Open Q&A on Transverse Myelitis (TM)

You can watch the video of this podcast at: youtu.be/ZEm_nDbAhf8

[00:00:00] **Krissy Dilger:** Hello, and welcome to the SRNA "Ask the Expert" podcast series. I'm Krissy Dilger with the Siegel Rare Neuroimmune Association. For this episode, "Open Q&A on Transverse Myelitis," I was pleased to be joined by Dr. Shuvro Roy. Dr. Roy is an assistant professor of neurology at the University of Washington, specializing in neuroimmunology with a specific focus on multiple sclerosis and related neuroimmunologic disorders. You can find his full bio in the podcast description.

[00:00:38] SRNA is a nonprofit focused on support, education, and research of rare neuroimmune disorders. You can learn more about us on our website at wearesrna.org. This episode is made possible in part by the generous support of Amgen; Alexion, AstraZeneca Rare Disease; Genentech; and UCB. Hello, everyone. I am pleased to welcome Dr. Shuvro Roy from the University of Washington. Thank you so much for joining us today, Dr. Roy.

[00:01:15] **Dr. Shuvro Roy:** Of course, yeah. Good morning, good afternoon. If anyone's in a specific time zone, good evening. It's great to be here.

[00:01:24] **Krissy Dilger:** Just to start us off, Dr. Roy, can you begin by giving a brief overview of what transverse myelitis is?

[00:01:33] **Dr. Shuvro Roy:** Of course. Yeah. So, transverse myelitis is a bit of an umbrella term, and I'm sure we'll get to that in a moment. But essentially, what it is inflammation of some kind, basically impacting the spinal cord. Most commonly, we tend to see that with inflammatory conditions. This could be due to something like multiple sclerosis. It could also be due to other inflammatory conditions like neuromyelitis optica spectrum disorder, MOG antibody disease, and even other conditions like sarcoidosis.

[00:02:16] Less commonly, we can see transverse myelitis due to infectious disorders. Certain infections can cause inflammation in the spinal cord. And the way we really define that, if we're getting really nitty-gritty as a physician, is we're looking for evidence of inflammation. There are many things that can cause damage to the spinal cord, but we are really looking to see: is there inflammation?

[00:02:43] That could be based off of what we see on an MRI. For example, are there some signs of enhancement—IV contrast making its way into the spinal cord where it normally should not be? Or if we get a lumbar puncture and we're looking at the spinal fluid, looking for white blood cells, which should normally not be there.

[00:03:09] And so that can really help clue us in that, okay, if somebody is presenting with, say, new symptoms or damage or evidence of damage to the spinal cord, it's from an inflammatory or infectious cause. And then from there, it's about narrowing down what that could be.

[00:03:28] **Krissy Dilger:** Got it. Thank you. So, you hinted at my next question, but what causes TM?

[00:03:38] **Dr. Shuvro Roy:** Yeah, and there's any number of possibilities as to what causes transverse myelitis. And oftentimes, it depends on what is driving that or what the cause is. So, with, for example, MS, we see that transverse myelitis is often caused by attacking the white matter in the spinal cord or basically attacking the myelin or causing demyelination.

[00:04:10] But in other conditions, it may be due to something else. So sometimes, folks will have—after an infection, your body fights off the infection, but then in the process of developing antibodies to fight off that infection, the body may develop something called molecular mimicry, where, say, a tissue in the spinal cord or in different neurologic tissue looks a lot like the infection that you just fought off, and thus, those antibodies accidentally get directed towards that tissue.

[00:04:50] And so there can be a post-infectious transverse myelitis, for example. Other things, of course, include all of those other disorders, some of which we're still trying to totally understand. For example, with MOG antibody disease, we are trying to understand the pathophysiology or the exact mechanism by which it causes transverse myelitis.

[00:05:17] But in other disorders, we have a better answer. For example, in NMO, we know that basically these antibodies are attacking these water channels in the spinal cord that can lead to a lot of disruption with certain cells called astrocytes, which I call the scaffolding of the spinal cord.

[00:05:40] And with destruction of that comes a lot of inflammation, a lot of swelling, and of course, really severe neurologic damage. So, it definitely varies by each indication or—excuse me—by each different type of disorder, but they all can cause that inflammation, just each in their own specific way.

[00:06:05] **Krissy Dilger:** Got it. So, I feel like you might have already answered this question, but I guess I will ask it anyway to see if there's anything further, you'd like to talk about. Can TM be a symptom of another disease? And can you explain the difference between a TM diagnosis and TM as a presentation?

[00:06:26] **Dr. Shuvro Roy:** Yeah, so of course. Even if we have already touched on this, I'm glad this question's being asked because, believe it or not, I even answered this question for our trainees a couple of months ago when I was on service. This was the exact question that they asked me: is transverse myelitis a specific diagnosis, or is it a specific presentation?

