An open moderated panel session to discuss trending topics in rare neuroimmune disorders

You can view this presentation at: youtu.be/yFtm49ptgoc

[00:00:00] **Dr. Michael Levy:** This is where we get to ask these distinguished panelists any kind of questions that we have for them. I have some questions, there'll be questions posed online. And if you have questions we can ask, we can ask here in this venue. let me start with introductions. You've heard me this morning, Michael Levy at Mass General. I'll let each person; I think your mic's turned on. Just give a brief introduction of who you are again and anything else that you wanna say.

[00:00:42] **Dr. Carlos A. Pardo:** My name is Carlos Pardo. I am a neurologist at Johns Hopkins School of Medicine. And I have basically responsibility to take care of the Johns Hopkins and Myelopathy and Myelitis center. That was the first myelitis center established in the world in 1999. And we have the privilege to take care of a lot of patients and also to train a lot of very good doctors and immunologists.

[00:01:17] **Dr. Grace Gombolay:** Hi everyone. My name is Grace Gombolay. I'm from Emory and Children's Healthcare of Atlanta. I'm actually a pediatric neurologist. I established the first and only pediatric neuroimmunology and multiple sclerosis center in Georgia. And I get referrals from Florida and South Carolina because there's no one there either. Thank you.

[00:01:37] **Dr. Melissa Hutchinson:** My name is Melissa Hutchinson, and I'm also a pediatric neurologist. And I am at Nationwide Children's Hospital in Columbus, Ohio. Also affiliated with Ohio State University.

[00:01:49] **Dr. Michael Levy:** And I believe we have online. We have Dr. Flanagan. There he is.

[00:01:54] **Dr. Eoin P. Flanagan:** I am here. Yeah, thanks. My name is Eoin Flanagan, and I'm a neurologist at the Mayo Clinic. I see patients with myelopathy and other neuroimmune conditions. And I also work in the Mayo clinic neuroimmunology lab where we do some testing for some of the antibodies. So great pleasure to be here.

[00:02:14] **Dr. Michael Levy:** All right. I'm gonna start off just pitching a couple of questions to these guys. But again, do feel free to jump in. Let's start with Dr. Pardo. Dr. Pardo, people have all kinds of reasons for spinal cord dysfunction. Some of them transverse myelitis, neuromyelitis optica, a lot of the inflammatory conditions we talked about here today and yesterday. But that's not the only thing that can look like these

conditions, right? Aren't -- what other main issue in the spinal cord could be -- could mimic these conditions, especially in older folks?

[00:02:58] **Dr. Carlos A. Pardo:** Well, Michael, thank you so much for this loaded question. The first thing is we discussed this yesterday, that we have been using the term transverse myelitis. The term transverse myelitis has been used in the past 70 years. It was introduced back in the mid-40s and early 50s, and it was always associated with inflammation of the spinal cord triggered by infections. And since then, has been used by many clinicians around the world. And one thing that actually we have encountered in our center, and this is part of a word that we started back in 1999, was a very different phenotyping of all the patients that were evaluated in our center with the diagnostic transverse myelitis. And when I say phenotyping, that's the word that we use to define a very good characterization of what is going on with the patients. So, the clinical phenotyping of all the patients that came to our clinic, for example, in the past 20 years were recently published, and actually last week it was published and it's going to be available to you on the SRNA website. But what we learned is after seeing approximately 1,200 patients with the diagnosis of transverse myelitis is that only 70% of those patients really had myelitis.

[00:04:33] So that means that 30% of the patients actually didn't have myelitis, in other words, they didn't have inflammation of the spinal cord. And unfortunately, some of those patients were misdiagnosed. Other disorders basically were misdiagnosed and given the diagnosis of transverse myelitis. Which were those problems? Probably the most frequent one and most concerning one is a spinal cord has a risk of strokes. In the same way that we have a stroke in the brain, the spinal cord has a stroke as well. And the -- what we have learned is actually almost 10% of our patients that came to our clinic with the diagnosis of transverse myelitis have, not necessarily myelitis, had strokes of the spinal cord. And even some of them were managed with plasma exchange, IVIG, and even immunosuppressive treatments. They didn't need that, there was no need for use of those medications. So, one thing that we learned is basically we need to be extremely cautious about how to approach patients with acute onset of the spinal cord disorders, because in the spectrum of those acute problems is stroke of the spinal cord.

[00:05:50] And even in other patients, there is a possibility that long-term symptoms like happen particularly in men over age 60, those actually may be associated with vascular problems that are chronic in the spinal cord, and those are frequently associated with something that's called dural arteriovenous fistula. Those are abnormalities of blood drainage in the spinal cord, and those actually represent in our experience more than 7% of the cases. So, in other words, we have, and we encountered that almost 15-17% of our patients actually have vascular causes of spinal cord disease. So, the main message that I think that we are learning from all of this experience is, yes, we need to be paying attention about myelitis, NMO, MOG but if we have unusual patients in which they don't respond to steroid treatment or even they worsen with the steroid treatment, you need to be very concerned about vascular etiologies.

[00:06:57] Many patients with the stroke of the spinal cord having gone on for several months like a dural AV fistula actually they get worse with IV-admitted prednisolone or oral prednisone. So that is a flag for establishing the diagnosis. So, in summary we need to be open-minded, so not everything is NMO, not everything is MS, not everything is MOG. So, the clinician is obligated to do a very good characterization of the clinical profile, MRI findings, a spinal fluid analysis as well as blood testing before committing to a more definite diagnosis.

[00:07:38] **Dr. Michael Levy:** I think we need to push on our radiology colleagues to improve the MRIs of the spinal cord. I think that that's a real difficult position that we're put in there. OK, Grace, I'm not gonna be as easy on you, because Carlos was my mentor, so I pitched him easy questions. I've got a kind of hard one for you.

[00:08:00] **Dr. Grace Gombolay:** Bring it on.

[00:08:03] **Dr. Michael Levy:** Vaccines. Whether or not they're linked to transverse myelitis and other conditions and relapses. I think a lot of people have very strong feelings about whether to use them or not and in which situations. How do you counsel parents when they ask you if their kid who had transverse myelitis three months ago should get the COVID booster? How do you answer that question?

[00:08:32] **Dr. Grace Gombolay:** Yeah, I think that's a great question and I think a lot of things about vaccinations is that we do know that they can cause inflammation in rare cases and there's that association. So, association means two things are linked to each other. It doesn't mean causation. And that's what's really hard because a lot of things are linked to each other and probably one event causes the next one, but we can't really prove it in a lot of cases. And so, for me, it's all about risk versus benefits and that's where it all comes down to. And when you think about it, when we talk about tests -- the testing that we do, we try to do tests that are minimally invasive, meaning nothing that really goes in. Like every time somebody comes in with a brain issue, it's not like we immediately say, let's go on with surgery and take out a piece and see what's going on, right? We try to do less invasive, less potentially harmful interventions, because that outweighs the risks of those interventions. Same thing with medications and treatments, we've heard a lot about when to start treatment, and especially in MOGAD, we're still learning about when we should think about those things.

[00:09:31] And it goes back to that risk versus benefit where some of these treatments there's some risks associated with it, but the benefits outweigh the risk It makes sense to move forward. And so that's what I talk to my families about with vaccinations, and I've seen lots of even young kids, you know, babies, I have two babies of my own right now, like they get vaccines like every three to six months when they're really, really little. Like my infant has gotten so many vaccines, and I've seen a couple of cases of transverse myelitis or acute disseminated myelitis that was associated. Again, I can't prove that it caused it, we think probably there's a link, but we can't prove it. But at the same time, I still get my kids vaccinated and that's what I tell families. I think it's powerful, that personal experience, because we call it anecdata, right? I can quote all of the studies in the world, but if you know somebody personally where something personally has happened to them, it trumps all of that data and all that research. And so, what I tell them and what I think in my mind is what is the risk versus benefit of the vaccination?

