In-Person Breakout Session I

NMOSD

You can view this presentation at: youtu.be/1PGEjGb0iQo

[00:00:04] **Dr. Tammy Smith:** Thanks all for coming to this session. I'm Tammy Smith. And we have a few slides here, but we're really not looking to rely on those. The idea was to give you all an opportunity to chat with us and ask questions. And if slides will help support that, then I'm happy to pull things up on a few of these images. I did put a few ideas for talking points, clinical criteria or diagnosis, diagnostic testing, that happens to be one of my favorite topics.

[00:00:41] And then treatments on and off label, future immunotherapies, symptom management. All of these things are things that I thought would be potentially useful topics for discussion, but I'm not married to any of these. So, you can really just use this time to chat with us, ask questions, and we're happy to be a resource to you.

[00:01:03] **Audience Member 1:** I bet you are a lot of fun at a party.

[00:01:05] **Dr. Tammy Smith:** Yeah. And I can also walk around with the microphone when people want to pop in with questions. So, like, holler out what you want to talk about, happy to take a list of ideas.

[00:01:26] **Audience Member 1:** Symptom management.

[00:01:28] **Dr. Tammy Smith:** Okay. That's an excellent one. Symptom management, I'm hearing.

[00:01:43] **Audience Member 2:** I have a question regarding switching to one of the FDA-approved treatments and hearing that you are not supposed to be on IVIG at the same time.

[00:01:44] **Dr. Tammy Smith:** Okay. So, a question about FDA-approved treatment switching and concomitant use of IVIG. All right. Anyone else want to throw out some topics? So, therapy switching, symptom management. All right. How do you want to take this, Dean? Hi. And Peter's here. All right. We'll grab another chair. There's certainly spares there.

[00:02:30] **Audience Member 3:** New targeted treatments?

[00:02:32] **Dr. Tammy Smith:** New targeted treatments. Yeah. Good question. All right. Happy to make time to talk about all those things. All right. We'll catch Peter up, who just joined us. So, we were just taking a survey poll here on what people mostly would like to talk about. I put together a few slides with some talking points and then we have images on some of those.

[00:02:56] But big questions are symptom management, therapy switching, and the use of IVIG, and future targeted therapies, as you just heard. So, all right. Dean, you're a pro here. Why don't you start us off?

[00:03:12] **Dr. Dean Wingerchuk:** Well, that's a good start. With symptomatic therapies, that's a big topic. Was there anything specific people wanted to start with there?

[00:03:22] **Audience Member 1:** Yeah. I brought the topic up. And I wanted to know if there's anything new in terms of, I have severe pain, which is basically uncontrollable. I do get trigger point injections all over my body. The abdomen's the best. I do use cannabis at nighttime, but it has limited results.

[00:03:55] They did have me on opioids, and I just didn't like the whole reaction to it and all-day drowsiness and all of that. And I'm just wondering, for pain control, whether there's anything on the horizon or anything that anybody recommends? I'm open to anything.

[00:04:21] **Dr. Dean Wingerchuk:** Excellent question and a common problem. We probably can't really give you personal medical advice, of course. But, generally speaking, what we try to do when we're dealing with pain is determine where the pain is coming from. Because many times, people have more than one cause of pain. Sometimes it's primarily or directly related to NMO, so spinal cord involvement in particular. And sometimes it's secondary pain that might be indirectly related, or a completely separate condition altogether.

[00:05:02] And so, it helps to try to understand what the mechanisms of the pain are. We like to be able to find approaches that are targeted if there's localized areas of pain. And so, you mentioned, sir, trigger point injections. The idea there is that you've got pain that's usually increases with some physical stimulus, either movement, or touch or pressure in that area.

[00:05:40] And that you can break the cycle of pain or interrupt it by directly intervening, injecting something, or stimulating the area perhaps. And that's the theory behind some of the neurologic stimulator devices as well. With, of course, some of the advantages being that then you don't have medication floating through your whole system and causing side effects.

[00:06:07] But the reality for many people is that they have more than one type of pain, and at least some of that pain is caused by neurologic damage or neuropathic pain. And we are in some ways limited in our options for explicitly targeting that pain from the pain standpoint. But we have quite a few options of off label and experimental, if you will, approaches to pain management. I think there's a session tomorrow, if I saw that Mike Levy and somebody else are doing, specifically addressing neuropathic pain and some new devices and potentially medications that are up and coming or might have potential. So that's going to be an area of some focused discussion. So I--

[00:07:15] **Maureen:** [Inaudible] I mean right after this series is a session.

[00:07:17] **Dr. Dean Wingerchuk:** Oh, is it today?

[00:07:18] **Maureen:** Yeah.

[00:07:19] **Dr. Dean Wingerchuk:** Oh, okay. And who else is doing that session, Maureen? It's Michael and somebody else.

[00:07:37] **Maureen:** It is at 3:15, it's Dr. Michael Levy and Dr. Paula Barreras Cortes.

[00:07:38] **Dr. Dean Wingerchuk:** Oh, okay. Well, any other comments about general approaches to pain management? It's such an individual thing.

[00:07:53] **Dr. Tammy Smith:** For myself, certainly, I'm fortunate to work in a big academic center where I can also talk to my colleagues who specialize in pain management to see what other options there are that might be outside of my comfort level for prescribing. And then, I'm also affiliated with the VA Medical Center, and they have a nice biofeedback program. So, a non-pharmacologic method of pain control that some people find to be beneficial.

[00:08:22] And so, I think, one of the most important things is just talking to your care team about the symptoms that you need addressed for quality of life. So really making it clear that pain is an important factor for you but recognizing that medications do come with side effects and treating to a zero on a pain scale or a two might really come with market side effects. And there could be other options that are non-pharmacologic that augment it. Right? That don't bring your pain down to a zero but help improve your pain, so you have a better quality of life.

[00:08:58] **Audience Member 1:** I'll settle for a six.

[00:09:01] **Dr. Tammy Smith:** That does sound unfortunate, but, yeah, that's a lot of people.

[00:09:05] **Audience Member 1:** By the way I'm lucky enough to go to MGH. And I participated in a bunch of those different studies, like, with spinal stimulation and all that. [inaudible] I really haven't found tremendous amount of [inaudible] a little bit around the edges, but nothing profound.

[00:09:33] **Dr. Peter Sguigna:** And I think from my perspective, at the risk of stealing some thunder that they'll talk about later today. Maureen's in the room, so I'll share. So, one of the things that there's been tremendous interest in the NMOSD space is the scrambler] So there has been research studies on that, and there is, to my knowledge, one company that has obtained FDA approval. It's not as widely disseminated these days, so centers are starting to get a little bit of experience with it. But I think they'll be speaking more to that later today.

[00:10:07] And just to echo some of my colleagues here, everything that we do for pain in these situations is what is considered off label. And so, in that sense, we would try something. And if it works, great. If it doesn't, we move on to the next thing. So, there's continuous work with the health care team and the individual.

[00:10:31] In addition to a tremendous amount of research in the therapeutic space for pain, there's the benefit of, there's a number of conditions that do have pain as a symptom. So, there's companies developing therapies not necessarily specific to NMOSD, but for other neurological conditions that cause pain. And there's no reason to believe that we couldn't also use some of these therapies off label down the road. So, I think there's more to come.