[00:06:54] This actually led into, "Oh, this is a great question," and led into me giving a lecture to our team literally last week to answer that specific thing. So, it's a great question and totally worth asking. The short answer is both. It can be both.

[00:07:14] Let's maybe start with: can transverse myelitis be a symptom of another disease? And the short answer is yes, very much so. And that's actually often what we're trying to sort out when somebody presents for the first time. Say somebody's coming to the hospital and they're experiencing new symptoms with weakness or difficulty using the bathroom, you're certainly concerned as a neurologist that somebody has a spinal cord disorder.

[00:07:47] And then from there, figuring out, "Okay, it looks inflammatory," based off of either the MRI testing or the spinal fluid testing that we talked about. But then the question is: is there some other disorder that is

driving this process? Because, of course, if it is from another overarching disease, the question would be, "Does the patient have an increased risk of it happening in the future?"

[00:08:17] So that's where we're doing a lot more testing, such as sending off certain antibodies or doing other tests. If we're looking for sarcoidosis, getting things like a CT scan can help establish if there is something else. A lot of different inflammatory disorders can cause transverse myelitis, as we mentioned.

[00:08:39] But oftentimes, we will complete that full workup, and then at the end of it, we don't necessarily find that, "Okay, this person is at risk of further attacks." The antibodies are negative, and the spinal fluid otherwise is unrevealing for things like infection. And we don't find other inflammatory disorders like sarcoidosis.

[00:09:09] And if that's the case, we complete that full workup and we get to give the reassuring news of, "All right, this looks okay. This doesn't seem like you are at risk for another attack based on the information we have right now." Then we would give the diagnosis of what we call idiopathic—or basically, "Hey, we didn't identify a particular cause"—transverse myelitis.

[00:09:37] And so that is where we would use that as both a diagnosis, and then the presentation is basically when somebody presents with that as an attack. And if there is some other overlying disorder, then sometimes, yeah, there can be different presentations of those disorders. But this is a great question, and I think the answer to all of them is yes. It's just putting it in that context.

[00:10:13] **Krissy Dilger:** Very interesting. And I think that is something that for our community can be hard to understand in terms of your diagnosis. If you are diagnosed with NMO, but you had TM as one of your presentations, then you might be asking, "Do I have NMO or TM?" That's a good explanation, so thank you. So, we get a lot of questions about recurrent TM. Is TM considered a monophasic disease, or can it be recurrent?

[00:10:49] **Dr. Shuvro Roy:** Yeah, it certainly can be a recurrent disorder. And if there is a recurrence of transverse myelitis where on the first go-around there was not an identified cause, I think it really raises a red flag that, okay, we should be checking again. Because there are not too many cases of folks just having idiopathic transverse myelitis several times in their life.

[00:11:26] If we did that full workup, looked for the disorders that we know tend to cause recurrent attacks of transverse myelitis, and it was negative, then we really need to think about, "All right, what is going on here?" And maybe we need to repeat some of that workup. Because, in general, if it is just idiopathic transverse myelitis, most of the time, yeah, it is going to be monophasic. But if it is recurrent, we really need to reconsider: is it NMO, MOG antibody disease, or neurosarcoid? Those are really the main three that I'm thinking about.

[00:12:05] Could this be what we call a seronegative variant, especially if those antibodies are negative? We all know there is seronegative NMOSD, for example. And with that, if you have a relapse, I think it really prompts us as a provider to say, even if we don't necessarily find a cause, we really do need to get somebody on some sort of protective agent, some sort of immunotherapy to prevent further attacks down the line.

[00:12:42] And so that could be with a variety of different immunotherapies. I think most commonly, we would probably use something like rituximab, which has been used for many years in the NMO space, or even, say, an oral immunosuppressant—an oral pill that folks can take once or twice a day to try to help calm the immune system and just provide some extra prevention. And so those are the main disorders that we would be looking at, and then I think that's also how we would be guiding our treatment.

[00:13:18] **Krissy Dilger:** Got it. Thank you. Someone wrote in, "What are the do's and don'ts, especially when it comes to food?"

[00:13:27] **Dr. Shuvro Roy:** Okay, yeah. I love this question. When it comes to doing any sort of research as it relates to food and neurology, it's always really tricky. And I say this as somebody who has done research in this area—sometimes it can be challenging to get a sense of, one, what are folks eating? Because the best way to do that is often things like food diaries, and that's also asking a lot of folks to say, "Hey, just write down every single thing that you're eating," and then correlate that with information.

[00:14:12] But the good news is we are getting better about it, and we're having new tools available to us. For example, there was some work that was looking at basically the volume of people's spinal cords, and they actually looked at what people were eating and how that impacted things.