[00:10:29] There's a lot of infections out there where the risk of getting that infection is very, very high. It can cause even worse neurological morbidity and actually, kids can die from those infections, than getting the vaccine. And so, we sort of talk about those risks. It comes on the case, a case-by-case basis, especially if you had an event associated with a vaccine. We have to really talk about those things. Sometimes we do it where we space them out, do one at a time instead of giving them in groups, I've definitely done that before. And we also talk about when this is the timing to be correct. And so, for example, for the COVID vaccination, because that's a common thing that people are talking about nowadays. I think for me, and there's lots of studies showing this, the risks of hospitalization and severe COVID especially if you're on an immune treatment. So, rituximab or some of these CD20 agents is a good example of that. Your risk for getting serious complications is higher if you get COVID infection versus if you're vaccinated and vaccination protects you against those serious complications. So, for me again, it goes back to the risk versus benefits for those things.

[00:11:36] **Dr. Michael Levy:** Okay, Melissa. The ethics of children in clinical trials, there's some who say that it's not ethical to give a kid a place -- to enroll a kid if there's a chance of a placebo. And then there are some who say, well, if you don't do the science, you'll never know if a drug works for a kid. Where do you land on that in that debate? And how do you justify that position?

[00:12:03] **Dr. Melissa Hutchinson:** These are getting tougher. So, I actually have a ton of families that ask, where are the trials? Can I sign up for the trials? Can I be a part of the science? And they're really wanting and craving an opportunity to learn more about these disease processes and learn more about the potential treatments for these disease processes. And so, you know, for me again, it's just this is the theme of the weekend, which is it's nuanced and it comes down to those conversations with families. And I think for myself, I'm not sure it's my role to decide whether or not a child should be enrolled in that clinical trial. I think it's my role to talk about what that family's goals and priorities are and where they land and their -- what their ethical stances are. Certainly, there are lots of ethical decisions in the design of trials and that's kind of taken out of the hands of families. But once the trial is designed, I think it's really important to talk with families about those opportunities and give them the knowledge and the tools to make that decision for themselves.

[00:13:14] **Dr. Grace Gombolay:** I was just gonna add one more thing, because I agree with what Dr. Hutchinson just said. I think the other thing is that we have to think about clinical trial design, right? Because right now, the gold standard, what we've been taught especially in medical school is placebo versus your actual medication. Does this medication work better than the placebo? 'Cause we talk about the placebo effect, which is where you're given this treatment that's not supposed to do anything but may potentially have benefits. So, you're comparing those two. I've definitely seen other cases where we're talking about non-inferiority trials. And that's something to think about, again with the risk versus benefit of not treating somebody with the condition where you're comparing two treatments to each other. 'Cause right now we're saying one treatment is better than the other, but can we say one treatment works similarly to the other? And I think we should think about scientifically if we can think about trials like that so that they are ethical. We are giving patients treatment if the risk of having a relapse, or an episode or worsening disease outweighs the risk of not being on something.

[00:14:12] **Dr. Michael Levy:** Okay. Dr. Flanagan, are you online?

[00:14:16] **Dr. Eoin P. Flanagan:** I am right here.

[00:14:17] **Dr. Michael Levy:** Okay. You did a lot of testing at the Mayo Clinic. And still, a lot of my patients are double-seronegative. They have no MOG antibodies detected and no aquaporin-4 antibodies. So, do they have other antibodies? And how do you go about discovering new antibodies?

[00:14:41] **Dr. Eoin P. Flanagan:** Well, that's a good question. So, I think we can learn a lot from how we did it before. So, Dr. Lennon in the neuroimmunology lab at the Mayo Clinic initially recognized a pattern on some of the mouse tissue that we run our testing on. And that turned out to be aquaporin-4 antibodies. And then we were able to develop a test now with the live cell-based assay that's very reliable and available around the world. So, I think with some of these cases they offer a real opportunity for discovery. So, we can analyze those and use different techniques to try and discover if there is a target antibody in those cases. I think it's also important to look at other things, other diseases that we know like multiple sclerosis or sarcoidosis or other conditions that can mimic.

[00:15:33] And like Dr. Pardo mentioned with this nice recent study a comprehensive evaluation is really important in these cases. Not just the antibodies, but reviewing the MRI Pattern, reviewing the spinal fluid findings, other tests to make sure that there's not a different diagnosis out there. But if not, then I think we have to initiate treatment as best as possible and also utilize those cases for discovery. So sometimes we're sending those to the lab, and I think in the future we'll be looking at some of the immune signatures in those cases, something called cytokines which are some of the immune markers that can be elevated. And some of those can be targeted and they lead to treatments for neuromyelitis optica and other conditions. So, I

think in some of those cases in the future we may have more of a precision type treatment aimed at those cases rather than going blindly with some sort of immunosuppression. So hopefully if we can't discover the target at least we could give them more guided treatment to those cases.

[00:16:37] **Dr. Michael Levy:** And the double-seronegative, do you think that they have another antibody if the disease sounds fairly convincing, or are you pretty confident that maybe it's something else?

[00:16:51] **Dr. Eoin P. Flanagan:** No. I think there's probably other antibodies out there. I think just when you get into that double negative category, that's probably half of those cases at least that turn out to have something different like sarcoidosis or multiple sclerosis. But there certainly are cases that look really like a double-seronegative NMOSD, and they've probably got a different antibody I would imagine. So, it's something more for us to discover. So that's why we get up in the morning every day to try and learn about these things and figure them out.

[00:17:25] **Dr. Michael Levy:** Are there any questions online or from the audience before I go back around?

[00:17:34] **Audience Member 1:** There are quite a few questions that are coming in online. One about MOGAD, is pregnancy related to relapse and or disease worsening?

[00:17:45] **Dr. Michael Levy:** In MOG. Let's see. How about Grace? I guess you're asking about pregnancy.

[00:17:52] **Dr. Grace Gombolay:** I was gonna say most of my patients are not pregnant. This is not something I've come into contact with.

[00:17:56] **Audience Member 1:** Yeah, pregnancy.

[00:18:00] **Dr. Michael Levy:** Carlos, do you wanna take this one?

[00:18:03] **Dr. Carlos A. Pardo:** Let me see if I understand the question. What is the effect of pregnancy?

[00:18:07] **Dr. Michael Levy:** On disease activity in MOG?

[00:18:09] **Dr. Carlos A. Pardo:** To be honest, I have no idea. The reason is we base our observations on basically observational studies and so far, to my knowledge, there is not any study that have evaluated the pregnancy in patients with MOGAD, so that's the fair answer. But if you'd like to speculate based on what we experience in other immunological disorders, pregnancy may have some effects that modified the evolution of immunological problems during pregnancy. But the aftermath of the pregnancy is going to be probably problematic in some way for triggering more immunological reactivity. But again, at the present, to my knowledge, there is no evidence of any observational trials that evaluate the effect of pregnancy in patients with MOGAD.

[00:19:07] **Dr. Michael Levy:** Yeah, we know in MS, pregnancy is helpful and in NMO pregnancy is a warning sign that right after pregnancy relapse risk is really high. But in MOG, I think the data has not yet been collected.

