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The Approach to the Complex Patient

Hello, my name is Ilene Ruhoy and I am a neurologist and I am the medical director of the Chiari EDS Center at Mount Sinai, South Nassau. And I am very happy to be here with you today to discuss the approach to the complex patient and I thank you for the invite. I do not have any disclosures or conflicts.

So what is a complex patient? A complex patient is a patient with chronic and debilitating symptoms that seems to be refractory to most interventions, certainly first line, second line, and sometimes even third line treatments and management options to their symptoms. And it's usually because there is an unclear single etiology for their symptoms, which definitely sometimes impairs the ability for a physician to treat them appropriately and successfully.

It's multifactorial in its etiology and it leads to several diagnoses. And sometimes we refer to these patients as SEPTAD patients or some say PENTAD. Now it's DECTAD, I think because there are a lot of different diagnoses that can apply. And those diagnoses include connective tissue disorders such as EDS, mast cell activation syndrome—and we're going to talk more about the mast cells—small fiber neuropathy, craniocervical instability, and and even intracranial hypertension. These symptoms do not easily localize, and it's usually because there's more of a systemic contribution, but even that systemic contribution isn't obvious, so it's not an obvious autoimmune diagnosis, not an obvious metabolic diagnosis, and CSF leak patients almost always have evidence of connective tissue compromise.

And in fact, sometimes you don't see it. And usually a CSF leak obviously presents with very debilitating symptoms, very acute symptoms, and that needs to be addressed in a fairly urgent manner and is probably the most important thing to address for the patient and how they're feeling and their quality of life.

But if you gather the past medical history of the patient, or even the current medical history, you will very often find evidence of connective tissue failure as well. So, connective tissue disorders, they're both heritable and acquired. There are several hundred heritable disorders of connective tissue that go beyond Ehlers Danlos, which we often talk about.

There's Stickler syndrome, Marfan syndrome, Loeys Dietz, and there's several others, lots of skeletal dysplasias. But the Ehlers Danlos subtypes are well recognized and often discussed. There are 13 clinical subtypes that are recognized. They comprise defects that have been, that are found in 19 different genes.

And these defects include defects in the architecture and the metabolism of the fibrillar collagens, which are one, three, and five, though some others have been identified. They're modifying enzymes, but also defects have been identified in some of the extracellular matrix molecules. The proteoglycans, the glycoproteins, the glycosaminoglycans.

So there's lots of different defects that, and because the connective tissue is so complex, speaking of complex patients, the connective tissue is very complex. And so there's a lot of different defects that have been identified that contribute to its lack of structural integrity, and there is still more being found all the time.

The hypermobility type, EDS, we sometimes refer to as hypermobility syndrome it has been molecularly elusive. We have not found the genes that has been associated with hypermobility type. I think it's polygenic, but there are several labs that are looking into it, and some feel like they are coming close to finding one.

But as of yet, we have not found the genetic variant associated with hypermobility type EDS. Connective tissue disorder symptom complex: so, it's estimated that one in 5,000 are affected by a connective tissue disorder. I think we're going to find that it's actually greater than that. And because connective tissue is just everywhere in the body, there can be many different manifestations.

And that can be really hard on a physician because it's generally a pan positive review of systems for that patient. But all of these organ systems can be involved, and these patients can have a wide variety of symptoms that might wax and wane over their lifetime. If you take a history that goes back to even their childhood, you'll find things that were bothersome to them at that time, and their parents had taken them to doctors and they were just told it was nothing to worry about and just sent home, and over times they would have periods where a certain organ system was involved and they had a certain pain syndrome, they had difficulty with autonomic control, they had difficulty with allergies or breathing, they had difficulty with pain, they had rashes, they had sleep disturbances, they'd been, they were diagnosed with different kinds of pelvic disorders.

They've had lots of exposures is often a piece of history that you'll get with regards to infectious exposures or other environmental contaminants or toxicants. And that's an important piece because, as I said earlier, you could also have acquired connective tissue disorder. It doesn't have to be genetic, doesn't have to be heritable.

Sometimes when there's lots of exposures, that immune response, that inflammatory response from chronic exposures can result in degradation of connective tissue and result in certain symptoms. The human body has four major subtypes of tissues, the muscular, epithelial, neural, and connective tissue. But connective tissue is by far the most abundant and diffusely present.

It is structural and mechanical in its function. So it strengthens, it supports, it binds, it buffers, it protects. Its composition with regards to the fibular collagens and the extracellular matrix can vary based on where it is in the body and what organ system it's involved with. It overall supports the functioning of all body tissues, though, and the, where an anatomical component is in our body is genetically predetermined, and the human body is a cohesive network of tissues, and if things aren't in their right place because the connective tissue isn't doing its structural job, then it's not as cohesive.