[00:11:33] **Audience Member 2:** [inaudible] NMO from 20 years now that I know [inaudible] when I saw a pain specialist [inaudible], so I believe in medicine and all that, so I did see a pain specialist and the options back then was (implantable) device or a cord stimulator. But the drawback of the option was to have MRI and not

move. So, it's like, well, I get probably, I don't know, 10 MRIs in a year. So, I never worked with options. I don't want to go back and try anybody to go play with my spinal cord. So, is there still a situation, if you're looking for an implanted device? Like [inaudible].

[00:12:10] **Dr. Peter Sguigna:** So just to make sure I understand the question, is your question specific to spinal stimulators, whether there's spinal stimulators that are MRI compatible? That's a good question. I honestly don't know the answer off the top of my head. I know of ones that are not. I suspect there are at least some that are at least 1.5 Tesla compatible. But those are very individualistic determinations.

[00:12:53] **Audience Member 2:** [inaudible]

[00:12:54] **Dr. Peter Sguigna:** It's hard to generalize in this. I would say for most of the time, we are may able to make clinical decisions based on those results.

[00:13:04] **Maureen:** Sorry, guys. Really quick. We are actually recording this for our community members who can't be here today. So, as we converse, if we can just pass around the mic and talk into it, that would be really, really helpful. Thank you so much.

[00:13:36] **Dr. Dean Wingerchuk:** Sure. So, let's go back to the question about switching therapies. Who had that question? And maybe we'll just have you repeat it.

[00:13:48] **Audience Member 2:** Okay. I was referring to switching from an off-label treatment to one of the FDA-approved treatments. As a result of the off-label treatment, I have to be on IVIG. And I've been told that there are reasons not to do Enspryng and IVIG.

[00:14:11] **Dr. Dean Wingerchuk:** Okay. What were the reasons that were explained?

[00:14:15] **Audience Member 2:** The doctor told me that they just could not be taken together. Didn't say that you had to space it out a week or anything, but just said they could not be taken together. And I can't find that information from Genentech or anyone.

[00:14:36] **Dr. Dean Wingerchuk:** Okay. Yeah. That might be a very individual situation that you could get some advice through consultation from people who use an approved therapy like a neurologist, but then also somebody who uses a lot of immune globulin therapy, either like an immune allergy specialist or a hematologist to determine your particular situation and how that might be handled. I think there was another question about therapy. Targeted therapies was the question. Yeah. Well, yes, sir. Whether there were new targets for therapy being developed. Was that your question?

[00:15:34] **Audience Member 3:** Yeah. The newer therapies that better target the source of the problem with NMO from a neurological standpoint. So more versus the umbrella targeted interventions that are now a little bit wider band that are hitting versus more targeted.

[00:16:06] **Dr. Dean Wingerchuk:** Okay. Yes. So generally speaking, if we think of the evolution of the preventative treatments for NMO, things that we're using to try to prevent attacks. Before we had any approved therapies in 20 or more years ago, we were using a lot of general immune suppressants. Right? Off label therapies like mycophenolate or azathioprine. And then, we had rituximab, which is a B cell depleter and sounds more targeted. But we know that B and T cells communicate a lot, and you do have fairly broad effects on the immune system, even with just B cell depletion.

[00:16:52] And then, now, with what you could say are very targeted therapies, especially the approved therapies that target complement or interleukin 6, that is on the one hand very targeted, yet it still has very complex effects on the immune system because of the network of connections between all of these elements of the immune system, how they work together. Obviously, the approach in the long term, the quest for a cure would be to do something that eliminated the antibody itself altogether, because we think that that antibody is the actual cause of the disease. So, either eliminate its production or restore the immune system's ability to be tolerant of antibodies against aquaporin-4.

[00:17:54] And we could do that in theory with a variety of strategies, but you'd like to do that in a way that was long lasting, ideally permanent, and something that had no long-term adverse offence. So, if we think of the therapies we have now, although the ones that I listed before in all of our approved therapies, none of them get rid of the antibody. They interfere with the immune process that the antibody seems to trigger, and that's very helpful. But the antibody is still there and circulating. And if we look at all of the other medicines that have been tried, really, the only approach that so far that is maybe a hint towards getting rid of the antibody was one of the small reports of stem cell therapy done in Chicago.

[00:18:57] So that therapy is, of course, where people they have cells removed and stored, immune cells. And then they're given chemotherapy that doesn't wipe out the immune system completely but takes it to the brink. And then the stem cells help restore the immune system pretty quickly. And the idea is that you've hopefully rebooted it, and it behaves itself. Well, in actual fact, the treatment there is the chemotherapy, at least in the immediate and intermediate term. But what was quite interesting about that approach is that at least for the first few months to 18 months or so, most, but not all of the people who underwent that procedure went from having detectable antibody to no detectable antibody.

[00:19:58] And that's distinct and different from what we see with the other therapies. So, could we do that in a way that was, as you say, sir, more targeted and hopefully safer, both in the short term and in the long term than having to wipe out the immune system totally? What's exciting, I think, is that the technologies that have been developed even in the last three to five years, many of which have been extrapolated from cancer therapy, look very, very promising to be able to, at least in theory, accomplish those kinds of goals. So, engineering cells in the immune system to be very targeted smart bombs, with limited side effects and very limited effects elsewhere in the immune system and in the nervous system.

[00:21:05] In fact, I would say right now, Gesundheit. I'd say right now, there are so many different technologies that have been developed. The challenge is determining which ones of these actually have the most promise for an autoimmune condition like NMO. The benefit in NMO is that we know the antibody, and we know it's targeted, and we know the antibody is actually doing the damage. It's not a condition, say, like multiple sclerosis, where we don't have really an understanding of what the antibodies or antibodies are. We think it's autoimmune, but we haven't proven it.

[00:21:48] NMO is a condition where, because we have much more advanced knowledge of exactly what's going on scientifically, we've got more to learn. But because we're more advanced compared to other diseases, I think there's this ability to apply some of this emerging technology in a way that could give us a valid answer more quickly and might have a very big impact towards this next step of trying to get to a cure. Everybody's grateful for the advances that have been made and the benefit of our current therapies, but they come at some cost.

[00:22:35] I don't mean just financial cost, but all of the potential risks and indefinite use that with maybe an unknown long term side effects, we'll have to see. But that's my sense of where things are at right now. So,

immune therapy for cancer is not new. It's been about a 40-year history of trial and error, mostly error with cancer, except in the last three years or so, where we've seen this real explosion of technology that I think is now turning from cancer to autoimmune disease. It's pretty exciting. Do either of you want to expand on any of that?

[00:23:29] **Dr. Peter Sguigna:** You have a wonderful slide that was very nicely illustrating some of the points earlier about the medications that we have and the mechanisms.

[00:23:43] **Dr. Tammy Smith:** So, this is the overview one I pulled that I like. All right. So, I feel like talking to the people in this room, you guys are very thoughtful and knowledgeable about your disease. You came all the way here to talk to us about future treatments. So, probably a lot of this will seem like repetition, but I feel like it's a useful overview. So, on the top left of the slide, you see those plasma cells and the plasma blast cells that are making the antibody AQP4. Right? So at least in AQP4 seropositive patients. We know that that antibody can then cross the blood brain barrier, that's that wall of cells you see, and then get in and cause a variety of types of damage to those astrocytes.