[00:19:21] **Audience Member 1:** Okay, thank you. I have -

[00:19:23] **Dr. Michael Levy:** Yeah, bring them on.

[00:19:24] **Audience Member 1:** All right. I am an NMO patient, double negative. Is research occurring or in the plans to look into a possible cause for us? Has any research been done reviewing common symptoms or progression of double negative NMO patients, as comparison of aquaporin-4 positive and MOG positive have identified variations?

[00:19:44] **Dr. Michael Levy:** Yeah, I think I'm gonna pose this to Dr. Flanagan. But I'm gonna start by saying that we've talked a lot about categorizing double seronegative and saying okay, we're gonna develop a trial for these people. And then the question comes up what if there's more than one type of patient in this category? What if there -- what if there are two different diseases in there? And Dr. Flanagan is gonna find the two antibodies and then we're doing a trial in two different diseases. So, I'm inclined to lump them together and to try different therapies, but I wanna know what Dr. Flanagan thinks.

[00:20:18] **Dr. Eoin P. Flanagan:** Yeah, that's -- it's complicated. I think you know, there could be more than one antibody, like you say, accounting for those cases. So, it's a little bit of a challenge to tease out. I think, like I mentioned earlier, looking at some of the immune signatures like we know with the neuromyelitis optica spectrum disorder, that the GFAP which is a marker of damage to one of the brain cells called the astrocytes, and that tends to increase in the blood with neuromyelitis optica. If we look at some of those markers across the seronegative NMOSD, we may be able to get a signature and divide them into different categories and then really home in on which these different diseases are. But for now, I think like Michael said, we have to kind of take a practical approach and try and treat these patients as best as we can. Unfortunately, in the clinical trials for NMOSD, really the aquaporin-4 positive patients did best with the treatment than the seronegative patients and didn't seem to have as many benefits. So, I do think there were the further study though, and we need to try some sort of treatments for them while we're awaiting these discoveries.

[00:21:36] **Audience Member 1:** Questions from the -- I'm gonna -

[00:21:37] **Dr. Michael Levy:** Yeah, Dr. Pardo has a -- would like to -

[00:21:41] **Dr. Carlos A. Pardo:** So double negative is an interesting terminology. And one thing that I always emphasize when we see patients with negative antibodies is that we need to keep our mind very open to the possibility that there are other factors either immunological or other type of factors including genetic factors. And we haven't mentioned too much about genetics. In the field of neuroimmunology in the past 10 years, we are learning more and more about the role of genetics in some of the brain inflammatory disorders. There is a group of disorders that is called autoinflammatory disorders, and some of them actually show up in the brain looking like NMO, looking like MS, and later we realize oh, they are not responding to any treatment. And the reason is because they are no classical neuroimmunological disorders. These are disorders that are associated with genetic factors, mutations in genes associated with immune pathways. And I think in the future those group of patients that are tested every time and they keep testing negative, negative, negative, the clinician needs to be very critical with the data and raise concerns. Okay, is there any other immunological factor? Is there any genetic factor? And I think that we are learning about that.

[00:23:12] **Audience Member 1:** Okay, thank you. While we have you, Dr. Pardo, there's a question for you. How do you tell if someone has had a spinal cord stroke? How do you treat a spinal cord stroke?

[00:23:24] **Dr. Carlos A. Pardo:** That's a very interesting question, difficult question. So, we have identified the clinical profile of patients with spinal cord strokes. So vascular myelopathy can be divided into two major groups. Those ones that show up acutely, and those are the acute strokes, and those ones that may evolve chronically. Those are patients, as I mentioned before, the prominently men above age 50 that develop

chronic symptoms, weakness and sensory problems, bladder dysfunction. It looks like myelitis, it looks like myelopathy, but this keep progressing over months, and eventually, they can get even paralyzed. So those are chronic vascular myelopathies. If we would like to diagnose a stroke of the spinal cord, we are going to use mostly clinical parameters with the help of MRIs and the help of the spinal fluid. So, one thing that we have found is the patients with a stroke of the spinal cord that happened acutely they have very interesting characteristics. First, they show up in a very hyperacute manner. In other words, these are patients that develop symptoms in matter of minutes, hours, and in three hours are paralyzed quick.

[00:24:53] And they reach basically a plateau, and they are completely paralyzed. Second those patients, the initial MRI may be negative. But if the MRI is done three or four days later the MRI Is going to show a lesion. And the lesion is going to be frequently localized in the gray matter rather than in the white matter. And frequently those patients don't have enhancement in the initial stage of the spinal cord damage. The third feature that is very frequent is if the spinal fluid analysis is done early, spinal fluid is going to be normal. And you may have experience, or some people have experience say, "oh, my spinal fluid was normal at the beginning and my symptoms were very quick and my myelitis is not getting better." Well, that is not myelitis, that's a stroke. So, in other words to diagnose a spinal cord stroke, you need to combine in an equation first, the clinical profile, second the MRI features, third the spinal fluid analysis, and four, it's extremely important to go and take a look anyway of the markers that we already recognized for myelitis. Like NMO, MOG, or even rheumatological markers. So, the clinician needs to be very critical about that approach.

[00:26:16] **Dr. Michael Levy:** It rarely happens that we have a case that's so clear cut where we could say it meets all of your criteria for a stroke. But let's say we have that, I call you at the ER, I introduce you to the patient. The story is perfect for a stroke. What do we do?

[00:26:33] **Dr. Carlos A. Pardo:** Good question. First, those patients are not going to get better with IV methylprednisolone. Those patients are not going to get better with IVIG those patients are not going to get better with plasma change. What they need, unfortunately, they need to get in a very stable situation. For example, frequently patients with strokes develop an important spike in blood pressure. They develop blood pressure that go to 200 over 150. So, the clinician should avoid fighting the spinal -- the blood pressure. And this is something interesting, because unfortunately, we have seen the opposite, the patients come to the ER, the clinician sees oh the blood pressure is 220 over 100. They don't realize that they are having a spinal cord stroke and they start pushing the blood pressure down. Big mistake, because by pushing the blood pressure down the perfusion of the spinal cord is going to be decreased and the spinal cord stroke is going to worsen. So yes, we don't have too many tools to treat spinal cord strokes. And unfortunately, the tools that we are using for treating strokes in the brain are not useful at this moment for a spinal cord stroke. I mean we don't have the luxury to do interventional angiography, to do thrombectomy is because the technology is not there, and we still have no expertise in doing very good procedures for that. So, we are at the mercy of management to avoid complications. So, in other words don't push for things that may worsen strokes like IVIG or plasma exchange in those cases.

[00:28:13] **Dr. Michael Levy:** No one has done clot-busting drugs?

[00:28:15] **Dr. Carlos A. Pardo:** At this moment there is no experience with that. And probably an important aspect of future management of spinal cord strokes is to come with better avenues to treat those patients.

[00:28:29] **Audience Member 1:** Okay. This is a MOGAD question. To date, longitudinal studies indicate that no maintenance strategy is 100% effective in preventing relapses in pediatric MOGAD with multiphasic phenotypes. Are there any updates on this front? Are there any current clinical studies that look promising?

[00:28:52] **Dr. Michael Levy:** Grace and Melissa, how about you guys? What are your favorite drugs? And what do you think is on the horizon?