[00:14:36] And while there's no one particular diet that says, "Oh, hey, here's the transverse myelitis diet," what we have seen is, for example, the Mediterranean diet has been associated with healthier spinal cord volumes than other diets. And the Mediterranean diet is one that I think makes a lot of sense, just in terms of common sense.

[00:15:07] Lots of fruits, lots of vegetables, lean protein, and then a lot of omega-3 fatty acids, which can be found in things like olive oil, avocados, and fatty fish like salmon. I have to make sure I mention that as somebody here in the Pacific Northwest. And omega-3s are quite important for neurologic health and building neural tissue, so that all makes sense.

[00:15:36] I would say, in terms of the don'ts, I think what we generally see is that highly processed foods or foods that generally are pro-inflammatory—whether that may be something like a lot of red meat or alcohol—are things that do promote just more inflammation in the body and maybe are not as generally healthy.

[00:16:03] It could also lead to just worsened cardiovascular disease. Our spinal cord is like any other tissue in the body where you are getting delivery of nutrients through the blood, and so we want healthy blood vessels being able to do that. If we're eating foods high in cholesterol or high in sugar, these are notorious for causing things like plaques in the blood vessels or even developing diabetes, which is notorious for damaging the blood vessels as well.

[00:16:38] And, of course, that basically means that nutrients have a harder time reaching our spinal cord. In terms of food, I think trying to follow as healthy a diet as possible in terms of, say, that Mediterranean diet probably has the best evidence behind it. But within reason and within moderation—I would never tell anyone like, "Hey, you can just never have a burger the rest of your life," or, "You can never have a beer after a really long day at work," or what have you while celebrating. We're coming up on the Fourth of July next month, but within reason and, of course, in moderation.

[00:17:22] **Krissy Dilger:** Great. Thank you. We get a lot of questions about aging after having a transverse myelitis diagnosis. Someone wrote in, "Many people who have experienced idiopathic TM seem to experience a sharper decline in mobility, strength, and endurance as they age compared with the average population. There are people who also experience strokes, heart attacks, et cetera. The initial severity of the TM attack is presumably a contributory factor in this, but what other issues might contribute to this, and how might we be able to combat them?"

[00:18:06] **Dr. Shuvro Roy:** Yeah. This is awesome. This is a great question. I'm extremely biased because it is also an area that I am quite invested in from a research standpoint. But I think this is really something

that gets at so much of what drives neurologic progression in a number of disorders, not just transverse myelitis. We see this...

[00:18:31] Actually, we're starting to get this really looked at in the MS space: this idea of someone's—what I'll call—their metabolic health. And there's even colleagues—I have to shout out a former colleague of mine at Johns Hopkins, Parvin Bhargava, who was looking at metabolomics and this idea that your medical comorbidities may say a lot more about your long-term risk and your health than just your age as a number.

[00:19:11] For example, you may be age 55, but if, say, you're somebody who is exercising frequently—we recommend at least at our center 150 minutes a week of moderate to strenuous exercise, so stuff that gets your heart rate going. If you are getting a good night's sleep, if you are eating well, you're not smoking, and you're avoiding alcohol [again, within reason], your body may actually be more like a 45 or even 40-year-old than, say, 55.

[00:19:49] On the other hand, of course, if you are doing the opposite of all those things that I said— if you are smoking cigarettes, if you are pretty sedentary and eating, say, a lot of highly processed foods, your body may age faster than what that number would say. And with that comes increased comorbidities and, as a result, difficulty with maintaining that neurologic reserve—that ability to maintain that mobility, strength, and endurance as was brought up—which can erode over time.

[00:20:34] The other things that we have to keep in mind, and this is getting backed up by some newer studies, including one by a colleague here at the University of Washington, Sarah Simmons, who's a physiatrist—but actually, the really high importance of exercise, not just in the prevention of things like strokes, heart attacks, et cetera, which we know would certainly accelerate the process of aging.

[00:21:07] But what it does in terms of both maintaining connections or synapses between neurons to try to maintain that neurologic reserve, and then also to essentially make sure that you are having ongoing delivery of those nutrients through the bloodstream. So, what do I mean by that? For example, whenever we are physically active—not just for the prevention of cardiovascular disease, but what's happening is we're starting to signal the top of our brain, the cerebral cortex, and that is being passed down through the brainstem into the spinal cord and then out to the peripheral nerves just to conduct a movement.

[00:21:59] And what that does is it actually tells our body, okay, one, we need to maintain our existing connections. Even if there is damage to a part of the spinal cord, we need to maintain those connections because we're still getting use out of this part of the body. But then also, our bodies do naturally remyelinate to some degree, AKA repair damage to the nervous system.