And when it's not as cohesive, cellular signaling is not as optimal, and you can have, and the result could potentially be symptoms and disorders. The most abundant fiber is collagen protein, but it also has elastic and reticular fibers as well. So the cells of the connective tissue include many. The fibroblasts, which produce the collagen, but also the adipocytes and the chondrocytes and the osteocytes, which is why there are a lot of skeletal dysplasias.

There's mast cells, which we'll talk more about. The macrophages erythrocytes. They all arise from the mesenchymal cell lineage. In addition to fibers and cells, there is also, as I said, the very complex extracellular matrix, which has a lot of non structural collagen fibers as well as the proteoglycans, the mucopolysaccharides, the glycoproteins.

And what's important about the extracellular matrix is that it doesn't just help support and buffer the structural role of the connective tissue, but it's actually where a lot of metabolism takes place. So there's circulation, and so there's exchange of nutrients and oxygen and carbon dioxide and other metabolic and cellular waste byproducts.

There's metabolite transfer. There's also immune cells that are present. So there's a lot of immune presenting cells that are presenting antigens that result in an immune response or an inflammatory response. So there's a lot of immune system activity that goes on within the connective tissue, both innate and adaptive.

And so the connective tissue is present all over the body, including the nervous system, the meninges. The dura is a dense layer of connective tissue. The glial cells makes up 90 percent of the brain. And it provides basically a matrix for the other nerve cells of the brain. And so it provides, it almost acts as if it were part of the connective tissue of the brain.

It provides a forum for communication and input and output and function of those nerve cells of the brain. It also lines our vessels. So, the vessels become very compressible because of the lack of structural integrity of the connective tissue. And so, even the slightest mechanical pressure can cause compression of the vessels.

And that's why we see a lot of compression disorders in hypermobility type EDS patients. So CSF leak for the dura mater is, as I said, is a fibrous membrane formed by fibrous dense regular connective tissue. It's a little stretched. The collagen fibers have an indistinct spirality that are densely layered one above another.

And so the composition and architecture of the dura can change in a patient with connective tissue disorder. Certainly. But it also, if there is a any kind of systemic and chronic inflammatory response or immune response, as we very commonly see with complex patients, and this can weaken the dura and put it at risk for a CSF leak.

And it can also weaken the very complex extracellular matrix. And that can contribute to the loss of dural integrity and also increase risk of a leak by causing weakness, tear, and the meningeal diverticula. And it's the heterogeneity of the connective tissue disease which is a challenge for both the diagnosis, the risk stratification, and for further research, but it really does start with a very comprehensive complex history of the patient, which I realize that very few doctors have the time to do And that's such a disservice to the patient, because if we can recognize the connective tissue component, then there's a lot more that we can do for the patient, and certainly a lot more with regards to preventative and maintenance care if we have that understanding.

And so this is a nice picture of just how complex and how dense the human dura matter is with regards to its connective tissue layers. And so mast cells are, they're everywhere as well. They're ubiquitous. They are part of our innate immune system. They are our first responders. But they are very much in high concentration in connective tissue, and they have a sentinel location in the tissue environmental interfaces.

So if you can just imagine if the connective tissue isn't as taut as it otherwise would be, those mast cells are a lot more exposed. The dura has mast cells, and mast cells in general are very close to nociceptive neurons. The, so the nociceptors on sensory nerve fibers, specifically small fibers, which is why there is very much a coexistence of small fiber neuropathy and so mast cells can cause a lot of pain for sure.

But it, the dura matter express genes that code for mast cell proteases and inflammatory cytokines. So these proteases love collagen fibers, and there are different proteases for different collagen fiber types, and there's also lots of inflammatory cytokines from, that come from these mast cells when they degranulate, so it just increases the level of inflammation and the level of degradation of these collagen fibers, and these occur when it's under any kind of duress. So, stress, again, inflammatory responses from exposures, whether that's pathogen, such as infectious exposures, or even environmental contaminants or toxicants, but even just from internal or external stress, stressful factors, stressful stimuli can create more of a chronic perpetual inflammatory response.

And mast cells, of course, being near the perivascular, especially within the dura, can wreak havoc on the blood brain barrier, so start to break down that very, those very tight junctions of the blood brain barrier that are meant to protect our nervous system. So the approach to the complex patient, as I've said, a comprehensive history is super critical.