[00:24:29] So that's that big blob on the right-hand side of the screen for you. And so that damage can happen in several different ways, but, ultimately, those astrocytes are responsible for supporting the other cells in your central nervous system that keep the myelin healthy and happy to allow normal nerve conduction. And so, if those AQP4 antibodies get into your central nervous system and affect the astrocytes through a variety of different mechanisms, you lose those astrocytes and their protective function. And so, in the bottom part of this slide, I just like how this one illustrates how you have these B cells that there are these stem cells that eventually become the plasma cells that generate all of those destructive antibodies.

[00:25:18] And this shows where each of those main treatments that we currently use, so rituximab, so off label but an anti CD20, which cells that affects. And then, as you move to the right, Inebilizumab, which is an anti CD19, it depletes cells on a broader lineage of those B cells. And then the satralizumab on the far right on the top of the slide, that's the one that targets the IL-6 receptor, and you can see that that's affecting the tail end of these antibody producing cells. And then eculizumab and ravulizumab are just up into the right there from the satralizumab. Those are affecting the complement system. So, each of these works in discrete ways to prevent the aquaporin 4 antibodies from causing so much destruction. What do you want to add, Peter?

[00:26:15] **Dr. Peter Sguigna:** Absolutely nothing.

[00:26:18] **Audience Member 1:** So, I do have a question. And this--

[00:26:21] **Dr. Tammy Smith:** Hold on. Let's get you a microphone.

[00:26:25] **Audience Member 1:** Not that I'm loud enough.

[00:26:26] **Dr. Tammy Smith:** Not for people online.

[00:26:29] **Audience Member 1:** I have a question because this is an extremely useful pieces of information. But what I find is there is the beginner's version and then there's research studies. And there's like nothing in between that connects the dots between a study that was done in Japan five years ago with- I'm on Enspryng.

[00:27:02] So can youget the manual? A 4th grader can read that manual. And what I find is we talk about new treatments or things to do or whatever, very, very hard to connect the dots. And then you come into a session like this and it's very helpful, but that's not available next Thursday.

[00:27:32] **Dr. Tammy Smith:** Yeah. I think that's a huge challenge. Right? We all went to medical school, and graduate school and spent a whole lot of time learning how to pronounce really big words so that we would sound smart when we talk to our patients. But it is challenging to talk to people who have expertise in other fields that are not medical and non-research to help connect those dots.

[00:27:53] And that's where I see organizations like the SRNA, a lot of the information they provide on their website, the Sumaira Foundation, lots of the foundations really try to bridge that gap for patients to make this information more understandable. But it's a problem. Right? We all work to be able to communicate well and clearly to our patients, but we don't know what we're failing to communicate until you tell us. So, opportunities like this to interact directly with you and find out where we're dropping the ball and how we can communicate better are so important.

[00:28:39] **Audience Member 4:** Okay. So, my question is a little bit more related the scale of this disease. And I was curious if you all could comment a little bit about just the prevalence of this disease, and also the incidence. So, like, how many new cases are we seeing every year? I realize that's really difficult with people still debating how to diagnose this and this piece being a part of this piece. But I was really struck by the conversation earlier about we know for us as patients not having access to a team of providers who know what's going on can be catastrophic.

[00:29:16] And so, I think for me that means, like, resources, connection, where are areas that are unserved or served. It's like rural is like huge. So, what does that mean? And so, I was really curious if you could all comment on how many new cases do we know of NMO each year? And if we don't know that, how do we get there to gather that information? And do you believe that there are a lot of cases out there, which we know already, that are missed? How many other people just don't even know that they could be and they're out there existing? And we're talking about a rare disease, but I'm just really curious if you could comment on what information to really know the scale of this potentially?

[00:30:05] And if there's anything to believe that you think that incidence of this is increasing aside from just the diagnostics. So that maybe we can start thinking a little bit more of there's already so much science that's been done, and we're lucky that we have it. But even just thinking bigger picture, especially since we know that like certain groups of people, there is a higher prevalence of this disease in certain groups that have had historical trauma. And so, I think I would love for your comment on it, big, big picture, like outside your clinic, beyond the scope of your practice and what you're seeing across the country and across the world with this condition.

[00:30:51] **Dr. Dean Wingerchuk:** Well, I could try to start. That's a big and important question, or questions. If we look just at the United States, the estimates of how many people there are, so the prevalence of NMO ranges from maybe a low of around 6 to 7000 to as many as 22 to 25000. But one of the realities of our health care system is it's pretty disorganized. It doesn't lend itself well to those kinds of studies to know exactly or even roughly how many people there are. But that's the estimate at least of prevalence.

[00:31:49] There are some so called population-based studies [inaudible] but even when you look at those, they use different methods. They were done at different times, used at least definitions. They may not have access to the antibody testing, which is a big difference. And just as an example, on the one hand, we think that there is reason to think that people who are of black ancestry, African or African American, but especially African heritage or Asian heritage, are at increased risk. Let's say, here's a white population. But if you were to look at the studies that have been done in Africa, the estimates of how common it is there are actually quite low, not because that's the right answer, it's probably because those studies have not been able to capture the people who really have the disease.

[00:33:14] And I say that not from personal experience but just talking to people who actually work in that region. So, just as you hear people across the world not having access to neurologist or MRIs or antibody testing, well if that's true, then it's going to be pretty difficult to estimate how many people actually have the disease that live in those areas. And that does limit us somewhat in understanding what is the true incidence of prevalence of disease worldwide. Does it differ between racial and ethnic groups? I think it's the evidence where different populations have been studied in the same geographic areas suggest that, yeah, there probably are some trends there.

[00:34:10] Women are much more affected than men. That's very consistent for seropositive disease. But there's a tremendous amount more work to do there. It's one of the reasons one of the things we have in mind is we update the new diagnostic criteria to try to make those kinds of studies more practical and more consistent? [inaudible] I think, it is important decisions of just asking, is there evidence that the disease is increasing? No. If it is, it's probably because we are able to diagnose more of it, not because more of it exists necessarily. But we won't know that for sure until we are systematically able to assess people and populations over time.

[00:35:05] That's what has happened with multiple sclerosis over the last several decades is, especially, in countries where they have a single payer health care system, and they can pretty confidently capture everything that's going on in your country health wise. We can see that the incidence of MS has increased. It's not just capture new cases by MRI. The real incidence is increasing. Furthermore, it looks like the ratio of women to men is increasing in MS. Those are important observations in trying to understand the cause of the disease.

[00:35:49] And I think the same principles hold for NMO. If we could capture those data reliably, we might get some very important clues of why it happens in the first place. So, yeah, the antibody causes damage. But something's got to happen to cause the autoimmune process to occur in the first place. And why does it turn out to be NMO instead of some other disease? Those are important questions. They probably have some genetic and some environmental influences and those kinds of studies [inaudible].

[00:36:28] **Dr. Tammy Smith:** Who else has a question?