[00:22:29] And what we've seen with some of the studies that have looked at things like external spinal cord stimulation is that when you do stimulate those areas, whether through exercise or with even just a little bit of an electric current, that helps the body preferentially target, "Okay, we're still getting use out of this area. We have to repair this area as well." And so that's something where we do see that patients, especially after a transverse myelitis in the months that follow, those who do have more physical activity have far better long-term outcomes than those who do not.

[00:23:18] And then it's the same sort of thing when we're looking at—I know we've gotten away from the question of looking at some of these medical comorbidities. But even in, say, the MS space, there was a really excellent study that recently came out of the CMSC where they presented data looking back at patients who had three-plus medical comorbidities versus those who did not. And what they found was that the folks who did not have all of these medical comorbidities—whether that be something like diabetes, COPD, certainly

a history of heart disease, et cetera—those folks had far lower rates of disease progression over time than, say, those who did.

[00:24:10] And so it does seem that drives a lot of that eroding of that neurologic reserve, and it is why, at least when I meet with my patients, we're not just talking about transverse myelitis. We're talking about their overall cardiovascular health to make sure that we're giving the body the best possible chance at long-term recovery.

[00:24:36] **Krissy Dilger:** Great. That's all very interesting, and I would love to have you on a separate podcast one day to talk specifically about aging because I think there's a lot of interest in that topic.

[00:24:53] **Dr. Shuvro Roy:** Absolutely.

[00:24:53] **Krissy Dilger:** This person wrote in, "I've recently heard how peptides, specifically BPC-157, can do healing for some different things. Has any research been done in this field regarding TM?" And then they also want to know if there's any progress in research having to do with stem cells.

[00:25:21] **Dr. Shuvro Roy:** I would say first, upfront, with peptides, this feels like something that is getting looked at in a variety of different ways. But the first caveat is that everything that I have seen is preclinical—a preclinical model, AKA never been tried in a human body. BPC is, I believe, body protection compound. And it has been shown in some animal models, primarily mice and rats, to basically provide some degree of neuroprotection in models where we're trying to recreate essentially multiple sclerosis.

[00:26:15] There are a couple of others, other types of peptides, that all do different things. Peptides are basically just different proteins that kindle or stimulate different parts of the body. And so, some may activate certain blood vessels, or others may stimulate... This one, BPC, is actually a gastric compound, or something coming from the stomach.

[00:26:42] But while it seems like these may show some degree of benefit theoretically in terms of, say, reducing inflammation and perhaps even trying to promote remyelination, I think we're still a ways away from any sort of clinical validation. And so, of course, moving that from those animal models into, say, early studies with humans.

[00:27:18] I don't pretend to say that, okay, this is a strong area of research for me that I have a lot of experience with. But I would say what's interesting as a neuroimmunologist is we're really starting to see a lot of different molecules for remyelination. At last year's—I believe it was CMSC—they had a list of 50 different molecules, including several peptides, that were being investigated.

[00:27:47] And the question would then be, okay, does that mean that some of these will eventually move to clinical studies or clinical trials? The answer is I would hope so. I would hope so, so that we can maybe use some of these for treatment in the future. It's more just the understanding that it'll certainly take some time before we're necessarily there. Was there...

[00:28:14] oh, yes, stem cells. Okay, stem cells. So, it depends on what we're talking about with stem cells. I think where we have seen stem cells applied the most in the neuroimmunology space has actually been for MS and trying to almost do this immune reset. And essentially, what we're looking at there is—this has been a trial here in the US called BEAT-MS. We are actually a trial site for that.

[00:28:54] And then in Europe, they've been using stem cells for, say, the treatment of multiple sclerosis, and with varying benefit. It seems like basically doing a stem cell transplant almost does reset the immune

system to some degree, where folks usually five to seven years after a stem cell transplant don't seem to have new inflammatory attacks in the brain, the spinal cord, or the optic nerves.

[00:29:28] Where the data is a little bit more mixed is: does it help with progression? We just talked a lot about how progression—a lot of that process—may be driven by aging and factors around aging, and how healthily we age. And, of course, a stem cell transplant doesn't necessarily touch on that. It may calm down some inflammation, but it doesn't address every single factor that drives aging.

[00:29:55] Beyond that, I haven't really seen any data that suggests that, say... I think oftentimes I'm asked this question in the clinic in the context of, "Okay, if I get a stem cell transplant, is that going to repair my transverse myelitis?" I've seen nothing of the sort to suggest that would happen.

[00:30:15] That's where we are with stem cell transplants. What I will mention along that same line, because I think when folks talk about stem cell transplants it's almost a broader conversation into what I would call cell-based therapy. Because truthfully, I don't know that a lot of people are really looking at stem cells anymore. I think we've almost left that technology behind, and that's just my personal opinion.

