Episode 224: Misunderstood and Misdiagnosed: A New Look at ME/CFS

Lindsay Weitzel, PhD:
Hello everyone and welcome to HeadWise, the videocast and podcast of the National Headache Foundation. I'm Dr. Lindsay Weitzel. I'm the founder of Migraine Nation, and I have a history of chronic and daily migraine that began at the age of four. I'm excited to be here today with Dr. Ileen Ruhoy. Hi Dr. Ruhoy. How are you?

Ilene Ruhoy, MD, PhD:
Hi, I'm fine, thank you.

Lindsay Weitzel, PhD:
Thank you for being here. Dr. Ruhoy is a board-certified neurologist who specializes in chronic and complex illness. She is the founder of Anthurium, a medical clinic that helps patients with illnesses that are often misunderstood or mistreated by mainstream medicine. She's a very interesting person, and I have been wanting to have her on as a guest for quite some time now, so this is a special day.

Our topic today is myalgic encephalomyelitis/chronic fatigue syndrome [ME/CFS] and its relationship to migraine and other headache disorders. Dr. Ruhoy not only treats patients with ME/CFS, but she is a well-known published author in this field. I'm excited to ask her all the questions that we maybe haven't been able to ask other people and get an answer to.

Dr. Ruhoy, can you just begin by telling our audience a bit about yourself and why you choose to work with people who have invisible or misunderstood illnesses?

Ilene Ruhoy, MD, PhD:
I think there's a couple of reasons why I sort of found myself in this space. My background, first and foremost, I'm a board-certified neurologist, as you had stated. I have a PhD in environmental toxicology. I've always been sort of aware of the effect of exposures on our overall health, but specifically our neurologic system.

And then also about ten years ago, I was a patient myself, and no one would believe me. And everyone told me that my symptoms were anxiety, I was stressed, I was working too hard, I knew too much, I missed my family, I should just go home and work less. And it was very frustrating. And these were colleagues of mine and I was a neurologist. And I realized that they now, in retrospect, were seeing me as female first before they saw me as a neurologist or as a doctor or as a colleague.

And that was very distressing to me. Regardless, an MRI showed my diagnosis, which is not the case for most of my patients. Imaging is usually normal. But I knew what it felt like not to be believed, to try to convince people that, no, I know something is wrong. What I'm feeling, it's not right.

So, I sort of had this newfound sort of compassion and empathy for patients who have symptoms and know their body is not right, know that their brain is not working as it should, and doctors aren't believing them, and tests are usually normal. So, all of that sort of led me into private practice, where I just started to give myself time to really get to know my patients and hear their story, because everyone has a story.

And once I listen to that story, it sort of gave me insight into what I can help these patients figure out. And it sort of actually renewed my love for medicine in general and neurology in specific. I love the detective work, the investigative work that's involved. Anyway, so all of those things led me to the space where I am today, where now I see chronic and complex patients almost exclusively. Though I still get a lot of referrals for neurology symptoms that are refractory to everything that we try and everything that we know. And then I work to figure out what else we can do and what else we can figure out.

Lindsay Weitzel, PhD:

Well, that sounds awesome and amazing. And I think that we're all very glad that you do that because it's so needed in our space. I have been wanting to do an episode on ME/CFS for a very long time. I know for a fact that there are people in our audience who experience or have experienced chronic fatigue in its various forms throughout their migraine and headache journey.

Some have constant low-level fatigue. Some have bouts so severe that if you go downstairs, you might not make it back up that day. It can be very frustrating. And I've heard those stories numerous times. I have had a couple bouts back when I was much younger. And when I had my very first bout of severe fatigue, it was after a hospitalization, and I had a doctor tell me that it wasn't considered a real diagnosis.

So I know what that feels like. And I'm excited to say that it is now recognized and we can do a podcast on it, and we can talk about what we do know. So, can you please begin by defining for us what ME/CSF is?

Ilene Ruhoy, MD, PhD:

The National Academy of Medicine in 2015, which I think used to be called the Institute of Medicine at that time, they have criteria that we still regularly use. And it's a diagnosis that requires the patient to have one of the following three symptoms: [1] a substantial reduction in the ability to engage in pre illness levels of activities that persist for more than six months and is accompanied by fatigue, [2] post exertional malaise, which generally means that after even minimal activity, there is a sense of fatigue and exhaustion, and sometimes that's delayed onset, and/or that there is just a prolonged recovery period from that activity, and [3] unrefreshing sleep. And at least one of either cognitive impairment or orthostatic intolerance.