[00:36:38] **Dr. Tammy Smith:** Thank you. I love your question. It's a big one. And it's a question that we've had at the Foundation since 2008. And it was so hard when people would call and they'd say, I understand you're studying NMO and you're providing research and such. How many patients in the US have NMO? First, they'd say in the world, and then they'd say in the US. And at that time, we had to say, we don't have a definitive number. We have an estimate, but it's a very rough estimate. It's now 15 years later, and I would give the world to tell you we have more definitive knowledge to answer that question, but we can't.

[00:37:42] About a year and a half ago, we opened an NMO helpline. It's 24/7. And so, now we're saying, my team is saying just yesterday, they said, I don't know what's going on. There are more and more patients who are not getting treated immediately. They go to see their doctor. Their doctor suspects they have NMO, but they can't get in to see a neurologist for six months, and now they're in the hospital. And this is happening more frequently. Will that mean that it's actually happening more frequently, or is it that our helpline is just available and they're getting more calls? So, we have to be so careful.

[00:38:03] And I loved Carlos Pardo's talk this morning when he said we need more than 10, or 20, or 50 or 100 to gauge a pattern. And, at least, just speaking for our foundation, and I'd love to hear what SRNA says, that's what we need. We need more time to see whether there's a pattern. We can't jump to conclusions yet, but I can't wait for the day that there's a number for you, because we would love to know that, and we have to be careful.

[00:38:41] All I can say is we think the number is increasing or are more people simply learning about it and getting a better diagnosis? That's the other part. So, anyway, I love your question. I hope I see you in a few years. And we can say, Yay! We've got a number for you. Thanks. Andrew, right? I met you last night. I remembered. Okay. Thank you. Thank you.

[00:39:09] **Dr. Tammy Smith:** And, I think, Dean's been around since making up the diagnostic criteria back in the day, but now with modern medical record billing, ICD codes, it is actually really important for any disease to have its own ICD code, and that's something that happens over time. So, some of the rarer diseases, other than NMO, NMO has its ICD code now, but before it did, it's hard to distinguish from multiple sclerosis or other demyelinating diseases. Right?

[00:39:42] So to be able to answer these questions from a bigger epidemiologic perspective, you sometimes have to do a lot of advocacy to get the medical records and the coding systems to reflect the diagnosis to help improve these things going forward.

[00:40:01] **Audience Member 1:** I have another question. So--

[00:40:05] **Dr. Tammy Smith:** Hold on. Wait for your microphone.

[00:40:09] **Audience Member 1:** So recently with doctor advice, I started using cannabis. Now, I only use it at night to mute the pain a bit and help me get to sleep, but I'm seeing more and more comments online and other places about the use. And the stuff's very, very mixed. And I know there's a session on this, but I just wonder your opinion. Is this useful, not useful, or we're still looking at it? Anyway, that's my question.

[00:40:58] **Dr. Tammy Smith:** Anyone want that ball of wax? I practice at the VA. So, cannabis is different depending on what state you practice in the United States even. Right? But I think just the federal government's stance on the use of cannabis over many decades has impacted research. So, we don't have great evidence to guide this in a lot of cases.

[00:41:26] And then, the other issue is what is cannabis? That's not one thing. So that's a genus of a plant. Right? And so, I think the formulation you get, depending on where you're getting it from, whether it is a synthetic cannabinoid, or a THC and what the ratios are. I would say from what I know, we don't have enough experience from any distinct subset to give you advice other than to be cautious, and talk to your doctors, and be open, and know where you're getting your things from and everyone's different. Not an easy answer for me.

[00:42:14] **Dr. Peter Sguigna:** So, as Dr. Smith had indicated, it's a little bit of a sticky subject, and every state has its own rules. Right? So, I'll try and be careful what I say. But at least in Texas, there is something called the compassionate use registry of Texas. And, basically, under certain indications, certain physicians that are registered with the state are able to dispense or at least prescribe the therapy. And it's a therapy, and as Dr. Smith was indicating, one of the limitations is you probably get multiple things, so it's hard to know what's working and what's not working.

[00:43:01] And sometimes, like any other therapy, hard to maybe deal with side effects, especially as you are dispensed certain batches, if you will. So, it's pretty easy to regulate how much satralizumab someone gets, but it's very hard to tell a plant what to do. So that's the concerns and basically, each state has been watching that closely. It's promising, but I think number one, you got to be careful. And number two, you got to do under the supervision of prescriber, at least in my opinion.

[00:43:45] **Audience Member 1:** Which I do.

[00:43:46] **Dr. Peter Sguigna:** Yeah. Exactly.

[00:43:57] **Dr. Tammy Smith:** I'm sure other people are learning from all of your questions as well. So, thanks for speaking up.

[00:44:04] **Audience Member 4:** Can you all talk a little bit about and I know there's a session actually about this too. So, I don't want to steal from that session later about just not prognosis in terms of the disease itself, but whether folks with NMO, patients with NMO are at risk of other health conditions or those developing that are on your horizon. I really like the question about building a multi-disciplinary care team for managing this disease, but I'm curious if there is anything at all or maybe it doesn't put us at higher risk of developing other chronic conditions.

[00:44:40] Just putting it out there or other things that you're seeing in your practice, particularly now as we know folks with NMO are living a lot longer. Are we at higher risk of other things that just come with aging more than other people as a result of our conditions or as a result of our treatments. But if you could talk a little bit about this. I'm a young person diagnosed young and I'm like, oh, my gosh. My pillbox is way more intense than my 94-year-old grandma. And I want to live a long life. What does that mean?

[00:45:13] And I know you all can't, I can go to my psychic for that what my future holds. But if you can say what you're thinking about now that you know people are living a lot longer with NMO, and what care might look like down the road? Or things that you might want to refer to or keep an eye on, I go to my primary care doctor and he's like, oh, you seem fine to me. I don't understand any of all of that. But he's like, I'll just check your A1c and other things. But, yeah. If you could just make comments about that.

[00:45:54] **Dr. Tammy Smith:** That was a lot of questions in one. But Dean's reaching for the mic, so.

[00:46:01] **Dr. Dean Wingerchuk:** Oh, well, not because I have the right answer necessarily, but, yeah. It's an excellent question, of course, and one probably everybody has. Right? What's in store for me in the future? How is this condition going to behave? But what does it mean for the rest of my health? So, what do we know now? Well, we know that people who have NMO with the aquaporin-4 antibody, some of them at least will develop other autoimmune conditions. I think you shared this morning that you've got more than one. Right?

[00:46:40] **Audience Member 4:** Yeah, I also have lupus.

[00:46:43] **Dr. Dean Wingerchuk:** It sounded suspicious for that. So, again, perhaps precise, but they're reasonably consistent throughout the world that at least a third of people who have NMO have at least one other condition that's autoimmune affecting their system either in one organ like the thyroid or multiple organs, something like lupus could do. And if you just measure antibodies and ignore symptoms, you'll find more than half of people have multiple antibodies. So, what does that mean? Well, it probably means, or at least a hypothesis is that there's something going on that puts people at risk of autoimmunity in general.