[00:30:45] But I think where we are moving is into other cell-based technologies. The most intriguing ones to me are what we call CAR-T cells. So basically, where somebody goes through a similar process to preparing for a stem cell transplant—of receiving some degree of chemotherapy—and then actually T cells [white blood cells] are drawn from the blood and trained outside the body to then target something in particular.

[00:31:20] This is being looked at in neuromyelitis optica and even actually in multiple sclerosis. And then those T cells, after they are trained for several weeks, are then reinfused into the body. And I mention this because, at least from a safety standpoint, CAR-T, from what we've seen so far in autoimmune diseases, is way better tolerated and way safer than a stem cell transplant, whereas a stem cell transplant is notoriously rough on the body.

[00:31:53] And so folks can have a lot of complications in that process, including the process of what we call conditioning, or essentially receiving all of this chemotherapy to be in a place to receive the stem cell transplant. And then, of course, with a stem cell transplant, there can be a lot of long-term issues, including what we call graft-versus-host disease, where basically the body starts to attack that transplant.

[00:32:22] We have not really seen that in CAR-T because we are essentially using someone's own cells to do that. And there's a lot of promise, I think, overall, in what I call cell-based therapies as a broader terminology. And then with stem cells, I think it's one of those things where, yes, it has been looked at, but the question of whether the juice is worth the squeeze, I think, has started to shift towards it may not be, because there actually may be more promising, safer options down the road.

[00:33:05] **Krissy Dilger:** Great. Thank you so much. Someone wrote in: what causes the fatigue and difficulty sleeping with TM? And as a part two to that, are gummies safe to use to help with sleep?

[00:33:20] **Dr. Shuvro Roy:** Got it. Fatigue and difficulty sleeping are, of course—if this were somebody in clinic with me, I'd have tons of follow-up questions, of course, because fatigue can be from many different things. Whether that's a medical condition like a common thyroid issue, a low iron count, or just even like a low B12. In transverse myelitis, I find that fatigue could be due to many things. And commonly in a lot of my patients, it's a disruption of sleep. And that can be from complications related to the transverse myelitis, whether it's, say, muscle spasms at night. That's easily the most common issue that I run into when chatting with my patients—muscle spasms at night disrupting sleep, leading to really excessive daytime fatigue.

[00:34:25] And so usually my first approach is, "Okay, how can we target sleep? What's going on there?" and, of course, keeping in mind that folks with transverse myelitis can have many other medical conditions, so making sure we're screening for that. Does somebody have iron deficiency anemia? Do they have sleep apnea?

[00:34:48] That becomes an issue for some of our patients with TM where, if you're, say, less mobile, understandably that can lead to some weight gain. And then with that comes sleep apnea, disrupted sleep, so on and so forth. So even just doing a sleep test is really valuable on my end, and I really lean on our sleep clinic here for a lot of our patients.

[00:35:14] Sorry, there was another bit of the question about, oh yeah, difficulty sleeping. And actually, it's such a common issue that we also work with our neuropsychologists here at our institution. And I've told Krissy this story: the reason I took the job at the University of Washington is because we have four neuropsychologists in our clinic dedicated to our patients with neuroimmunologic disorders.

[00:35:41] And they actually even run a workshop throughout the year on difficulties with sleep and what are strategies for that. I think that even just difficulty with sleep is also what we call multifactorial. There are many different issues that could be at play there beyond what I just mentioned. Of course, there is sleep hygiene.

[00:36:06] I say this as the world's biggest hypocrite—I myself have horrible sleep hygiene. I am looking at patient charts and screens and blue light right up until bedtime every day, which, of course, depresses melatonin production, delaying our body's ability to fall asleep by two to three hours thereafter.

[00:36:28] And, of course, leads to fragmented and disrupted sleep. Somebody asked about gummies, and I would imagine that is basically CBD or THC-containing gummies. And I would say for the most part, yes, that is relatively safe, just depending on, of course, dosing—dosing is a big part of that.

[00:36:54] I won't get too much into that, but I would always recommend touching base with your medical provider on that particular advice. In general, for all of these disorders, I recommend, if somebody is going to use any sort of cannabinoid or marijuana product, I would prefer that they use gummies over, say, smoking.

[00:37:21] And that's mostly just because the smoke itself is going to create a pro-inflammatory environment in your body. And, of course, that in general is just going to worsen a lot of your symptoms, maybe even increase your risk of disease activity. We certainly see that in MS—that with smoking, there's an increased risk of further relapses. And that would be my recommendation there.

[00:37:56] **Krissy Dilger:** Great. Thank you. So, we've gotten several questions regarding pain. This person was diagnosed with TM over a decade ago, and they've tried many different medications that have not been effective. What would you recommend for someone who has failed a bunch of traditional medications for pain?