And I think these are good criteria. And I think that they're good for doctors that are just first coming into this field. But I will say that those of us who see on a regular basis ME/CFS patients, we've expanded those criteria. We just sort of know all that it entails.

And it's very easily diagnosed, in my opinion, based on a patient's symptoms. We have the SEPTAD diagnoses, like the small fiber neuropathy, the POTS, the hypermobility, which is a risk factor seemingly for ME/CFS. And then there are a couple of others in that SEPTAD diagnosis.

But I will also just add quickly that I think long COVID, which a substantial number of my long COVID patients have in ME/CFS phenotype, but the research in long COVID, I think, is the reason why ME/CFS has become a little bit more mainstream if I dare to say, a diagnosis that's really that's not nearly as controversial as it used to be when I first started seeing these patients. So, I think that that's one of the reasons why it just has taken a little bit more seriously in terms of these symptoms.

Lindsay Weitzel, PhD:
If I could back up one second and ask you to define something for our audience. Your last step in those criteria, you said orthostatic intolerance, I believe, is how you put it. Can you just tell everyone what that is, briefly?

Ilene Ruhoy, MD, PhD:
Sure. So there is a level of autonomic dysfunction that happens in ME/CFS. And to be honest, it varies from patient to patient. Many times patients are told that they have POTS, especially if they meet the criteria on tilt table testing. And they do have POTS, there's no question. But there's usually a lot more with regard to the autonomic dysfunction, because the autonomic nervous system controls a lot of what our body does and how it does it.

And so there's a lot of other symptoms that are related to the autonomic disorder. And so, it's not just POTS and it's not just orthostatic intolerance, which is basically that you stand and your heart rate goes up and your blood pressure goes down. If it's just POTS, your heart rate goes up, your blood pressure is sort of stable.

It really depends upon what the blood pressure does, because you can have either orthostatic hypotension or POTS. And both of those are under an umbrella term of orthostatic intolerance. But again, I think that that's just sort of the surface and that there's a lot more symptoms that can be related to the autonomic dysfunction.

Lindsay Weitzel, PhD:
I believe now that there are categories or levels of severity of ME/CFS that people can experience. What are those categories?

Ilene Ruhoy, MD, PhD:
I'm sure that there are some clearly defined labels of those categories, but I just sort of see it as mild, moderate, and severe. And that's usually how I label it. In the severe forms of ME/CFS, these patients are truly just bedbound or at least housebound and really can't do any of the activities without that post-exertional malaise and fatigue kind of feeling. And they are really impaired, and their quality of life is severely impacted. And then there are patients with less severe forms that are able to do some minimal activities of daily living. Some are even able to work from home. Some are actually able to go to work for short bursts of time.

And there are flares of it too. And so sometimes the patients are stable in between flares, but then something will trigger a flare, and then they're once again in sort of the state where they can't really do much of anything. And that's severely distressing. I mean, my most severe patients are literally in dark rooms with blindfolds and earplugs because they can't tolerate sound, they can't tolerate light. Any movement can trigger that post-exertional malaise feeling. Even an exam can be difficult for them because a neuro exam requires some level of a physical movement. So, it can be really severe for some patients and then less severe for others.

Lindsay Weitzel, PhD:
It seems like I've commonly heard people talk about the problem of, oh, I went downstairs to fix a meal, and then I never made it back up the stairs that day. Or I once heard someone tell me that it was so bad in one flare that they couldn't hold a magazine. That was too heavy for them. That was too much exertion, which just sounds so extreme and difficult to me.

Ilene Ruhoy, MD, PhD:
Some patients can't be upright for any period of time. That’s part of their symptomology. And that sort of leads into the idea of the role of the connective tissue, which is why I say hypermobility is a risk factor. And I see that time and time again with a lot of these complex diseases and complex presentations. And I don't think it's inconsequential or irrelevant. And I think it needs to be talked about more often, how the connective tissue plays a role.

Lindsay Weitzel, PhD:
That is interesting. Since you brought it up, why don't we discuss that briefly? Because we do talk in previous episodes about how connective tissue disorders are fairly prevalent in people with head pain. What is the relationship in fatigue? Why is that related? Do we know?

Ilene Ruhoy, MD, PhD:
Obviously there’s a lot of theories. And I will say that empirically, because I see these patients every day and have for years. I know it to be true. But to be evidence based requires a lot of different studies, trials, and publications, which really have not yet sort of entered the scene just yet.