[00:47:32] And for whatever reason, I don't know. Maybe it's like remember in The Price is Right, that Plinko game where the ball just bounces in bunch of directions and then ends up somewhere, maybe it's that random, but maybe not. That if you have the right or wrong pattern of genes, and then the right or wrong environmental exposures that adds up to NMO or maybe just a pattern that then chance leads you to NMO. But it's got to be more than chance in the sense of this multiple autoimmune condition problem. So, we know that.

[00:48:12] We also think about just I bring up MS again, not because it's necessarily that similar of a disease, but you think of people in the United States, people who are diagnosed and treated for NMO are typically

followed in an MS clinic as well. Those patients are usually part of the same division or department. And in MS, we've seen evolution over the years of understanding concepts like comorbidity. What happens is people get older with MS and get associated conditions. It turns out that the more comorbidities people have like hypertension and cumulative arthritis and obesity and things like that the worse their MS behaves. And that's now an area of research in NMO. Is that the same for NMO? We don't know yet.

[00:49:19] Another area in MS is this concept of a prodrome. So even before people have neurologic symptoms that turn out later to be MS, they tend to use the health care system more. They visit doctors more. They go to urgent care centers more. They go to emergency clinics more. They see psychiatrists more. Why is that? Maybe the disease itself is becoming active in a pre-neurologic way. And now, there's some research suggesting that that may actually happen in NMO. So, all that to say that our knowledge is gradually evolving about this. What I can tell you though is I have quite a number of patients who have NMO who are elderly. They're in their 70s and 80s. And as long as we've kept them attack free, they've done really well.

[00:50:16] And one of the big differences between MS and NMO seems to be this tendency for MS to convert to a gradually progressive course. You've probably heard of secondary progressive MS. That's a big deal in the MS field. That's quite rare in NMO. So, that's a distinct difference, I think, between some of these diseases and NMO. If we stop attacks for most people, we can keep them healthy. Then you also brought up what are the long-term implications of my treatment. And that's a really important one. That's, I think, one of the drivers for us when we think about, yes, we're very pleased with the fact that we've got now four approved therapies for the disease, all of which are excellent, but they're not cures. Right?

[00:51:11] And we know that for people that have the antibody, it seems that they're always at some risk of attack, meaning they probably need indefinite treatment. We don't know that for sure, but we need to get to that next step where we can achieve something close at least to a cure that relieves people of having to take decades worth of immune therapy. Because we don't really know what the long-term effects of some of our newer therapies are going to be, especially for a younger person like yourself.

[00:51:52] The good thing is there's a lot of people engaging in this kind of research now. This whole field, including NMO and related diseases, is attracting more and more neurologists and scientists. In fact, it seems to be pulling them away from MS into this field, which I hope will mean that the progress will accelerate. Anything you guys want to add to?

[00:52:26] **Dr. Tammy Smith:** I guess, I would just add because I do tend to take care of a lot of older patients with neurologic disease, often the neurologist ends up functioning almost like a primary care provider because the neurologic disease is their main issue. A lot of my neurology patients are very healthy compared to their peers except for their neurologic disease.

[00:52:48] And I just would stress to not forget things like routine cancer screening when it's age appropriate, which your neurologist may not be thinking about. Have you gotten your colonoscopy when you turned 45 now? It's 45 now, folks, not 50. Or breast cancer screening, routine malignancy screening that's age appropriate. Just making sure that you're paying attention to that. You have a primary care doctor overseeing those things.

[00:53:17] **Dr. Dean Wingerchuk:** That's a great point. Because of the fragmentation of our health care system in the US, that kind of care is very uneven. Some people are fortunate and have a subspecialist neurologist and a primary care physician or other provider who's very engaged and up to date on all of that. Many people don't. You have to take that into your own hands and make sure you're covering the primary care bases with somebody. You don't want to rely on your neurologist for that. They may be helpful, but they may miss something.

[00:54:09] **Audience Member 5:** Hey. So, I'm a NMOSD aquaporin-4 patient. I was peds. I've had it since I was six. My question is, basically, I have moved to Florida, which is a kind of an absence of good health care. So, I'm currently seeing an MS specialist, and he's a little bit perturbed about my brain's MRI. Because I guess when you're an MS specialist, you see MS in everything.

[00:54:36] So he keeps looking at my brain scan and he thinks perhaps it's MS. And I'm like, I literally have the blood work for aquaporin-4 positive antibodies. I don't know. Is it common to have an MS reminiscent brain scan in NMO? I have black hole lesions. I have all those kinds of factors, but I'm not sure if that actually is just MS exclusive. Can you have NMO and have black hole lesions? Basically, what I'm asking.

[00:55:12] **Dr. Dean Wingerchuk:** Great question. You feel like an MRI question? I feel like I'm talking too much.

[00:55:25] **Dr. Peter Sguigna:** That's fair. So, if you go back to the pathophysiology of aquaporin-4, we think that this antibody itself plays a significant role in driving the pathophysiology. And it's necessary, but not necessarily sufficient. So there has to be as Dr. Wingerchuk was hinting, a second issue that for most people is hard to identify. But we focus scientifically a lot on the aquaporin-4 antibody, and we do believe that for most people, it is pathogenic. So, this whole concept of if you can get rid of the antibody, you might be able to cure the disease. And as long as the antibody isn't present, the disease, theoretically, might be in complete remission.

[00:56:14] If you look at the central nervous system the target for this antibody, the aquaporin-4 is expressed in the brain in a number of different places. Some very highly within the optic nerve, as well as the area postrema, and other places not expressed as much, but still expressed. And so there is at least some evidence to suggest that patients with NMOSD can develop lesions outside of the typical three lesions within the central nervous system. So, it's possible, it can be quite tricky. And so, there's a lot of research in that space, and it's really hard to say anything definitively. But it is simultaneously hard to argue with the positive aquaporin-4 antibody.

[00:57:11] **Dr. Tammy Smith:** I will argue slightly with it. What year was that that you were diagnosed?

[00:57:15] **Audience Member 5:** I was diagnosed in 2008.

[00:57:18] **Dr. Tammy Smith:** 2008?

[00:57:19] **Audience Member 5:** Wait. No. Not 2008. 2010. I was sick when I was taken to [inaudible]

[00:57:25] **Dr. Tammy Smith:** Okay. So not all diagnostic testing is created equally--

[00:57:29] **Audience Member 5:** I also did a secondary Aquaporin-4 test when I was 18. I also scored positive.

[00:57:37] **Dr. Tammy Smith:** Okay. Well, then that's maybe less to play into what I was going to say. But I do think as patients, it's really important, you're your best advocates. Right? So, to know what was done to diagnose you and keep those records for yourself. But one key thing is really the testing that's used to diagnose. So, in the olden days, one of the initial tests that was really commercially available, and it's still done at a couple of diagnostic labs in the country is something called an ELISA. And we don't recommend an ELISA as the diagnostic test nowadays. We recommend a cell-based assay. But that's really based on this data and then other groups have looked at this as well.

[00:58:20] But if you look at an ELISA, whenever we do a laboratory test, we take a 100 totally normal people and we run their test and we say, well, this is the level that a normal person has. And then we take a 100

sick people with NMO, and we say, okay. Here's the level that these guys have. And then, ideally, we run a couple of people with some other neurologic disease but not NMO to try to get the idea of where our cutoff needs to be. Okay? That works pretty well until you start testing thousands, and thousands, and thousands of people. And when you do that, those cutoffs have a lot more stutter or if you test thousands if you have that 99% curve, you're going to get some of those people on the tail on either end. Okay?