[00:28:58] **Dr. Grace Gombolay:** Yeah, I'll start. As I say, my usual go-to is IVIG. Luckily in the state of Georgia most insurance companies actually now have MOGAD as an approved therapy for IVIG, so it's less fighting for me for the insurance companies. That being said, I will fight the insurance companies, because in my experience IVIG seems to work better than some of the other agents. I have actually really good success with CellCept also mycophenolate mofetil which is a by-mouth medication. My patients do well with that. I have a couple of patients who are on rituximab, but rituximab's hit or miss in MOGAD, in my experience. And then we've had a couple of patients who needed tocilizumab, which is an anti-IL-6, blocking IL-6 cytokines. So far, my patients are doing well with those therapies. I haven't needed anything else, but I'm looking forward to Dr. Levy's trials including the 12 to 17-year-olds who are technically still pediatric patients because I think those are gonna be very important studies. And same thing like we do in the MS world, right? We trial these drugs in adults first and then when we know that it's safe and effective in adults, then that's moved on to pediatric studies. That's my hope, is that--thank you for the adults who are part of the studies--and then you're paving the way for your children to be able to receive those therapies too.

[00:30:11] **Dr. Melissa Hutchinson:** I'm not sure I have much to add to that, because that's been my experience as well. IVIG Is our go-to in our mainstay. Certainly, as we learn more about the presenting symptoms in MOG and the clinical phenotype upon presentation, I oftentimes don't hesitate to give IVIG even with the acute steroids up front. If it's a classic presentation that the imaging and the story, and the exam really seem like it's going to turn out to be MOGAD. Certainly, patients that improve over time and then have another relapse, I talk about upfront, about being on monthly IVIG, because I think that's where the literature supports right now. And again, I'm also looking forward to the trials in pediatric patients, because my patients are asking about those trials and trying to understand what other options could be coming down the line.

[00:31:10] **Dr. Michael Levy:** Let me just ask a follow-up question, Melissa. You mentioned you're collecting data on cognitive function. I have a lot of MOG patients who are stable on IVIG. They're not relapsing but they're still really tired. They've got tons of MOG fog, thank you Julie for coining that. And kids are not doing as well in school. Is that -- what is that? Is that the IVIG? Is that the trauma of going to the hospital? I -- or is that the actual biological process? What is going on there?

[00:31:44] **Dr. Melissa Hutchinson:** So, we certainly see this exact same thing. And Dr. Wilson, who's in the audience here today is our neuropsychologist in our clinic that does neurocognitive screening and testing for all of our patients that come to our neuroinflammatory clinic, and we're seeing the same. I don't know what that is exactly, and I think it's a little bit of everything. I think it's some of the inflammatory process in the brain. I think it's some of the medications, some of the medical trauma. And this is happening at a time of rapid neurodevelopment for these kiddos. And I think that's what we're interested in learning about and trying to understand and describe through our data that we're collecting in our clinic. Is really what is the profile? What is the neurocognitive profile when this happens at two years old versus six years old versus 17 years old? And how does that impact our patients -- our patient's learning and development at different ages and stages of growth and development. We are also pairing that with neuroradiology studies and trying to look at structural and functional changes of the brain and the pathways of the brain, and how that relates to their neurocognitive profiles as well. So certainly, there's a lot to learn in this arena, but I think that is certainly the experience of our patients.

[00:33:11] **Audience Member 1:** Thank you. Another question, how is the research going for inserting cells into spinal cord to regenerate myelin?

[00:33:20] **Dr. Michael Levy:** Where is Dr. Greenberg when you need him? Dr. Greenberg has been preparing a trial with stem cells in the spinal cord for as long as I've known him. And I think that the -- it was almost about to launch, and they were -- they had FDA approval and IRB approval. Does any -- Carlos, do you have some experience?

[00:33:48] **Dr. Carlos A. Pardo:** So, to answer the question the clinical trial that actually SRNA is participating as a sponsor is almost ready to be initiated. This is a safety trial, in other words, is a trial in which there is going to be an assessment to see if those cells are safe to be engrafted in the spinal cord. At the present, there is no real studies have demonstrated that those stem cells are safe and successful to regenerate spinal cord myelin. So, what we are learning is from animal models, the animal models. Again, there are some studies that are very promising there are other studies that still show that is not too much. So, the trial that is being done at UT Southwestern, Kyle, I don't know if you can add a little bit on this. Is still ready to go. But I think that we are waiting for more for patient recruitment and movement in terms of the implementation of the plan.

[00:35:07] **Dr. Kyle Blackburn:** I think that's about right. So, we actually did screen somebody and unfortunately, they screen failed. And these patients that meet the very strict criteria for a safety study don't come up very often. So, I think we're rearing to go whenever the next patient comes available.

[00:35:25] **Dr. Michael Levy:** And what are you looking for exactly? What's the criteria that patients need to have?

[00:35:30] **Dr. Kyle Blackburn:** So, it's pretty strict, so it's -- there's a very tight time window around when the myelitis can occur. It has to -- we have to have some -- we're planning this trial and somebody who ideally has not had a recent episode, because we wanna see that they have been stable. But also, can't be too late, I think we've set the cap at 10 years. This has to be somebody where we think the risk of causing a worsening of their condition is going to be low. So, it's actually people who have what they call an ASIA A at a certain level. So, these are people that really are unable to move, and really most of them are gonna be from the waist down and then really have no sensation. So, it's the people that where we think the risk of worsening are low, those are the two major criteria. On top of that, a host of other criteria being looked at. But those are the two big ones.

[00:36:32] **Audience Member 1:** Dr. Flanagan mentioned sarcoidosis earlier. I have TM and have also had a positive blood test for sarcoidosis. I also have lupus. What if anything should I be aware of or looking out for regarding the sarcoidosis?

[00:36:49] **Dr. Eoin P. Flanagan:** Yes. Excellent question. Sarcoidosis is a common cause of myelitis in my experience at least at our clinic. And I think the way we generally diagnose sarcoidosis is we look for involvement in the lungs. So sometimes that involves a CT scan of the chest or even sometimes a PET scan which looks for glucose or sugar uptake within the lungs. And then usually we have to confirm with the biopsy where we would take a sample from the lungs and look under a microscope for a particular pattern of inflammation, because usually, we don't like to go into the spinal cord, although on occasion we have had to do that when we were concerned if there was a tumor or something else. So usually, it requires more than the blood tests and we'll require those additional tests to confirm that. It's complicated here in the setting of lupus and other conditions should be tested for in that situation, like aquaporin-4 for antibodies and even the lupus itself can associate with myelitis.

[00:37:53] So, it's difficult to comment on the particular case, but in general, the approach to sarcoidosis is to try and find it in the lungs and demonstrate that with a type of biopsy that often a pulmonologist has to put a camera down into the lungs to take a little sample which can be done safely and easily. But -- and that's the

best way to diagnose it. Can I make just one quick comment on the MOG in pregnancy? Because there was a study from France, I just was looking back up there to remind myself and it looked like that there was a reduction in the frequency of relapses during the pregnancy period, but they didn't notice any rebound after pregnancy, which was different to the aquaporin-4 where there was a rebound. That was a small number of patients. So, I think our data is still pretty small for MOG and we're trying to learn more about pregnancy. But that was -- there was one report from France published in the Neurology 2 journal.

[00:39:01] **Audience Member 1:** Okay. All right. Another question about MOGAD. MOGAD patients are frequently evaluated with EDSS which was designed for MS and puts a lot of emphasis on mobility. Is there a better-suited disability skill for MOGAD with a more balanced weighing for cognitive disability?

[00:39:21] **Dr. Michael Levy:** I wish. Let's see if the panel here has plans and suggestions for a better disability score for MOG.