But the relationship with the connective tissue and head pain is actually multifactorial. First of all, as I refer to the SEPTAD diagnoses that seem to support the ME/CFS diagnosis, one of those SEPTAD diagnoses is mast cell activation syndrome. So the brain has lots of mast cells. The meninges of our nervous system, the three layers that protect the brain and the cord, the dura, the arachnoid, the pia, they're all connective tissue.

The dura is actually dense connective tissue and has a high concentration of mast cells. And so if you have excessive activity of mast cells, there's a lot of release of the insides of mast cells. And of which we talk often about histamine because it is a major reservoir of histamine. But there are 1200 mediators, many of which are certain enzymes that break down collagen, so further degrade connective tissue. All of them are inflammatory to some extent.

And some of which are actually pain inducers as well. So just mast cell activation syndrome alone can create pain. So that's an important point first and foremost. And then some of the mast cell mediator activity contributes to the autonomic dysfunction that I refer to. And that alone can also have headaches because one part of the autonomic nervous system is sort of vasomotor control which allows for a blood flow distribution.

And when you have poor blood flow distribution, you could have pain, including headaches, including certain body pain. Also know that in ME/CFS patients there's a low cerebral blood flow velocity that we see on transcranial dopplers. That means that there's poor blood flow, poor blood supply, and likely poor blood perfusion into the brain parenchyma, which is the brain tissue. And so that can cause head pain.

And then, of course, there's the anatomical diagnosis that comes along with hypermobility or hypermobility type EDS, which is like cranial cervical instability and compression of the jugular veins. That can come from either the C1 tubercle or the styloid in hypermobility EDS patients. And that alone can cause a lot of pain as well, including headaches and neck pain and usually refractory kind of pain, because it's an anatomical problem.

And I can go on. I mean there's so many different etiologies of head pain in this patient population. And it's important to recognize that because it can change treatment. And very often I think patients in this diagnostic category are not getting the appropriate treatment.

I think there's a common misperception that you're born with hypermobility. And while oftentimes that can be true and there's a lot of signs of it early in childhood that usually I pick up on the history taking component, but you don't have to be born with it. It can be acquired, and that comes from the exposures of our environment.

And sometimes when you have had a history of recurrent infections, is just one example. And it is the most common exposure, infectious kinds of exposures. Because of the mast cell activity or the immune response that it provokes, you could have an inflammatory degradation of the connective tissue which is everywhere in our body.

It's not just joints. I think that that's an important point. A lot of patients will say to me, oh, I was the most inflexible child. I couldn't do gymnastics. I couldn't do anything. And that can very well be true. And then you can have an acquired form of hypermobility that results in all of these same kinds of things.

Lindsay Weitzel, PhD:
I have never heard that before, so that is so interesting. I'm glad that you brought that up. My next question is, is ME/CFS truly invisible? Are we at the point where we have some markers?

Ilene Ruhoy, MD, PhD:
We have some markers that have not been validated, is the best way to say it. I always say that they're suggestive of, or consistent with, the diagnosis. We know that there's certain immune markers that seems to be most prevalent in this patient population who have a diagnosis of ME/CFS. But unfortunately, we don't have the smoking gun, as we say, that gives you that diagnosis without question, that's unassailable in most medical circles. So, I think that one of the problems is, is that we don't have that smoking gun. We don't have that specific biomarker that unequivocally says that this is your diagnosis.

Lindsay Weitzel, PhD:
You went into a little bit about hypermobility and what can go wrong in your neck and cause that kind of pain. And it can be related to ME/CFS. What about people with migraine? Why do they seem to show up with ME/CFS and chronic fatigue so often? Do we have an answer for that?

Lindsay Weitzel, PhD:
I will say the migraine world has come a really long way in terms of treatment options and even our understanding a little bit of what migraines are about. And so, I think that if you are a migraine patient and respond to one of those treatment options, I think you have a migraine disorder. You have a migraine syndrome. You’re a migraine patient. And that's great that you're able to respond to some of the really phenomenal things that have come onto our scene with regards to therapeutics. And that's exciting. And I do a lot of migraine management for sure in my clinic.

But I think if you have refractory migraines that are not responsive or if you have any symptoms associated with migraines that are not classic migraine aura, migraine prodrome, or migraine variants even, I think that there is a very strong chance that it's related to something that I've sort of already talked about, one of either the SEPTAD diagnoses or hypermobility. And that should be looked at because that would be a different kind of treatment road, frankly. Even in my ME/CFS patients, I still very regularly use the CGRP antagonist and monoclonal antibody class of medications because they still are effective.