[00:59:05] And so way back, quite a few years ago, we looked at the ELISA and we saw that even though these people on the left piece of pie have a low positive, none of those patients actually had NMO. These people with the medium, the moderate positive, about two thirds of them had NMO but there were still some false positives. They had other diagnoses. And then if you had a really high level on this ELISA test, then a 100% of those people actually had NMO when we looked at them clinically. So, this is why we don't love the ELISA because you could get these positives where half of these patients with a low positive, their diagnosis is actually multiple sclerosis.

[00:59:46] So they have a low positive on the ELISA test. Whereas, if we do the modern cell-based assay, which I suspect if you were retested in the past couple years, though it's not definite because there are still labs that will run the ELISA, the cell-based assay is much more sensitive and specific. And I'm sorry about the image cutting off the words, but they're excellent tests.

[01:00:10] **Dr. Dean Wingerchuk:** I'll just add the MRI, of course, is very helpful, but it's only one part of the diagnosis. And if you look at, for example, diagnostic criteria for MS or NMO, they always say at the end, there's no better explanation for this condition because it recognizes that no criteria are perfect. They're really guides. They're guides for doctors to try to make the most accurate diagnosis possible. If you developed NMO as a child at age six, that's a rare event for an already rare disease. And we know that children with NMO sometimes present with more brain lesions and sometimes unusual brain patterns.

[01:01:00] And so, if that carries over into now your adult life, it could be simply looking at old injury that was indeed NMO years ago. And has some overlap with the pattern of MS because there is some overlap there. So, like you heard this morning multiple times, everything always goes back to what was the presentation and the course for some of these conditions especially children with MS, for example? It actually is the course over time that is one of the things that helps confirm and be confident about the diagnosis. The advantage we have for NMO is the high specificity of the antibody. If it's a convincingly positive result in the right context, it's going to be NMO even if the MRI has a flavor of MS. And it can cause these little black holes as well.

[01:02:03] So, I guess another area related to that is people often wonder, should I be having regular MRI scans if I have NMO? And, I don't know. There's no consensus answer about that. When we treat people with MS, we're usually doing as a default to an annual brain MRI. The reason for that is because we're looking for silent activity, they might not be aware of. Because if that's occurring, we think, well, maybe we should change their treatment. Well, does that happen in NMO? It's an area of controversy, but not much. If you were to scan people with NMO in their 20s and then compare it to people in their 40s and 60s and later, you'll see that over time, people accumulate more lesions. But some of those are just the kind of lesions we see as we age.

[01:03:04] But there are some data that suggest that if you do multiple studies on people, you can see some enhancing lighting up lesions coming and going. And that needs more study. We're not sure if that's really important or not. So, I think many of us who treat NMO don't necessarily follow the, you need to have an MRI scan every year because it usually doesn't show us anything actionable. At the same time, I don't like the MRIs to get too old. If somebody had an MRI for seven years and something new happens, well, that is a lot of water under the bridge. So, I usually try to do scans, keep the newest scan no more than about three years old. But that's just me. Tammy, you're doing all the hard microphone schlepping.

[01:04:01] **Audience Member 6:** Hi. My name's Melanie. I have a foundation called the Mellie J Foundation, and I focus on advocacy in shaping legislation. But specifically, I'm a seronegative patient with no biomarker. My doctors don't like double seronegative because they said there could be triple or quadruple. So, I have no biomarker. I have Sjogren's. I came up on a panel for lupus in the very beginning. They thought that was a red herring, but I just got referred to the genetics and genomics department at UCSF.

[01:04:35] And so, my question for you is, how do you see that shaping treatments for NMO patients who are specifically seronegative? Because I'm like the patient they say that keeps them up at night and I know I love my doctors and so I'm like, these people, if they can't save me, they know what they're doing. Right? And they always tell me they're doing old school medicine on me, basically, in terms of treatment plans.

[01:05:14] **Dr. Tammy Smith:** That's really challenging. I think, from a genetic standpoint in this disease and several of our autoimmune diseases, we get these associations, but we don't get one of those magic genes that you're like, that's it. This is the thing that's wrong that's causing this. Right? So, what we do tend to find are these genetic associations in regions that affect how your immune system responds to insult.

[01:05:42] Whether that's an infection, previous exposure to infection or allergens or whatever that is. And just broadly, those things can in the Plinko game of life maybe this time it's going to give you AQP4, and this time it's going to give you lupus or Sjogren's antibodies. But, yeah, I would say when we don't have a single target, which we don't in your case, certainly, double a--

[01:06:11] **Audience Member 6:** Sorry, I should have mentioned my event. I had, like, a 22-year diagnostic journey, and I woke up at 44 years ago, 45, with a black curtain coming down in my left eye. And so, I lost vision in the left, and then I had an attack in the right. So, I have bilateral optic neuritis too.

[01:06:31] **Dr. Tammy Smith:** Okay. So, a little clarifying information. So, 25-year diagnostic journey?

[01:06:34] **Audience Member 6:** 22 and I had vomiting and hiccups. I was in a lot of really good hospitals around the world when I was living in different places and just confusing doctors everywhere. And then woke up one day with just a black curtain that just came out.

[01:06:37] **Dr. Tammy Smith:** So maybe clarifying event more recently was waking up with vision loss in the left eye, but then ultimately developing bilateral optic neuritis. Yeah. And that's a hard thing in all of these diseases, is when a patient comes to us, we can test all the things all the time or sometimes we need to follow them over time. Right? Because the more testing we do for each and every patient, the more chance there is of a false positive or a red herring. Right? So, I can only imagine. I have not been on the other side. Thank goodness.

[01:07:30] But I can imagine how frustrating it is as a patient to have a doctor get a good exam, and get some basic labs, and history and maybe some imaging and then say, you know what? We're going to have to wait and see. I want to see you back in six months but call me if something changes. Right? And again, I can only imagine, but it must feel like they're not doing anything for you. But sometimes that's what we need to do is give you a little bit of time to declare yourself. So, in your case, after 22 years or 18 years, but then ultimately getting the optic neuritis that was bilateral that gave them the confidence that you met some diagnostic criteria for seronegative NMOSD.

[01:08:13] **Audience Member 6:** And then, the Sjogren's

[01:08:14] **Dr. Tammy Smith:** And then, the Sjogren's historically. Yeah. Yeah.

[01:08:17] **Audience Member 6:** [inaudible] the lupus, that's a question, and then the genetic team that I met with, and we just started. So, there's some talk of blood disorders too.

[01:08:26] **Dr. Tammy Smith:** Yeah. You're a fascinating case that no one wants to be. Right?

[01:08:31] **Audience Member 6:** And I donated a lot of spinal fluid too.

[01:08:34] **Dr. Tammy Smith:** And it is cases like yours that give us an opportunity to learn so much more. The people who follow the textbooks we just put them in the box, and we move forward. Right? But we can understand more about how the whole immune system can be dysregulated in some patients.

