people.

So we were wondering if there was some difference in the physiology to explain this. One of the ideas that Mr. Flint had, suggested that maybe some of the pressure was finding its way out of the brain and down into the syrinx. This pressure escape would suggest, therefore, that the brain was receiving less

pounding while the syrinx formed. Obviously, this anecdote is more just a curiosity that I wanted to throw in.

Allergies bear noting, as well. Most of our patients have a lot of allergies to drugs, foods, and environmental agents. They tend to have an increasing number of allergies over their lifetime. Some of my patients have three or four medical alert bracelets because they cannot fit all their allergies on just one. We have patients with true food allergies and many other patients with food intolerances that, if corrected, actually cause a secondary improvement in the intensity of their symptoms, especially gluten. That is a lesson that I learned from Dr. Kula.

And recently – I am glad to see that Dr. Maitland is here – we found the compounding factor of mast cell. When discussing this, we get into another argument of the chicken or the egg: gut and brain. All of us have seen irritable bowel syndrome and opioid constipation in these patients; but, again, we have been educated just this morning from Dr. Henderson's input regarding the effect of the vagus nerve and dysautonomia.

There is more information about inflammatory changes in the GI wall, especially when somebody has food intolerance to gluten. There are also some neurotoxins which get released and, again, compound the effect of the Chiari I malformation on their symptoms whenever we see these patients with an abnormal gut.

To conclude all this rambling about the cervicomedullary area, it is not too surprising that a system with multiple interacting variables can generate several different scenarios. This area has all these packed centers. There are many cables in the cervicomedullary junction, many different forces. Therefore, there are different pathologies, different pathophysiologic mechanisms from anterior, from posterior, from the side. Out of all these multiple possibilities, you're going to have some recurrent difference in areas, and there is not just one cookie-cutter presentation over and over.

But how many of these comorbidities are genetically linked? For example, the Chiari with EDS group seem to preset as a package, but, as was obvious

from many of the observations this morning, many patients have mixed phenotypes. So it is not like a patient will walk through the door wearing a label that says, "I have a classic EDS without any confounders." Well, many of the patients with connective tissue disorders we see, when they come in, they will fill out the forms with a little bit of everything.

Another important point to make is that genetic testing is a long and winding road. If the genetics group I mentioned earlier out of Duke is any example, we can learn that very often you can spend time looking in the wrong direction. Their group researched a few particular chromosomes for three or four years, realized it was leading to a dead end and was forced to regroup and go in an entirely different direction. So for us to just expect that the geneticists are going to come up with the in's and out's of all this is wishful thinking on our part.

The geneticists will receive much more help when we as clinicians tell them about the observations we have made. In fact, the observation of Chiari and EDS having similar genetic phenotype to Klippel-Feil came originally from a clinical observation that Chiari and EDS sometimes present together. The geneticists chose to look at that, Klippel-Feil and connective tissue disorder and they actually got a hit.

Another point and question, the Chiari is perceived in the medical community as a kind of mixed salad bowl, in which some of the diagnoses are the true-blue classic Chiari I malformation with a small posterior fossa, tonsillar herniation, and cerebrospinal fluid blockage, et cetera; but others are not really true Chiari malformations, but rather they are Chiari-like or Chiari plus something else.

So then what kind of salad is in the bowl of the cervicomedullary syndrome? As we see, if Chiari is already complicated, the cervicomedullary syndrome will then open a much larger Pandora's box.

Some other considerations largely follow common sense. For instance, encountering patterns requires a full immersion through large patient numbers. You cannot find any clinical pattern if you see only ten patients per year. Additionally, identifying those patterns require you to keep your eyes open for

them; understanding the patterns is easier when a close-knit team is involved and works together well.

I have been extremely lucky in my career. When in Italy, I was trained by the renowned Prof. Victor Fasano. When I came to the States, I was trained and then had the honor to work with Dr. Milhorat, Dr. Kula, Dr. Nishikawa, and then Dr. Rekate.

I was always the dumbest guy in the room. It was really a blessing to see and hear all these people pose the problem from different perspectives. It was wonderful to always have educated, stimulating and sometimes rather animated conversations about these topics. It was a blessing just living and breathing this kind of problem, 24/7.

I stole and I imitated many of these thinking patterns over the years. That has been, for me, a blessing. So I am sure that in the future, if we want to find more patterns concerning these kinds of problems, we should have to have a similar approach of discussion and stimulation. It helped me; it probably is going to help others.