The CGRP itself induces mast cell activity. So, at the very least it's effective because it's actually treating the mast cell activation disorder. And I don't know that to be 100% true, but that's what I suspect, because the CGRP does provoke mast cell activity. So, I think that there's still a place for all of the classic migraine treatments in the ME/CFS patient population with headaches. And the vast majority of them have headaches.

Lindsay Weitzel, PhD:
Do we know if people with classic migraine are more likely to have ME/CFS or not?

Ilene Ruhoy, MD, PhD:
I don't think they meet the criteria as easily. My migraine patients for sure have fatigue, of course. And on days when they have a migraine, obviously they can't engage in activity because they're light sensitive, they're sound sensitive, they have an inability to sort of integrate all of the sensory stimuli. They can't be in crowded rooms, in loud rooms and busy rooms. And so, I think that they feel almost like an ME/CFS patient does, but I don't think that they truly meet the criteria. Although I often wonder about the criteria with migraine that the pain gets worse with movement in terms of how it relates to the post exertional malaise kind of description. So there's a little bit of an overlap, I will say. But they don't technically meet the criteria.

Lindsay Weitzel, PhD:
Interesting. Are any other pain conditions more likely to have ME/CFS? Do we know of any other links?

Ilene Ruhoy, MD, PhD:
Yeah. I mean, I think for sure the central desensitization. We see a lot in ME/CFS patients. A lot of ME/CFS patients are chronic pain patients and they have central desensitization. They also have complex regional pain syndrome. So I think that they are very vulnerable to these chronic pain syndromes. I always believe that you have to have the right diagnosis. And it could be several. It doesn't have to be just one. I mean you could say ME/CFS. And that's why we talk about the SEPTAD, because under the umbrella there's all these different diagnoses. And the right diagnosis and the right label will actually change treatment and give a better chance for a treatment that is effective and that brings relief to the patients. And I think that that's an important piece of what we do in the complex and chronic illness space.

Lindsay Weitzel, PhD:
This is an important question because I think a lot of people struggle with this. If you are struggling with ME/CFS, what sort of doctors should you be seeking help from?

Ilene Ruhoy, MD, PhD:
I think any doctor who's willing to take the journey with you. I don't think it's relegated to just one specialty, frankly. I mean, I'd like to think that it's neurological, but that's just my biases as a neurlogist, I think. But a lot of the manifestations are neurological: the headache, the dysautonomia. But it's also under the immunologist's purview. But again, I don't really believe one specialty owns it. And I think that what you really need is a doctor who's going to go on the journey with you to really identify and define specifically your diagnoses.

Again, there could be more than there usually is. I mean, there always is more than one. And to really help find treatment options that at least address that particular diagnosis and then get you better. Find that treatment option that works for you. If there was a magic bullet, everyone would be cured. The key is very individualized. What one patient responds to, another patient won't. And the reasons behind that we don't really understand yet other than I think it's in in our genome.

I think that's how we're all different in terms of how our genome controls what our body does and the different pathways. But that's a whole other podcast topic maybe. But I do think that everyone is so individualized that it requires a personalized kind of approach. And so the doctor that will do that for you is the right doctor.

Lindsay Weitzel, PhD:
Is the current thought that people with ME/CFS will improve or is it thought to be sort of a lifelong, it'll ebb and flow, but it's always there type situation.

Ilene Ruhoy, MD, PhD:
That's a great question. I definitely see patients improve. I have even seen patients feel like they are all better, but I also have been doing this long enough to know that I don't think you're ever fully away from it. And I think that forever more, you have to nurture your body. You have to protect it. You have to try to not get inflamed.

Because I think that the vulnerability to relapse or to regress on any level is sort of always present. And to the extent that it's present in any individual patient is really hard to quantify. But I've just sort of seen patients be well for a couple of years and then some sort of stressor event happens, whether it's again, an exposure, a physical trauma, a motor vehicle accident, a family trauma.

Then they will describe a flare of symptoms that they thought were long gone. So I really do believe that there is a sense of always sort of being protective of your health and your body for the rest of your life, frankly, I think is what needs to happen.

Lindsay Weitzel, PhD:
And are there any formal treatments that seem to do well for a majority of people, whether they be natural treatments, vitamins, or anything? Or is it just we aren't there yet?

Ilene Ruhoy, MD, PhD:
There's nothing that, again, has stood out as being magical for these patients. I often, listen, I did a lot of work in integrative neurology. I did a lot of training. I did the fellowship in integrative medicine with Andrew Weil, and I've done a lot of integrative kinds of courses. And so my point being is that I believe in more natural approaches when appropriate.