[01:08:53] I don't have an easy answer for you about the genetics or the path going forward except that when we don't have a single clear diagnosis or target, we do have to practice stone age medicine when it comes to treatments in the sense that we can't go for a targeted therapy if your whole immune system is out of whack.

[01:09:13] So we end up falling back on things like pulse dose steroids, plasma exchange at random intervals, or IVIG at intervals. Those are not terribly targeted therapies, but they have a broad effect on the immune system to cover our bases while we learn more. I don't know if anyone else has any good thoughts.

[01:09:35] **Dr. Dean Wingerchuk:** Yeah. Your problem is a challenging one, and I'm sure you've met other people in the same scenario. And I think it's certainly likely that the doctors looking after you want the answer just as badly as you do. Right? So, 20 plus years ago, nobody had a biomarker. And really what we did was we would evaluate people. And if it was their first event, first neurologic event, and it didn't look like multiple sclerosis, that's what we did. We just simply followed them and saw what happened.

[01:10:10] With aquaporin-4, it changed everything because it showed us that if you had one event, but you had the antibody, you were at very high risk for another event. So now, we call it the disease just with one event. You only need one event plus the antibody, and you have NMOSD. And we treat. We treat to prevent that next attack. So that's changed things. So, with MOG antibodies, it's a little trickier because those antibodies are harder to test for and often disappear spontaneously. So that's a more challenging situation, but it is a real biomarker. And there'll be more. I mentioned this morning about the diagnostic criteria evolving. And certainly, the hardest part of that, and the one we're going to try to get consensus on is addressing your problem.

[01:11:06] And that is what do we call and how do we approach people who have so called, what we're calling now, double seronegative NMOSD? How do we categorize and very carefully evaluate those individuals, characterize their particular condition? Is it one event? Is it multiple events? Is it only optic nerve and spinal cord? Or is it just one or the other? Or is it some other features? Those are the kinds of things that will help us ultimately discover and connect the new biomarkers that'll be discovered. So, it's a work in progress. I'm pretty confident we'll get there someday. There must be something going on in your system that just hasn't been fully detected yet.

[01:11:55] **Audience Member 6:** Yeah. I just had a fluorescence angiogram. They're looking at my retina because the disease activity, so I'm blind in my left eye but the right, I have damage in, but I can see, and I still drive. And my neuro-ophthalmologist he was happy. It was a positive result that everything was working normally, but, again, frustrating for them because there's definitely activity going on and it's just figuring out,

like, I will see things happening in my brain before they'll show up on, like, an OCT test or like a Humphrey visual field test or, right?

[01:12:42] And so, the second attack I had, I remember, on my right eye for about six months I could see this veil, this thing happening in my eye and it wasn't showing up on any MRIs. And then later, it took about 6 to 8 months, it did, and I had to go to the ER. And my neuro-ophthalmologist called me after my test. She's like, you need to go to the ER. And I did the corticosteroids and all the things, and I had plex, like, in the beginning with the left eye, but I usually know it's happening. Like, I can see the whatever disease activity that's happening when an event is happening, whether it's a flare or relapse or whatever.

[01:13:24] But it doesn't always show up until later. I think there were lesions later on the right eye and I know from the first attack, there wasn't any on the right. And then it was a year later they saw them, and they told me about it. So, it's a constant process. So, I'm excited about the genetic part of it because there's definitely something, but it just who knows?

[01:13:57] **Dr. Tammy Smith:** Thank you for sharing. We have another question back here.

[01:14:04] **Audience Member 7:** Yes. Okay. Multipart question. Won't make it too many. But to follow-up on what Dr. Wingerchuk said, you said that in NMO, the secondary progressive is rare, but you didn't say non-existent. Have you seen a case of it or multiple cases? And how does that apply to the people that are seronegative, double seronegative?

[01:14:28] I've got a friend that's on multiple treatments or been on multiple treatments. She's having progressive symptoms, but they don't ever call it a relapse. So, is that secondary progressive? And then last thing is with you all saying aquaporin-4 is found throughout the body. Why in NMO does it decide to only attack the central nervous system?

[01:14:55] **Dr. Dean Wingerchuk:** Wow. Great questions. Well, why don't I take a stab at the first one? Because I've been interested in that question for a long time, and that's this issue of so-called secondary progression. So, it really stemmed from observations that my colleagues and I made back about starting almost 20 years ago, where we were comparing and contrasting what happened in NMO versus what happened in MS. In MS, people as you know have flare ups. Most people have relapsing disease. 85% of people start that way. And we put them on immune therapies to try to prevent attacks. And new lesions on the MRI. And that's generally pretty successful.

[01:15:45] But what we're really trying to do in those people, nobody wants to have attacks, so preventing them is good. But what we're really trying to accomplish with our MS treatments is shutting down as much of the inflammatory response and relapses as possible, hoping that that will either prevent or delay a person from developing a later progressive course, where instead of having a flare up over a few days or weeks, they mentioned that, well, I'm losing ground with my walking. Last year, I could walk an unlimited distance. But now, after I walk a block and a half, my left leg is dragging. And then the next year, it's dragging all the time. That's called a secondary progressive course, because the disease started as a relapsing condition, and then secondarily became progressive.

[01:16:40] So that's a huge area of investment and research now in MS. Progressive MS is kind of the biggest unmet need in that disease. Untreated, it happens to roughly 60 to 70% of people with MS. We observed that it happens in people with NMO only about 2 to 3 percent of the time. Huge difference. Why is that? You would think that if it was just about damage to the spinal cord, number of lesions, severity of lesions, size of lesions,

recovery, or something like that, NMO, if anything, should have a higher rate of progression. Right? People who have spinal cord involvement in NMO, it tends to be more severe with each attack as compared to MS.

[01:17:30] And yet, people recover to whatever degree they're going to recover from their relapses. And in most instances, stay stable. And there have been some other studies that have kind of found the same thing over the years. It's an area of controversy because by the same token, there's research that shows that some people at least with NMO have thinning of their optic nerves over time or may develop some cognitive issues. Is that disease progression? We don't really know. But the huge difference between NMO and MS suggests some very important differences in the biology of the disease. So, we hope to learn about each condition from each other.

[01:18:18] What does this mean practically for people who are gradually getting worse? Well, first of all, it's what we call a red flag for a diagnosis of NMO. So, if somebody presents to a neurologist and says, I've been having walking problems gradually for the last two years, that's unlikely going to be NMO. If a person has NMO and they report something like that, what it means is we investigate why. Why are they getting worse? Do they have spinal stenosis that's pressing on the spinal cord, a separate neurologic problem. Do they have a peripheral neuropathy? Do they have orthopedic problems? Or other so-called comorbidities that are causing it?

[01:19:07] We do all of those investigations to try to understand why they're worsening before we conclude that they have progressive disease. So, you should never say never and never say always. So, it does happen occasionally, but it's quite uncommon. And so, for someone who has NMO and is gradually worsening, it requires a careful examination to find out why. I hope that answers your first question.

[01:19:44] **Dr. Tammy Smith:** And I guess regarding the second question AQP4 is predominantly within certain regions of the central nervous system and then in the kidney. And I don't understand why it doesn't cause renal disease. I've looked this up a few times, and I can't talk myself into why it doesn't affect that.