[00:39:29] **Dr. Grace Gombolay:** Yeah. I think this is the complicated thing for all neuroinflammatory diseases that we know, there's a lot of cognitive problems that's not as well capture with the EDSS. The EDSS Score is great so you can train people to do it. It can be done relatively quickly and it's an objective. So, you turn it -- symptoms and exam into actual numbers. One of the things we've been exploring is that there's a couple of others tests that people have used. So SDMT which is a Single Digit Modalities test is more commonly used in MS. But basically, what happens is that you have a picture of different symbols next to numbers and they give you these symbols in a row, you have to look at it and you have to decide which number matches the symbol. And it's supposed to be a similar profile compared to your four-hour neuropsychological testing that tests all those things.

[00:40:14] The challenge with that is that, A, its age limited, right? So, I'm seeing a ton of kids who don't even know how to pick up a pencil, much less write, much less be able to match these numbers. And, B, what if you're not able to physically write or physically speak to be able to do those things? So, one of the things that we've been exploring is that there's a test called the Cognitive and Linguistic Scale or CALS score is actually developed at Kennedy Krieger by Beth Slomine for assessing consciousness, language disorder and cognitive ability in patients with -- who are -- have very low -- they're not responsive sort of in a coma like state pretty much. It's still a little bit longer than your typical EDSS Score. So, it does take about 30 minutes, you have to be trained to do it, but it's shorter than your four-hour neuropsychological tests. And really captures a lot of these things in patients who aren't able to participate in some of these other cognitive testing. So, I'm hoping that that will yield some more information about the cognitive profile for these patients.

[00:41:09] **Dr. Michael Levy:** Yeah. The EDSS long-term for most MOGAD patients is like one or two which is barely any disability. But then you talk to the patients, and they have all these disabilities, and they can't work, and they can't keep their eyes open, and it's just not reflected in the EDSS. It's a tool that desperately needs to be revised for MOG specifically. Yep. Yeah.

[00:41:34] **Dr. Carlos A. Pardo:** So actually, the National Institute of Health, NIH, has in a group of resources that they have something is called the tools, the NIH tools. And one of the emphases that NIH Is making for many of the research studies is trying to use, unify, and standardize approaches for testing different disorders. In other words, there is no need for generating a specific test for MOG or a specific test for NMO. And one of the emphases the NINDS, that is the National Institute of Neurological Disorders and NIH is trying to adopt some of those tools are ready to implement the assessment of patient in -- the assessment of patients, pediatric, and adults for -- with those tools so we can compare and use the same tools across. So, if you are applying for an NIH grant as we always do, they are asking us to use those tools. So, there is no need for creating tools for any disease -- neurological disease.

[00:42:43] **Audience Member 1:** All right. This is another question. It came up earlier, but I think it's always good to perhaps repeat as some of our online audience lives across the globe and might not be awake. But this is a TM question, I'm on the highest doses of mixed medications for TM, but nothing is working. My pain management doctor won't give me opioids. She says it will make my pain worse in the long run. Should I try opioids for my Tm pain? I am very disabled because of the high pain level.

[00:43:17] **Dr. Michael Levy:** Oh, this is a difficult one. Dr. Flanagan?

[00:43:23] **Dr. Eoin P. Flanagan:** Thank you, Michael. Back to me. I think yeah, nerve pain from myelitis is unfortunately very common and really disabling for patients and can really impact their quality of life. So, I think it's really important to try and focus on that. And there are many different approaches and neuropathic pain medications that are available that can be utilized like Gabapentin, Pregabalin also known as Lyrica. Duloxetine, also known as Cymbalta. So, in general we try to utilize those types of pain medications, because in the long run, I think the physician is probably right that the opioids are going to cause problems and can cause issues with tolerance addiction, and additionally can cause a kind of rebound of pain too. So, there are other approaches, there are stimulation type approaches, there are spinal cord stimulators. If spasticity is a big issue, then spasticity medications like Baclofen or Tizanidine or even a Baclofen pump can be used. So, I think getting a good pain specialist and looking at a multimodal approach in terms of medications, stretching exercises, non-medication approaches, and stimulation approaches is probably the best way forward rather than moving towards opioids. Which can also cause worsening constipation and other issues as well which are also common in myelitis patients, so I try to avoid opioids in my patients too.

[00:45:07] **Audience Member 1:** Okay. Thank you. Another question, what are the upcoming trials with aquaporin-4 positive in NMO? I have a neurogenic bladder and an indwelling super pubic catheter. I'm on Myrbetriq and receive Botox injections regularly. I'm also on Baclofen, Tizanidine, and Oxcarbazepine for spasticity and clonus. When I'm not on the last three I use an intrathecal baclofen pump. I'm getting chronic recurring UTIs that are needing IV antibiotics each time. I've tried all of the known preventative, and none work. I don't get systemically symptomatic from the infections. They cause increased spasticity and spasms that can be controlled with medication. What can be done than a radical cystectomy?

[00:45:55] **Dr. Michael Levy:** I'm gonna kind of reframe that question a little bit and ask Carlos to talk about the approach at Johns Hopkins when you come to clinic of having access to multiple different types of providers all in the same place. Urologists, with neurologists, with neurosurgeons, and having them all together and discussing these cases. Can you talk a little bit about this type of approach and how you found it to be?

[00:46:25] **Dr. Carlos A. Pardo:** Yeah. So first the question is coming from a patient who has a very complex and difficult situation. And many patients with myelitis may experience that. A patient with increased spasticity that are already on several medications for spasticity plus a baclofen pump, that means a lot. And frequently, this requires a team effort, a team effort with the rehabilitation specialist, a team effort with the pain management specialist, and importantly just to make sure that there is a good coordination. And this is critical, spasticity is one of the most difficult symptoms to manage in myelitis and myelopathy. So, I think that we need to combine different strategies. The first and most important strategy is to have a very good plan of physical therapy, rehabilitation that address those issues, because there are several approaches to manage spasticity from a rehabilitation point of view.

[00:47:33] And the second is obviously the use of good medications for managing of the symptoms combining three or four different spastic medications in one patient probably is not the best approach. And that means that there is need to really address the use of medication, because it's possible that one of the medications is not maximized and the patients need to receive advice from the clinicians, what will be the best option

for management. There are several other options for management of spasticity, including the use of Botox treatment. Many rehabilitations specialist help with that approach and obviously the baclofen pump. The baclofen pump is the last resort for the management of spasticity.

[00:48:20] First, because baclofen pumps are very powerful for management in spasticity. But also, that -- the use of those devices may imply potential risk, risk of infections, risk of other complications that are going to be very difficult to manage in patients with these complexities. So, in other words, this type of situation in which there is problems with the spasticity, bladder control requires basically a team effort and a very good coordination. Probably I didn't answer your specific question, you are listening to this answer. But I think that the most important encouragement is start with your clinician and make sure that your clinician is connected very well with the rehabilitation specialists, and neurologists to manage the complications of all of these symptoms.

[00:49:13] **Dr. Michael Levy:** In regarding trials specifically, I'll refer you back to our presentation on the TENS unit Transcutaneous Electrical Nerve Stimulator for neuropathic pain and the cannabinoids, the nabiximols study that we're doing for spasticity in NMO -- aquaporin-4 for NMO

[00:49:33] **Audience Member 1:** Great. Thank you both. And one final question for now online. What about autonomic dysfunction with TM evaluation and treatments?

[00:49:43] **Dr. Michael Levy:** Autonomic function, Eoin, Dr. Flanagan.