[00:38:21] **Dr. Shuvro Roy:** Yeah. And this is something that truthfully, I'm also even digging into. I don't know how many folks will be at RNDS, but that will be my topic to discuss: pain management. Which, much of it depends on what sort of pain somebody is experiencing.

[00:38:39] With transverse myelitis, patients can certainly have what we call neuropathic pain—or that electric sensation, burning pain—that is managed by almost one set of medications and treatments. And then there's also issues with muscle spasticity, which is managed differently as well.

[00:39:05] I'll quickly run through, okay, what is our stepwise approach? With a lot of our patients, I actually don't necessarily start with medication. I start with lifestyle. I bring that up because we presented some work

recently at the CMSC and the American Academy of Neurology, and then hopefully we'll publish this relatively soon, where we did look at, for example, a patient's metabolic health, going back to a couple of questions ago.

[00:39:39] And at our center, how did that impact patients' symptoms if, say, they were on one of the GLP-1 medications, or they were getting more physical activity, or if they had a certain degree of weight loss? And actually, our strongest signal was with body pain, seeing at least from what patients told us and what they reported and scored their pain as.

[00:40:05] Over the six months that we followed folks, that was the most impressive change that we saw in terms of the improvement of their symptoms. And I often start with, okay, what can we do in terms of just whether it's physical activity or targeting lifestyle? And I mention that because, say, let's start with muscle spasms or muscle spasticity.

[00:40:28] The most natural way to stretch our muscles is just movement. And that leads to them remaining relaxed throughout the day, with lower rates of muscle spasms. And so that's something that we target upfront. Now, for the person who wrote in, it seems like, okay, they've probably been through a lot of different things.

[00:40:52] But the next step would then be prescription medications, whether that's like a gabapentinoid—AKA gabapentin, Lyrica—or other medications. Duloxetine is one that I use a lot of for patients. But if that doesn't work, then that's where we're getting into emerging areas of treatment.

[00:41:18] So for example—again, I will just say this is what I do, others may do different things— but for example, I've found that things like low-dose naltrexone, which admittedly does have some controversy around it in our space, has been helpful for some of my patients who have had refractory nerve pain, utilizing that at a dose of, say, like 4.5 milligrams.

[00:41:49] It's a little tricky because you need to get it through a compounding pharmacy, and unfortunately, some of my patients do have to pay some degree of the cost out of pocket. That has been something that has been helpful for some folks. Another really interesting area is this idea of what we call neuromodulation.

[00:42:12] That could be something like a TENS unit, which some patients have used. And for anyone, say, through the VA, that is often available for free. Unfortunately, that's not the case for folks not at the VA. There's something called transmagnetic stimulation—or transcranial magnetic stimulation, TMS for short.

[00:42:34] This is very much like still up in the air, but this is being looked at, and has been looked at for a few years, at a couple of different institutions. The main one I think of is Stanford, where they look at that for neuropathic pain and whether it helps folks. And then I mentioned briefly before spinal cord stimulation, and there are implantable spinal cord stimulators.

[00:43:00] Where we are doing some research with one of my colleagues is what we call cutaneous spinal cord stimulation. So, over the skin, applying an electric current and seeing if that promotes repair and reduces pain. We had primarily been looking at that in folks who had involvement of the cervical cord.

[00:43:22] We'll see what that shows. The early results are somewhat promising. Where that's a little dissatisfying as an answer is there are some things that are not yet totally ready for prime time or totally approved. Those are things beyond your typical oral medications, which are areas that are under investigation right now.

[00:43:52] **Krissy Dilger:** Great. Thank you so much. That's very helpful. So, someone wrote in that they were diagnosed with TM over a year ago. They no longer have inflammation. Their attack is under control. But

they were told by the neurologist that physical therapy is the way to—is the last thing that they have left to go forward. They were wondering, how long does it take to get back to normal with physical therapy?

[00:44:27] **Dr. Shuvro Roy:** Okay. Again, lots of follow-up questions. And I think a lot of it depends on what type of transverse myelitis was this? If this was, say, caused by, say, like NMO, unfortunately, we do see a lot of folks have incomplete recovery. And I think this is often a conversation that patients have with me of, "Okay, am I going to get back to normal? Am I going to have some degree of symptoms?"

[00:45:01] Really only time will tell. But what we do see is that physical activity makes an enormous difference in what that trajectory looks like, especially early on in the first couple of years after a transverse myelitis. One, we know that the nerves are incredibly slow to heal and to regenerate—literally millimeter by millimeter.