It is really important, and I know it takes a lot of time, but trying to identify and recognize where there is other connective tissue problems, or where there has been exposure to something that could be inflammatory on a chronic level.

These days, long COVID has been obviously on the forefront and we're finding a lot of connective tissue compromise in the long COVID patient population.

We've always found it in the ME-CFS patient population. And so a lot of these infection associated chronic illnesses are showing that there is a connective tissue compromise. And the work up includes a real important mast cell activation syndrome evaluation and treatment, and it's not just about the histamines and the tryptase. So, a lot of institutions will use a tryptase as a, if tryptase is normal, then they'll just tell the patient they do not have a mast cell issue.

But that is not true at all. And it's also not just about the histamine. And a lot of patients are put on antihistamines because the mast cells have almost a thousand different mediators. And so there are, and as I've mentioned, there are proteases that can break down collagen, fibro types, and just even if it were a heritable, connective tissue disorder then if you have mast cell activation that are releasing and degranulating proteases, it's just going to make that connective tissue even less less, more compromised, I should say, and have less uh, structural integrity. But also inflammatory mediators, there are a lot of mediators that come out of the mast cells that are very inflammatory in their nature, so are just going to contribute to the perpetual inflammatory response that is seen.

So it's not just about the antihistamines. The treatment has to stabilize the mast cells and try to counteract some of the other mediators that are released by those mast cells. Patients with suspected dural tear should be evaluated based on the criteria by the International Headache Society for sure because obviously a common symptom in most patients with a CSF leak are headaches, headaches that obviously worsen when patients are upright, and most patients are unable to be upright for any period of time.

Sometimes these headaches worsen during the course of the day, they're usually better in the morning. But we should also consider evaluating patients, especially those with recurrent and chronic CSF leaks, by the current hypermobility type EDS criteria. And I put the link here. The EDS Society actually has a form that you can fill out for patients to see if they meet the criteria for hypermobility type EDS.

So the complex patient, as I said, the connective tissue is everywhere. The joints, the vessels, the skin, the dura, the visceral organs, it lines hollow organs, it holds the visceral organs in place, and the nerves, the sheath of the nerves is connective tissue, the fascia of the muscles are connective tissue.

It really is so ubiquitous in our body. And it explains the heterogeneous nature of the phenotypical presentations, results in many different manifestations and it, and I really do worry about the recurrent leak patients that were missing a connective tissue disorder. I've had patients with a recurrent leak that clearly have more associations with connective tissue, such as we see, newly present tonsillar ectopia, newly present sphenoid sinus dehiscence. So sometimes knowing that there's a connective tissue disorder makes you look for other causes of their symptoms when there's a recurrent, a presentation of seemingly a recurrent leak.

And I've had patients who've had recurrent leaks and have had several treatment s, including blind blood patches, or when a leak has been identified on imaging such as a myelogram or even just an MRI, they've had blood patches, they've had fibrin patches, but they still have persistent symptoms.

And what I find is that if I, if there is a connective tissue component to their history and they have mast cell activation and they meet some of the other diagnoses of that septad presentation in a complex patient, and certainly if they have a history of exposure, then I go looking for other reasons for these symptoms and you can often find them and which is nice because then you have other treatment plans instead of just continuously trying another blood patch.

I think patients get very attached to the blood patch because they've had such relief from them in the past, certainly early on, but sometimes, again, with connective tissue patients, you have to look for other reasons and other etiologies of their symptoms, even though the symptoms can very often overlap.

And I will say that a lot of connective tissue patients, especially those with craniocervical instability, tend to have elevated intracranial pressure, which also puts them at great risk of a CSF leak, because it puts pressure on the dura, which then can actually form a tear or a diverticula, and then they get low pressure, they have CSF leak, and now they have intracranial hypotension, so their symptoms shift.

And then sometimes when we fix the CSF leak, those patients start, their pressure starts to rise and they go through a period of normotensive pressures, during which they'll report feeling better than they had in years, but then once again they sit in that intracranial hypertension state of which they had been chronic at, which put them at risk for the CSF leak as well.

So it's important to recognize when there's craniocervical instability, or when there's other reasons for the elevated intracranial pressure, such as IJV

compression and some other compression disorders. that have been identified. And I also think that we have to recognize that connective tissue patients don't come in that typical demographic that we always think of IIH patients of being, middle aged females with a high BMI.

Because most connective tissue patients do not fit that demographic. And so I think, again, once again, it does a disservice to just put these kinds of diagnoses into little boxes and not think outside the box, because patients really do require a comprehensive approach, a comprehensive perspective, and real consideration.

And that is my talk and thank you for having me, and I really greatly appreciate being here.