[00:49:49] **Dr. Eoin P. Flanagan:** Yeah. So, we can see autonomic dysfunction and that can involve males' erectile dysfunction for which we do have medications such as Sildenafil or Viagra which is used and can be effective, so that's one approach. And we do work with a urologist or other things that can help with erectile dysfunction. And in terms of autonomic function, the bladder and the bowel or the other areas that get affected. And in terms of bowel function and we do have a variety of medications. And polyethylene glycol is what we commonly use which can be given once or twice a day to try and help keep bowel movements regular. We like patients to be passing bowel movements at least once a day. But we -- in some patients, we'll require suppositories or other treatments and for constipation. So, there's a variety of approaches. And then I think we do involve our rehab teams also to assist with this. And sometimes autonomic dysfunction can occur acutely where patients -- if they get a urinary tract infection or other issues, they can get something called autonomic dysreflexia which can cause them some redness and discomfort above the level of the waist. And sometimes we have to treat and find the underlying infection or any blockage of urine and treat that appropriately so that's another type of autonomic dysfunction we can see.

[00:51:31] **Audience Member 1:** Great. A new question came in. My mom was diagnosed in 2008 with TM. She recently had a UTI, shortly thereafter she came down with conjunctivitis, herpes on the lips, and rash across the forehead that have lasted weeks despite standard medications. Could this be a result of a relapse triggered by the UTI?

[00:51:56] **Dr. Michael Levy:** Let's see. Carlos, do you want to take a step at this one? Sounds a little bit like Zoster, but I'm not 100% sure. Do you maybe want to repeat the part about the rash?

[00:52:07] **Audience Member 1:** So, Mom was diagnosed 2008 with TM. She recently had a UTI and shortly thereafter she came down with conjunctivitis, herpes on the lips, and a rash across the forehead that has lasted weeks despite standard medications.

[00:52:20] **Dr. Carlos A. Pardo:** Yeah, it looked like the rash on the head that lasts for several days may be related with some herpes-related infection on the skin that may be herpes type one or two or maybe varicella zoster, the virus that produced shingles. If that was painful then is extremely urgent that the patient be seen by the primary care doctor because that's a treatment situation. I mean we need to treat shingles and we need to treat this type of infections quickly, because they may worsen. Let's say that was not the case, so the question is, is this a relapse of transverse myelitis that happened many years ago, the answer is probably not. And if there was not any other neurological problem that emerged during that period of skin reaction and infection, I don't believe that there is need to be -- the patient needs to be concerned for a relapsing of myelitis.

[00:53:20] But remember as we get older and older, we are susceptible to viruses like shingles. And that actually brings the important issue that after age 50, 55, and every patient that has been treated with any immunological medication needs to be vaccinated for shingles. Those vaccines are very safe, the new version of the vaccine that is given is very safe and is needed otherwise patients are going to be in a higher risk of developing shingles. That is a very difficult, painful complication that may emerge in the setting of many treatments that we use like rituximab or Ocrevus, or many of the B-cell derived therapies or many of the immunosuppressive therapies.

[00:54:11] **Dr. Melissa Hutchinson:** Can I just add to this conversation? I'd like to highlight these are two really good examples of what we were previously talking about for transitioning pediatric patients to be prepared to take care of their health care as adults. And these are two really good examples of things that we need to be educating our adolescents about as far as side effects or emergencies that can happen. So, patients that have had TM obviously are at risk for things like autonomic dysreflexia and they need to understand what those symptoms are and what to do about those symptoms. So part of our transition process is to teach patients about their risk factors for emergencies such as autonomic dysreflexia and actually create a letter for them to be able to provide to an emergency room wherever they may be living at that time based on what their diagnosis is and what their risk factors are for something like autonomic dysreflexia and what to do about it, what that clinician in the emergency room can do urgently to help them.

[00:55:19] And I think that is something that we educate parents about quite nicely in the times in which pediatric patients are diagnosed. That's a very clear example of what we need to then be transitioning adolescent patients to know about. And I think a second example is your risk factors for infections while you're on these immunosuppressive medications. And if you have symptoms, if you have a fever, you need to be calling your primary care doctor, you need to be looking for rashes, you need to be looking for signs and symptoms of infection and urinary tract infections. Which is another piece of education which we do a great job educating parents about when their children are diagnosed. But then we have to kind of have to pass on to educate the adolescent about during that transition time.

[00:56:06] **Dr. Carlos A. Pardo:** Can I ask you a question and actually I love to hear the word transition. This actually, I have experienced this question frequently. What is the best approach for parents when kids are reaching age 18 and then they are struggling to find another provider? So, can you expand on your concept of transitional care? That is extremely important.

[00:56:35] **Dr. Melissa Hutchinson:** Absolutely, so we did have a conversation about transition of care and really talked about the word transition. I really associate it with the word journey because it's a multi-year journey to get patients, and families, and caregivers, and parents ready for that patient to accept responsibility and be empowered to make their own decisions on their health care. We start in our clinic at age 12 and we

start having conversations about “What is my diagnosis? How can I explain my diagnosis to others?” We have our pharmacist meet with our teenagers to go over their medications and their side effects. And all of these conversations are happening with parents and caregivers as well so that we can clarify understanding of what mom and dad do for you right now in terms of making appointments and refilling medications. And how are you gonna go about doing that and what are the skill sets and toolbox that you need to have in order to assume responsibility and feel empowered to be making these decisions?

[00:57:41] And so, it's a journey and we in our clinic have developed a five-phase journey where we have a packet for each phase, and we talk about it at an age-appropriate and developmentally appropriate level over time. And discuss all types of categories in terms of managing your medications, managing your symptoms, and your side effects of medications. And then we make sure during that transition, those years of transition preparation, we identify an adult provider and ideally have a warm handoff from the pediatric provider to the adult provider acknowledging that it's not just the neurologist that needs to transition care, it's certainly also the ophthalmologist and the urologist and the primary care doctor and the rehabilitation doctor and the pain management doctor. And so -- and the mental health provider and the psychologist. And so, there's a lot going into planning a transition and executing a transition. And I think that's something that we're trying to be a little bit more deliberate about and really have it embedded within the structure of our clinic.

[00:58:56] **Dr. Grace Gombolay:** I think there's a question in the back. I don't know if we have a microphone.

[00:59:07] **Audience Member 3:** Yeah, that was gonna be my question is, what are you doing for this transition? Because what we're seeing as an OT in the clinic, if we have a pediatric patient that's had this wonderful team that happens in children's hospitals and then they go into adult world and they're just dumped on their own, what are the hospital systems themselves doing to make that transition in a more integrated team approach happen? Because I'm just not seeing it.

[00:59:36] **Dr. Melissa Hutchinson:** I think you're articulating the challenge that we've all seen happen. And what we're trying to do on the pediatric side is build that patients' toolbox and skill set and know-how in order to feel empowered to advocate for themselves and to know what they need of their adult providers. And make sure that they have identified adult providers in all of these areas and they're not as integrated. And sometimes they're at various healthcare systems in that same city or a combination of community providers and at academic medical centers for example. And so, I think our approach has been to just be very transparent about the fact that it's gonna look different and we need to understand how it's gonna look different and individualize the transition plan for that patient and what they need. We are certainly trying our best to set patients up with an adult provider over at OSU. Actually, because we have a relationship with OSU from Nationwide Children's to OSU, certainly that doesn't exist everywhere. So, I think that definitely needs to be thought through very carefully.