The problem I think with patients with ME/CFS and any refractory symptom is that those kind of natural approaches don't do much of anything. They don't really move the needle enough for there to be a significant difference in the course of their disease. And I think early on in treatment, it needs to be pharmacologic in some way, or dare I say, even surgical or injection therapy. I think that that's the only thing that's going to sort of move the needle, get the body to a different place, where then I think more natural approaches are supportive and adjunctive.

So, once you're on a trajectory where you've gotten some improvement, I think that's when we can talk more about natural approaches. And again, I'm all about integrative approaches because I trained in that. I have a whole background in that. In fact, early on in my private practice career, people referred to me as an integrative neurologist because I do feel strongly about that kind of approach.

I even trained in medical acupuncture, So again, I'm a big fan of it, but I also know that it's not going to be very helpful early on in the course of these diseases, these post-exposure fatiguing illnesses.

Lindsay Weitzel, PhD:
When you say injection therapy and things like that, is there something in particular you have in mind?

Ilene Ruhoy, MD, PhD:
There are these injection protocols, prolotherapy, PRP, even stem cell injections, for a lot of these anatomical problems with regards to the degradation of connective tissue and how it creates malalignment. I mean, the body is just notoriously intolerant of lots of things, unstable joints, an anatomy that's not, like, held together well.

And fortunately, our body is just complete with connective tissue. I mean, even in the fascia is connective tissue. And so all the fascial planes are meant to keep our visceral organs where they are and even, like our muscle fascicles. And all of that is held together by connective tissue. So when it's not taut enough and keeping things like where they should be, things don't work as well, because the body's all about communication among cells and signaling and that gets into a lot of physiology. But there's an important role of our connective tissue. And so again, it's sort of the reason why the body is so out of balance early on in these diseases until we get it back into closer to balance.

And those injection protocols are meant to sort of tighten up the connective tissue to try to keep that body more held together. I'm trying to think of a better term than that, because obviously our bodies are held together because we're still walking about. But you know what I mean, I think. So that's what the injection protocols I was referring to try to do.

Lindsay Weitzel, PhD:
I have to say I'm very impressed, especially since here I am, I started this, I was interviewing a neurologist. I am so impressed that how it's come full circle and you keep bringing up connective tissue. And we do talk about that a lot on this podcast, but I didn't think it would be brought up so much in this topic. And I'm wondering if before we go, you would like to bring it full circle with why you keep coming back to that. Because I didn't know that was going to happen.

Ilene Ruhoy, MD, PhD:
I feel like everyone's always asking me about connective tissue and EDS, because I think that's sort of what I'm a little bit known for. So, I guess I'm just so used to talking about it, but I see it is such an important piece that we ignore, and I just believe that it actually plays a very significant role in our health and disease.

So, again, if a patient responds to our first line treatment, then we're good. We're done. We don't need to talk about connective tissue, but I don't see those patients. I get the referrals from patients who have seen a ton of specialists, including neurologists. And so I see the connective tissue as playing a very important role. Until that's addressed, then I don't think that they're going to make a significant difference in their symptoms.

Lindsay Weitzel, PhD:
Then it can play a role in both head pain and in the fatigue?

Ilene Ruhoy, MD, PhD:
One hundred percent. I see that all the time. Yeah, for sure. A lot of migraine patients, I find that there's a role of their connective tissue. And again if you take a very comprehensive history, even in just a classic migraine patient and they don't have any other concerns or symptoms. If you take an extensive history, you often find, though not always, you often find a very significant exposure history. Mononucleosis when they were in college, sometimes twice. They missed classes for two months and were in bed for a month. Or they had recurrent strep infections, or they were in several motor vehicle accidents, or they had childhood adverse events, adverse experiences. And so, there's just a lot in a background.

And we know that remote exposures actually result in delayed symptoms sometimes. And in fact a lot of neurodegenerative diseases. And I know I'm getting off topic now, but there's a lot of research that shows that remote exposures actually contribute to some neurodegenerative diseases. And it's about the mitochondria. It's about the cell danger response. And again, there's so much to talk about that I'm just going to sort of stop here. But I think that's important for patients who are not responsive to again, first line or even second line treatments to even migraines or head pain or fatigue. Then that requires further investigation.

Lindsay Weitzel, PhD:
All right. Well thank you so much. Thank you for joining us and for being here. And thank you everyone for listening today. I hope everyone learned something. And please join us again on the next episode of HeadWise. Bye-bye.