[01:20:18] **Audience Member 7:** My nephrologist was really never that interested [inaudible] that I have NMO, it's likely that I have AQP-4 NMO and he lit up and he's like that's also found in the kidneys, so I'm curious.

[01:20:19] **Dr. Tammy Smith:** Yeah. So, despite it being highly expressed in the kidney, I do not know of any pathologic association with renal disease.

[01:20:26] **Dr. Dean Wingerchuk:** Yeah. It's a great question though because aquaporin-4 is expressed in lots of organs in the body. It's in the lung, in the gut, in the retina, and we actually don't really see disease in those organs either. It's also expressed in muscle. And so, there are some people described to have NMO who have had myositis or muscle inflammation. And in fact, when their muscles were biopsied, they showed the same findings as you can see in the brain or the spinal cord of somebody with NMO.

[01:20:59] That's not that common, but it's a strong association. One of the hypotheses is that there are complement proteins. So, you have complement therapies in NMO, and there's complement proteins that are expressed in organs, but not in the nervous system that might explain the difference. But we don't really know for sure. So, it's another one of those mysteries to be solved.

[01:21:35] **Audience Member 8:** My question and this may be out of the wheelhouse, and you may discuss this sometime within the weekend, but what about your take on bone marrow transplants? When it comes to, I know that Selma Blair, who is a very famous MS patient, had that done, and she's done well.

[01:21:58] And so I don't know if there's research ongoing with that in NMO and if that's a possibility. Just a question. If that's out of your wheelhouse, I understand, but I'm just curious.

[01:22:11] **Dr. Dean Wingerchuk:** Well, I did mention before, not quite bone marrow transplantation exactly, but a modified form of stem cell transplantation, where instead of completely wiping out the bone marrow, you take it to the brink with chemotherapy and then replace those cells, speed up their recovery with stem cells. That's a safer thing to do. I also mentioned earlier some of the technologies that have been extrapolated from cancer and are now being applied to autoimmune disease. And you may have heard of things like CAR T therapy for certain types of cancers.

[01:22:53] There's something called double A CAR T that is a technique to basically engineer the body's own T cells to attack very specific targets, which you could imagine, can be helpful in diseases like NMO, where you know what the bad actor is. So, all that to say that I think bone marrow transplants probably not going to be the future for NMO, but more advanced and targeted and safer therapies that can accomplish the same thing.

[01:23:31] Which is effectively a reboot of the immune system or some kind of restoring of the immune system's tolerance to antibodies against aquaporin-4. Instead of them causing damage, the immune system recognizes, that it shouldn't do that. And all these therapies are converging in that direction. If you want to add anything else, you guys?

[01:23:59] **Dr. Tammy Smith:** It's almost like you were reading the slide that I made for us about those. So, you just listed them off one after another.

[01:24:05] **Dr. Dean Wingerchuk:** That was an accident.

[01:24:06] **Dr. Tammy Smith:** Just right. Stay tuned.

[01:24:12] **Dr. Dean Wingerchuk:** Yeah. We've got a number of things listed there, which are, you can see how and that's just a small portion of the list of things that are being studied now.

[01:24:23] **Dr. Tammy Smith:** And the challenge being rare diseases just make it that much harder to get the number of patients enrolled to see the effect. So randomized controlled clinical trials are challenging to do in any disease, but that much harder in rare disease.

[01:24:39] And patients who are engaged in their care and interested in participating in research should really keep their eyes peeled to clinicaltrials.gov, look up their disease, ask their doctors about what clinical trials might be available in the future for them to participate in, so that we have more answers for you in the future.

[01:24:54] How are we doing for time, everyone? We have four minutes left. What burning question has someone been hanging on to for the last four minutes? Anyone? We got one over here.

[01:25:12] **Audience Member 9:** Hi. I live here in Dallas. So, yay, Dallas. I'm only in month six of this journey, and I am double seronegative. Negative for MOG and NMO antibodies. I've looked up and down Internet and clinical trials and all these things. I see nothing being done focusing on people like me and you, and there's three of us that I know of in this room. So what's being done for us? Do we just not have that antibody period in our body if it's found in other areas, or did I just get tested at the wrong time? I just had some blood work done last week, so I don't know if it's showing up yet or not. But how do we get help?

[01:26:02] **Audience Member 6:** I've been tested so many times, and I'm always negative. And I know my doctors are like, you know, and then it comes back, and I have been tested [inaudible]

[01:26:14] **Audience Member 9:** Yeah. I have a really great neuroimmunologist, and she says I'm a classic case except for that one piece. So, help me.

[01:26:27] **Dr. Tammy Smith:** Well, I hope it helps knowing that you're not alone. It doesn't give you the answer, but you are not alone. It's really challenging. I think getting pre-treatment samples stored and banked at some academic center that does research can be helpful so that you might be able to get some answers in the future because a lot of the empiric treatments we use can then mask our ability to detect these antibodies when we do discover new antibodies.

[01:26:56] So if we have a bunch of stuff in a freezer from before you got treated, then it's nice to be able to resort back to that, when we do learn more. But for these clinical trials to enroll patients, often we do have this requirement for an antibody so that we really know we're looking at the right thing. So clinical trials are hard to do, they're expensive to do, and if we have a mixed population going in, the chance of us seeing a benefit and being able to apply that to patients in the future is that much lower. That doesn't give you your answer right now. Dean, thoughts about clinical trials or Peter?

[01:27:36] **Dr. Dean Wingerchuk:** That's a great explanation. I certainly understand your frustration. Mention what I mentioned earlier, which is, yeah, it's likely that your doctors want to find the answer just as much as you do. I think the reality is that, what is under the umbrella or labeled as seronegative NMOSD is likely a collection of a bunch of different things that we don't understand. It's a variable or heterogeneous group, as we often say.

[01:28:09] Although it might appear that nothing's being done, it actually is recognized as one of the biggest unmet needs in the field. So, when we did a poll, a survey of physicians and scientists who are engaged in NMO research, the number one thing they said that we needed to address was the definition and research moving forward for what we're now calling seronegative disease. So, it's happening. It's just not that visible right now.

[01:28:48] **Audience Member 6:** I volunteer.

[01:28:49] **Dr. Dean Wingerchuk:** You volunteer. We definitely need that. Yeah. Oh, Peter. Go ahead.

[01:28:57] **Dr. Peter Sguigna:** Just a few more things. So, for clinicaltrials.gov, most of the time, most of these studies are going to be therapeutic, and that's based on federal regulation. A few of the studies on there are what we say investigational. So, they're looking for people like you to take their blood and take it back to lab.

[01:29:17] And as Dr. Wingerchuk was indicating there's some people that think there's an antibody we haven't discovered. And there are a few research groups that are excited about a couple different antibodies, in the NMOSD, the double seronegative NMOSD. Finding those people, and they'd be happy to talk to you, I suspect.

[01:29:40] And the flip side of that is there are some people that think perhaps maybe it is more along the lines of multiple sclerosis if it's far as pathophysiology. It could be that there's not an identifiable antibody. And so, the fork in the road is where essentially you and your providers are at. So, the only way we're going to be able to cross that road is to get smarter.