[01:00:54] One of our main goals is to ensure that patients have an actual appointment on the calendar and have a follow-up phone call from our clinician -- nurse clinician that they actually made it to that follow-up appointment to actually established care with the adult neurologist. Because certainly we can all play the best plans out, but if they're not carried through and if it doesn't happen in the way we anticipate it to then certainly that's not a success. And so, there's a lot that we're trying to do to prepare children, but I think you're right. I think it’s certainly a challenge that we all need to be thinking more about.

[01:01:45] **Audience Member 2:** We go to a specialty clinic because nobody knows what to do with us. We're at Mayo or Hopkins or UT Southwestern, whatever, and then come back to the real world of our communities, and then we're stuck also. So, if with all the research and stuff that cures. That's great. But for those of us

who are living every day, I think there needs to be some efforts within this community to develop some benchmark best practices tool kits or whatever for extending care out from these major centers into the real world where we all live.

[01:02:24] **Audience Member 1:** Yep, thank you. And we got a comment here online. If we can please share the five-phase care packet for transition at some point.

[01:02:35] **Dr. Melissa Hutchinson:** We were just talking about how we can share that information.

[01:02:38] **Audience Member 1:** Yeah.

[01:02:38] **Dr. Melissa Hutchinson:** Thank you.

[01:02:39] **Audience Member 1:** Great.

[01:02:40] **Dr. Carlos A. Pardo:** And probably that's going to be the next topic for the podcast, Roberta.

[01:02:44] **Audience Member 1:** Ask the Expert, yeah.

[01:02:47] **Dr. Carlos A. Pardo:** You are recruited for the podcast.

[01:02:51] **Audience Member 1:** All right. Another comment here and question. They appreciate all the excellent information given over the past two days. What suggestions do you have for patients who live in a community without neurologist, physical therapist, and other specialists familiar with rare neuroimmune diseases?

[01:03:09] **Dr. Michael Levy:** Actually, I'll pose that to Dr. Flanagan, because he sees a lot of cases in Rochester, Minnesota. They come from all over, but then they go back. And how do you connect them to their communities?

[01:03:21] **Dr. Eoin P. Flanagan:** Yeah, it's a challenge. We see a lot of people from the rural Midwest, from the Dakotas where they're less well served with the neurologist, because in Rochester we have a lot obviously. So, in general, we try and partner either with the local general neurologist and get them on a treatment plan with some contingencies, what to do if there's a problem, and kind of try and provide our information so that they can contact back with us. As was mentioned previously, some of the virtual expansion was very helpful with the COVID-19 pandemic, because then we were able to visit with patients in their homes and able to give additional advice. But some of that has been more challenging now that more barriers have been put up to that. I think having a good primary care physician is really important, because they can then reach out to other experts to try and get advice and they can be your advocate. A lot of times the key is to get the diagnosis so we can get patients on the right treatment plan, so ensuring that you do get seen at an expert center if you are still struggling with symptoms and the diagnosis is not known, I think that's important. But then after that having a good primary care physician who can put the plan into place that has been placed by the neurology expert, then that can be very helpful.

[01:04:48] **Dr. Carlos A. Pardo:** So that actually is a very interesting problem that we have right now. And we mentioned this yesterday, we are not able to do telemedicine as we were able to do in -- during the pandemic. And unfortunately, there are legal barriers in different states for interacting with patients that are far away without any resources at all. And I think that my comments are one; is if you find at least a healthcare provider that is able to establish contact with any of the centers nearby, I think it is very possible to establish a communication and -- with the understanding that there are not going to be legal connections. In other

words, there are not going to be restrictions by states. So -- but I think that that is doable and that can be established even through SRNA. SRNA may provide connectivity with different providers around the United States, based on the state where you are. But the second thing -- and I apologize to bring the nightmare of our current social situation in. Health care is a right and in the United States health care is not a right. In other words, we don't have a right to have access to health care. So, every time that you are coming to vote, you need to remind the people that you are promoting for that position that you want to vote, that health care is a right. And unfortunately, many politicians in our country forgot about that. And it's very sad, because a large segment of our population doesn't have access to health care. And for people that live in remote areas, it's worse, they don't have access to anything. And so, it's important to remind that unfortunately, we need to think about those social aspects of life, and we need to raise our voice and say health care is a right.

[01:07:02] **Dr. Michael Levy:** I nominate you Carlos for House of Representatives from the great state of Maryland.

[01:07:09] **Dr. Carlos A. Pardo:** I can't.

[01:07:14] **Audience Member 1:** Another question here. Hello. I'm a myelitis patient. I was on my way to running again, but my joints aren't handling it. I never had joint problems prior to TM. Is this normal? I attend PT four times a week and have an at-home program.

[01:07:35] **Dr. Michael Levy:** Grace, I know this is maybe not a kid, but what do you think?

[01:07:40] **Dr. Grace Gombolay:** Yeah, I think that that can happen, and I think the first thing is like trying to figure out the cause for the joint issues because a lot of patients with myelitis have overlapping other rheumatological causes, especially. So rheumatoid arthritis can be a thing, lupus can be a thing. So, I think assessing for what's causing it is gonna be number one, and number two, figuring out the situations that you're in, where your joints are causing problems. So now we're starting to get into colder weather and for a lot of people, the weather really affects your mobility and affects pain and all of those things. And so, I think you have to figure out what their situations that make it easier on your joints versus others.

[01:08:19] **Dr. Carlos A. Pardo:** Michael, can I throw a microphone to a person that is in front of me over there? Dennis, pain in patients with transverse myelitis that are doing physical therapy? And if you don't mind introduce yourself.

[01:08:37] **Dr. Dennis Tom-Wigfield:** I'm Dennis, I'm a physical therapist at Kennedy Krieger. So, with the joint pain, when getting back to jogging without seeing you, I don't know, maybe there's some sort of gait kinematics that need to be changed to help you have better joint alignment and that will therefore help with decrease in pain. Maybe with your residual weakness, your joints are sort of taking up a lot of the stability and if you're hyperextending or things like that, that can definitely be a source of the pain, I would suggest if it's available to you, to try jogging in a pool instead so that you're in a buoyant environment, the hydrostatic pressure and heat on your joints can help with the pain and then you won't be putting as much force through your joints so you can still get that jogging training in without the high impact of overground gait training or jogging. That's all I got; I think.

[01:09:26] **Dr. Grace Gombolay:** For more information you should listen to his track two session It was excellent. Of all the resources available and other strategies. So, I would advocate for listening to that.

[01:09:35] **Audience Member 1:** Yeah, thank you. And that will be online for all of the participants joining us online in a couple of weeks as soon as we finalize the symposium, but definitely, all of the resources will

be posted. So, thank you. Also Dr. Pardo you got a virtual clap from people online based on your previous comment about health care as well, so you got double the applause. I just wanted to let you know. Another question slash comment here, my mom was told years ago that her TM onset was a one-time event. That it will not get worse or better and it's now just a matter of managing the impact to her, such as bladder bowel issues, spasticity, and neuropathic, pain etcetera. Can the lesion get worse? Can she relapse or is this as fixed as we've been told? We are in San Diego, but our doctors don't seem well-versed in the disease.

[01:10:28] **Dr. Michael Levy:** Maybe we can ask Dr. Flanagan how he would advise their doctors. Maybe what kind of testing or other markers of monophasic versus relapsing disease?