[00:45:31] But I think for this person, I'm implying by seeing the question, "I'm up to walking with a walker," implies that they may not have been walking before. And that's really encouraging that they've had improvement so far. Sometimes it may take years, and sometimes it may be that folks don't get back to themselves, especially depending on what parts of the spinal cord were involved.

[00:46:02] If, say, somebody has transverse myelitis from MS, where it tends to be rather a small segment, a small portion of the spinal cord, and then the rest of the spinal cord may otherwise be healthy— that's probably a better prognosis than, say, NMO, where it tends to be a larger proportion of the spinal cord that's involved, or versus, say, MOG antibody disease, where somebody could have the worst-looking transverse myelitis you've ever seen, and then you treat them with steroids and the whole thing completely disappears, and they do quite well long-term.

[00:46:36] So, I think a lot of it depends on the cause. But going back to the fundamentals of what we were talking about, whereas we see that continuous stimulation—those signals running through the spinal cord—it essentially promotes, one, that almost muscle memory of maintaining those connections between neurons, because if you don't use it, you lose it.

[00:47:05] And that just becomes more work for you to have to try to rebuild those connections. And then we do see that it leads to just more and more neurologic reserve and function over time. So, I would say to—this is one of those things where stick with it, stick with the plan.

[00:47:29] I think it's important to have a physical therapist who has some experience with spinal cord disorders and can help guide you in that way. But I've certainly seen patients who, even three or four years out, continue to make progress after an event by sticking with their plan.

[00:47:55] **Krissy Dilger:** Great. Thank you. I know you mentioned stimulation—spinal cord stimulation—as one of the things that are potentially used for pain and also function, potentially regaining function. But someone wrote in that specifically their rehab center offers ArcX therapy. I don't know if you've heard of that or are familiar, but do you have any experience treating TM with that, and would you recommend it?

[00:48:28] **Dr. Shuvro Roy:** This is literally essentially the same thing that we're doing at our center. The UPLIFT trial. So, ArcX. Yeah, this is something where we have been offering it, or at least—we're offering it when we were enrolling patients in the trial. Basically, it was a single-arm study where patients were receiving that sort of spinal cord stimulation at the site of a cervical injury or cervical spinal cord injury and then seeing what did that do in terms of their—particularly their hand function.

[00:49:13] I know this because those patients did have to have a certain degree of impairment in their hand function. I know this because I tried to enroll a few folks, so they were apparently too functional or doing too well to get enrolled. But this has been, I think, quite informative for me—this trial and this study—and really this mechanism of really suggesting to us that, yes, the more we stimulate the spinal cord, whether through an external stimulator or just through our own bodies by just trying to engage in exercise, it really does make a difference in how folks do.

[00:49:58] I'm hoping a lot of that initial study was with the hope that we can then start to apply this principle into a broader context, because it's a rather limited context of just cervical spinal cord injury. There's a lot more, as we know, of patients who have other issues. That would be something that I'd be quite interested in down the line.

[00:50:28] **Krissy Dilger:** Great. And someone, just as a spin-off of that question, asked: where would you apply the stimulation? Would it be at the site where the lesion was at?

[00:50:41] **Dr. Shuvro Roy:** Great question. We're still trying to learn. Is it best to stimulate, say, all the way at the top, say, at the level of the scalp, and then conduct it downstream? Is it better to directly stimulate at the site of the lesion? I think it's hard to say for sure. That's where I think, hopefully, the start of this initial study allows us to then ask these follow-up questions and continue to expand that work and get better answers there.

[00:51:22] But my hypothesis would be that directly stimulating as close to the site of the lesion as possible would make the most sense. But the spinal cord is a surprisingly complicated circuit. And so, I think that's something that is totally worth investigating in future studies.

[00:51:45] **Krissy Dilger:** Great. Someone wrote in that they are taking Pregabalin. What are your thoughts on them trying to stop taking it?

[00:51:55] **Dr. Shuvro Roy:** Yeah. Definitely talk to your provider on that, because I've had this happen where we've had patients who are taking certain doses and stopped without talking to us. And while it is not common, there is such a thing as gabapentin withdrawal, and patients can have—you know, basically almost like an overactivation of their nervous system as a result.

[00:52:25] So I would always just touch base with your provider on how to wean that off. I'm not going to provide instructions on that here because, again, I want you to talk to your medical professional. I think it is a medication that, if it's not working for you, it is reasonable to come off of it, but I just think it's important to do so in a controlled way to avoid that, again, small but very possible risk of some degree of withdrawal.

[00:52:57] **Krissy Dilger:** Great. Thank you. Someone asked: are there any new treatments or test programs available for TM that will consider a 74-year-old who is four years out from diagnosis?