The other downside is that very often some of these patients who are more problematic will be swept under the carpet by clinicians who know less, who are less informed or who simply choose to look the other way. Very often when we receive patients who have had previous surgeries, they will have the same litany: “I was treated by my doctor, I went back to my doctor and my doctor said that I am cured and that I should go away; but if I am cured, why do I have the same symptoms that I had before the surgery?” So obviously, if a bunch of patients are having this problem and we do not know how many since they are often swept under the rug, these patterns are likely going to be under-detected, underrepresented, and misunderstood.

Another problem is the *ipse dixit*. The Western scientific thinking has been heavily affected this *ipse dixit*, something Aristotle quoted in his generation in 400 AD and that had continued on until about the 16th century. There was a long gap and a long line of people who were just deferring upwards and saying, "That guy said it; therefore, I am not going to mess with it."

Instead of this constant deference, sometimes we have to look at all the facts and have to have the courage to say that something does not fit. Most of the observations that I have listed so far date back to just about ten years— and too many times to The Chiari Institute.

To this date, besides this group, most of the people dealing with Chiari in this nation and somewhere else either choose to not see these patterns or if they already have been informed about it, they for some reason refuse to see the patterns.

The question is: What are we not seeing? In all these patterns, what are we not seeing in the relationships among the pathologies? What are the patterns that we are simply blind to? What are we misunderstanding? What if, so far, we have just been patting each other on the back to convince ourselves that what we are doing so far is great and we can just blindly build on that? Maybe some of the things we are doing are, frankly, wrong and maybe we are going to have to realize it ten years from now.

I think that the best lesson that I have had so far came from watching Dr. Milhorat deal with failures. Whenever he was having a patient who was a surgical or a clinical failure, first of all, he was getting physically sick over it. I remember, some, he was losing sleeping about it; he would reiterate the case over and over and over.

I have a kind of silly story, but it will give you a better idea of the man. There was a patient that we could not fix and we were at the Long Island College Hospital in the first Chiari center. Dr. Milhorat calls me, puts me in front of the MRI that I knew very well and tells me the story that I knew very well. Then the door opens, and there is the senior attending in the place comes in. "Oh, come here, come here, Rick." And he starts the story over again, with me at his side. The same process continued after a few people walked in. Four hours and a half later, the guy sweeping the room came in. His name was Jose. And Jose, two minutes later, was next to Dr. Milhorat in front of the MRI. Dr. Milhorat was trying

to explain to Jose what we have done so far. So obviously, Dr. Milhorat was stressed about this patient and felt he had to talk to as many people as possible.

But because of that patient, we learned so many more things about what we should and should not do in a reoperation. Learning from that patient, we improved practically overnight in our ability to contain cerebrospinal fluid leakages.

So the issue is failures. If we have patients who do not fit the mold, patients to whom we have given our best and could not help, probably those are the patients that will be the key for us to understanding what we either are not seeing or are misunderstanding.

Thank you very much.

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DR. CLAIR FRANCOMANO: I just wanted to make a comment about the endocrine issues because I spent last weekend at the American Academy of Pain Management meeting in Washington, D.C.; and there was an internist there by the name of Forest Tennant, who was talking about endocrine consequences of chronic pain.

The patterns he has observed in the chronic pain patients really parallel with what we see in a lot of these patients with Chiari and hereditary connective tissue disorders.

So I wonder if it is a more common mechanism not specific to these patients but something that is typical to chronic pain.

One very, very interesting comment that he made was he has had something on the order of 20 patients with Ehlers-Danlos syndrome and chronic pain who have responded really well to oxytocin. So that was kind of an interesting anecdote.

DR. PAOLO BOLOGNESE: What do you think is the mechanism behind it?

DR. FRANCOMANO: Well, his hypothesis is that the stress of chronic pain then stresses the adrenals; and that in the initial stages of the chronic pain, you get

increased adrenal output, and then eventually, over time, diminished adrenal output.

I do not know the connection to the pituitary. But there definitely were, in his experience, decreases in FSH and LH.

DR. BOLOGNESE: On the other hand, a lot of other people have seen stress in the hypothalamic-hypophyseal axis. So it is kind of difficult at that point to determine at which point in the cascade do we see the common final pathway what is cause and what is effect.

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