[01:10:39] **Dr. Eoin P. Flanagan:** Yeah, that's a great question. And it just highlights the importance of a comprehensive assessment when you first present with transverse myelitis which is a big deal. So -- and studies have looked at this and they found that when you do all of these comprehensive investigations you can find a cause in up to 70% of cases that were initially labeled as unknown cause or what we call idiopathic transverse myelitis. So, the types of testing that we rely on the MRI can be very helpful, particularly looking at the pattern of changes, be it the signal abnormality or something we call the contrast enhancement pattern can be quite helpful in leading us towards the correct diagnosis. As mentioned earlier, we'll look at the lumbar puncture to see if there's active inflammation there. We also look to see does this look like a spinal cord infarction? Is the lumbar puncture showing no inflammation?

[01:11:36] And was the onset very fast? That might suggest that, because usually when that happens that's a once-off event and doesn't usually recur. We can test in the blood for antibody markers, you've heard about MOG antibodies and aquaporin-4 antibodies. And those might -- it would predict a higher risk of having a recurrence. And then looking at the chest for sarcoidosis, we talked about earlier, with CT scan or PET-CT can be useful to see if there is evidence of inflammation in the lungs that might suggest sarcoidosis. And then we look at other blood tests for other rheumatological conditions that have been a theme here today, lupus, rheumatoid arthritis, other things that can -- Sjögren's syndrome that can associate with myelopathy. So, I think for people out there who don't have an answer and are told that it's an unknown cause they should try and seek out an expert. And I think the SRNA on their website will have names in the locations where people are available. And seeking out that expertise is certainly worthwhile because many times an exact diagnosis can be given, and a more formal and specific treatment plan and prognosis can be given for patients. So, it's worth putting in that upfront effort to really try and get to the bottom of what's happening.

[01:13:01] **Audience Member 1:** Should I keep going?

[01:13:02] **Dr. Michael Levy:** Please.

[01:13:03] **Audience Member 1:** There's a question from the audience, yeah. From the in-person audience.

[01:13:15] **Audience Member 3:** This is just a helpful hint for the individual from San Diego. Dr. Graves at UCSD is great with rare neuroimmune disorders. So, if you have the ability to get there, potentially reach out to that office.

[01:13:32] **Audience Member 1:** Awesome, thank you. And another question.

[01:13:38] **Audience Member 4:** Okay. There was a member of my support group that asked me to ask this one. She was diagnosed with TM a couple of years ago. She recently felt that her symptoms were getting worse as far as pain and numbness and spasticity, and her doctor attributed it to, Wallerian degeneration. And he described that as it -- with a spinal injury, the tail of the axon nerve slowly dies over time worsening

the symptoms. He said that the area of her initial lesion had died and filled in with spinal fluid which can usually take up to 10 years, and he was puzzled that her MRI looked like she had had the event much longer than two years ago. Can you explain Wallerian degeneration and is that a factor in TM?

[01:14:32] **Dr. Michael Levy:** Dr. Pardo, can you explain Wallerian degeneration and these changes on the MRI?

[01:14:39] **Dr. Carlos A. Pardo:** So Wallerian degeneration is a term that we use to describe the structural abnormality of the wiring of the nerves. So, the nerves basically are comprised by a cell body and then there is a long wire that is connecting different parts of the spinal cord with other structures. When there is an injury in the spinal cord, we are basically observing damage of the wiring of that neuron. And a portion of those is going to be completely destroyed and the remaining structures of that wire basically are going to degenerate over years -- months and years. In other words, if we produce a local damage that is going to produce dysfunction of the nerve or the widening of the nerve. But over years the stumps that were part of the nerve actually are going to start degenerating as well. And that's a problem for all of us, patients, and health care providers.

[01:15:56] For patients, it's because frequently after years of the spinal cord injury is very possible that the function in many parts of the spinal cord may also to increase, or the dysfunction may increase. And that yes, is associated with Wallerian degeneration. Pain is not necessarily associated with Wallerian degeneration. The pain that happened in many cases of myelitis frequently is associated with the misfiring of the neurons associated with pain networks. In other words, the injury in the spinal cord is living a lot of neurons in the spinal pain pathways trying to fire again and means -- and that misfiring is increasing the amount of neuropathic pain that we frequently observe in patients with myelitis and myelopathies. It is a nightmare for the patient, is a nightmare for the clinicians, because it's a very difficult pain to treat. And frequently that's the reason we use medications like Pregabalin or Neurontin and Gabapentin. And those are basically medications designed to calm down the fighting of those sensory pathways that are producing pain.

[01:17:18] The fact that there was a hole left in the spinal cord in this particular patient doesn't mean that is associated with pain or is associated with the Wallerian degeneration, it is very likely that that was left, because the injury produced by myelitis or whatever produced the damage in the spinal cord. But again, one thing that actually is bringing another topic to the discussion is the aftermath of any inflammation in the spinal cord or in the injury may bring other long-term effects in the future. And that implies they were allowed in the generation that we're talking about, and that implied that actually is possible that later there'd be some worsening of some of the symptoms after experiencing the acute phase of myelitis. It's a little bit complex, but I think I tried to explain the best I could.

[01:18:19] **Audience Member 1:** Yeah. Just going back to vaccines, a little bit. Regarding the shingles vaccine we talked about earlier, is this recommended for patients who have never had chickenpox? Confirmed by blood test ordered by neurologists that I've never had chickenpox.

[01:18:39] **Dr. Grace Gombolay:** The shingles vaccine is recommended regardless of if you've had chickenpox, or you've had the chickenpox vaccine. The other thing that's interesting about the titers is that because we check it a lot, especially in MS patients because there's a medication called Gilenya, fingolimod. We don't use it in other neuroimmune conditions. But it was the practice to check to make sure you were -- had varicella titers or chicken pox titers. A lot of my patients are negative, but it depends on when you test for it, because there's been studies that show you if you just recently had steroids that's gonna affect your titers. The other question is there some immune dysregulation like something happening with your immune system that has those patients less likely to have developed a response? So, what we do is just make sure that you've had

the chickenpox vaccine at some point in time. But definitely, the shingles vaccine should be given regardless at the right age group.

[01:19:29] **Audience Member 1:** Yep. Thank you. Another question, I'm wondering if prednisone can cause voice changes. I've been having a dry mouth and my voice has been hoarse and would not return to normal. Several times. I almost lost my voice. I was told that this could be due to prednisone and that it's not Sjögren's, but I'm wondering if it could be Sjögren's because my aunt has been diagnosed with this.

[01:19:54] **Dr. Michael Levy:** Dr. Flanagan, do you think this is prednisone, Sjögren's, or something else?

[01:19:59] **Dr. Eoin P. Flanagan:** Yeah, I haven't seen hoarseness per se with prednisone, and prednisone can cause some kind of weight gain around the midline and around the chest wall. So, unless that could contribute somewhat if it compressed on some of the nerves. But I've not really seen that. Sometimes it causes a metallic taste in the mouth or changes there, but it might be worth looking into other possibilities in that situation. I will mention that sometimes prednisone can cause issues with the joints because that was mentioned earlier. And sometimes you can get hip pain from disruption of the blood supply to the hips. So, if you are on prednisone and you develop joint pain in your hips, it's really important to go see your doctor to get that assessed. But it could be related to Sjögren's here, the hoarseness or -- and although Sjögren's more causes a dry mouth, so if there was hoarseness in that setting, it could occur, but probably worth getting looked at by a specialist.

[01:21:09] **Dr. Michael Levy:** Wow, we've answered everyone's questions. That's amazing. Well, you guys have been a wonderful audience. You have more opportunities to ask questions in the next day. So, shall we close this session? Thank you very much, everyone.