[00:53:11] **Dr. Shuvro Roy:** Good question. And I will say, one of the frustrations I have with a lot of clinical trials or specific programs that folks are conducting out there is age restrictions. Where, for example, even in some of the MS clinical trials, they have limitations where patients had to be under age 55 for many years. And even with some of these newer progressive therapies, the clinical trials have a cutoff of age 65.

[00:53:50] But I think what we are starting to see more of is there are more programs really centered around rehabilitation and then trying to see, okay, how do those folks do over time? Kennedy Krieger—Kennedy

Krieger is over in Baltimore, for example—I think is conducting a lot of different studies looking at things like even just recumbent bicycling, and I think for us, we're looking at just overall physical activity.

[00:54:29] And even certain programs—we have a study on a program called Exercise Rx, which is literally a program where we as providers are providing encouragement to our patients on, "Hey, you're here, I see that we're tracking your exercise. I see you're doing a great job, keep it up." Also, of course, providing some input on what can we do or what types of exercises may be helpful for a patient. That's irrespective of age. And certainly, when we're talking about if we have a diagnosis and we're four years out, much of what we are trying to do is focus on recovery and functional outcomes.

[00:55:16] That includes even things like, for example, I don't know if we talked too much about Botox, but that's something that's been used more and more for the management of muscle spasticity, and that also does not have any sort of age limitation. But I think that's the overall theme of what a lot of these programs are looking at. And my hope is that would be for really anyone of any age at any point after their diagnosis and not necessarily focused on right after somebody's had an attack.

[00:55:57] **Krissy Dilger:** Great. Thank you so much. I think we only have time for probably maybe one, one more question. But this person was diagnosed with TM in 2019, and they had a slight relapse from COVID, but they tested negative for MOG and aquaporin-4.

[00:56:20] Recently, they had something that triggered spinal lesions again, and the MOG test now came up at 1:120. So, the question is: with no optic nerve or brain lesions, only spinal cord lesions, is that MOG positive enough to change their diagnosis from TM to MOG?

[00:56:45] **Dr. Shuvro Roy:** Wow, what a really—that's a really interesting case. So, I would say that certainly you've had transverse myelitis, and that is like a diagnosis that you could have in your chart irrespective. Now, per the diagnostic criteria, if you had transverse myelitis plus a MOG antibody titer above a certain threshold—and this is important because MOG is a really finicky antibody, as you have experienced, where it was seemingly negative before and now positive.

[00:57:27] If it's above a certain threshold—so more than 1:100—that's what we consider a high positive titer. And usually that's enough to make a diagnosis of MOGAD. The only thing that I think is a little strange, 1:120, admittedly, is kind of a weird titration just based on being a big nerd and knowing how these labs are titrated.

[00:57:53] That is not—and, admittedly, it was a paper I wrote several years ago with Elias Sotirchos. That's a little bit of a weird titration, but it may just be related to the test. I think with something like that, I'd probably want to test it again just to feel comfortable. And then, of course, I would want to look back at: was this a transverse myelitis that behaved like MOGAD just to be safe? And what I mean by that: was it in a typical location?

[00:58:23] For example, with MOG antibody disease, the transverse myelitis from that disorder tends to be a little bit lower in the spinal cord. Heading down into what we call the conus, so the very tail end of the spinal cord, it tends to respond really well to steroids. And oftentimes, the lesion tends to disappear again. And so, I think that would be something that I would certainly want to know. Sometimes there's been—in cases where it's a little bit questionable, sometimes providers will actually advocate for checking the MOG antibody, but in the spinal fluid instead of the blood.

[00:59:08] There's some work out of Italy that suggests that up to 15 percent of patients may actually only have the antibody positive in the spinal fluid. And those patients also seem to have a higher rate of transverse

myelitis than those with it just in the blood, where it may be more common to have optic neuritis. My suspicion is that it'll probably be enough, but of course, I would just touch base with your provider, and those are some additional things that I would consider in the context. It's a fascinating case and I'm sure challenging to navigate in terms of just some of that uncertainty. But I hope that we can get an answer for you.

[00:59:59] **Krissy Dilger:** Great. Thank you so much. That is the end of our time, but I appreciate all of your help and expertise, Dr. Roy. Thank you so much.

[01:00:10] **Dr. Shuvro Roy:** This was a blast. I really appreciate all these thoughtful questions and, thanks, Krissy, for setting this up.

[01:00:18] **Krissy Dilger:** Thank you to our "Ask the Expert" sponsors, Amgen; Alexion, AstraZeneca Rare Disease; Genentech; and UCB. Amgen is focused on the discovery, development, and commercialization of medicines that address critical needs for people impacted by rare autoimmune and severe inflammatory diseases. They apply scientific expertise and courage to bring clinically meaningful therapies to patients. Amgen believes science and compassion must work together to transform lives.

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