Live Q&A Session

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[00:00:00] **Lydia Dubose:** Welcome everybody who is watching live or who's watching the replay. We are excited to have a Q and A session with some outstanding experts. Today, we have two experts with us, Dr. Grace Gombolay with Emory University and Children's Health Care of Atlanta, and then Elena Grebenciucova, who is an SRNA James T. Lubin Fellow previously and is with Northwestern University and Feinberg School of Medicine. Thanks, both for joining and being a part of the conversation today.

[00:0047] **Dr. Elena Grebenciucova:** My pleasure.

[00:00:48] **Dr. Grace Gombolay:** Great. Thanks for having us.

[00:00:50] **Lydia Dubose:** So, we will jump right into some questions from folks. Before we get into very specific questions, we want to start a little bit more broad and just to learn a little bit about NMOSD. So, to start, what is NMOSD and how is it similar to other rare neuroimmune disorders? And there were some questions from folks. Is there a difference between NMO and NMOSD?

[00:01:25] **Dr. Elena Grebenciucova:** Yes. So, I can tackle this question. So, thank you for this very important question. So, when we apply the term neuromyelitis optica spectrum disorder, it includes people who are both aquaporin-4 antibody proven. And this is that classic neuromyelitis optica that we generally think about with a very specific mechanism of how this antibody if found in the blood, of how it causes the inflammation that leads to symptoms in the brain or spinal cord. That is the classic neuromyelitis optica that is aquaporin-4 antibody positive. And then, of course, some people are aquaporin-4 negative when we test it in the blood and in some instances in cerebrospinal fluid and yet the behavior of the disease, the amount of inflammation, the way it looks on the MRIs looks very similar, if not identical to what we see in those people who do have aquaporin-4 disease.

[00:02:30] A subset of people who have the diagnosis of neuromyelitis optica spectrum disorder where aquaporin-4 antibody was checked and was negative. First, we actually want to make sure it was checked with the most sensitive assay, which is a cell-based assay. A lot of times it's sent out to Mayo, but a lot of other labs do it as well. This is a critical step, because if a just an ELISA essay was used, it can sometimes miss the aquaporin-4 antibody and lead to a misdiagnosis or a false diagnosis. So, the first thing is that we want to make sure that a person what is called NMO spectrum disorder aquaporin-4 negative that they actually really did a thorough job at checking for aquaporin-4 antibodies via the most sensitive test in the serum, and that cell-based assay for aquaporin-4.

[00:03:26] And even if it's negative, it is recommended that it is rechecked in about six months, because none of these tests are 100% perfect, so we always recheck. But until then, there is another antibody that turns out to mimic neuromyelitis optica, that is aquaporin-4, and this is MOG, myelin oligodendrocyte glycoprotein

antibody. And it turns out that a lot of people that used to be grouped as neuromyelitis optica spectrum disorder that was aquaporin-4 negative of at least 30%, 40% of them now we know have MOG antibody and this is myelin oligodendrocyte glycoprotein, MOG associated demyelination, MOGAD, which is a disease that also has a very specific mechanism. There's a separate antibody driven process for some T cell involvement as well. But it also just like classic neuromyelitis optica this disease can cause optic neuritis, inflammation of the optic nerves leading to blurry vision, transverse myelitis with symptoms of weakness, numbness, tingling, bladder issues, et cetera. So those are major subsets.

[00:04:37] And then of course, there is this neuromyelitis optica spectrum disorder, which looks and behaves like aquaporin-4 positive NMO, and yet there's no antibody that we find. So, to date, these patients sometimes can behave a little bit different, because the question that scientists will ultimately always ask and all of us is there another antibody that we're missing or maybe we haven't found yet? What is the mechanism that unites all of these patients? Or is it perhaps there are different mechanisms? And that's why it's so difficult to sometimes create great treatment strategies for people who are antibody negative neuromyelitis optica. And this is why most of the FDA-approved drugs really focus on people who are aquaporin-4 antibody positive because there's more of a proven specific mechanism through which that antibody causes inflammation and damage in the central nervous system. And then my colleague, if you have any additional comments.

[00:05:42] **Dr. Grace Gombolay:** Yeah, I think that's lovely. I think that you really covered a lot within NMO and NMOSD. I just have very few things to add. And it's just that I think when I think about patients who have NMO versus NMOSD, it's basically the same thing. It used to be called NMO, neuromyelitis optica, or Devic's disease was the older term for it. But now that we're realizing there's a spectrum meaning there's not just optic neuritis and transverse myelitis, we know that the brain can also be involved in terms of parts of the brain and that thing. That's why we call it a spectrum. So, in my mind, NMO, NMOSD generally interchangeable, I think a lot of people are recognizing because of the spectrum, people are tending to use NMOSD, but I think it's okay to also say NMO.

[00:06:28] **Lydia Dubose:** Great. Thank you so much. This next question you both can answer. But I wanted to address Grace for this. How does NMOSD present similarly or differently for adult and pediatric patients? And how do the treatments change for adults or children?

[00:06:49] **Dr. Grace Gombolay:** So generally, what we think in terms of NMOSD is that younger patients tend to present with what's called ADEM, acute disseminated encephalomyelitis where you get a ton of brain lesions in your brain. And then you can have optic neuritis, where the optic nerves or the eyeballs are involved, and you can have transverse myelitis, where the spinal cord is involved. The older patients, usually in their 30s is what we think about. They tend to present with more of the classic NMOSD or just the NMO part where they just have optic neuritis and transverse myelitis, less likely to have that ADEM phenotype. But there's tons of overlap. I've seen both in both age groups, but generally younger patients are going to have more ADEM, and then the older patients are going to have just the optic neuritis and transverse myelitis.

[00:07:34] Treatments are quite similar, honestly, I think what we've shown in both groups is that rituximab or CD20 agents are going to be one of the first common ones used. And then there's a lot of studies that have been done in the adult NMOSD groups that we haven't started using in kids yet. But we're starting to, now that we know how efficacious and how safe it is in adults. I will say one thing is that there's some data to suggest, again, hard to know exactly because these are all small studies. There hasn't been a lot of comparative trials for this but tends that rituximab may work a little bit better in children than adults. But again, it's just based upon a few case series and some comparative studies, but nothing formal. But generally, the approaches wouldn't be the same. I will say in my experience for the children I see with NMOSD, all of them are doing quite well on rituximab. I have two who are not. And so that's pretty rare, but everybody else is doing really

well. That might be a matter of age of onset, but also be a matter of time also because I only see them when they're younger, and then maybe when they get older, hopefully their disease is going to continue to be controlled. But if not, then we'll have other treatments available for them.

[00:08:51] **Lydia Dubose:** Great. Thank you so much. We had a few questions about pregnancy. Are there certain recommendations for pregnancy and rare neuroimmune disorders, especially NMO? What are some considerations when it comes to medications? Are flare ups likely to occur during pregnancy, and anything else to know in preparation for getting pregnant when you're living with NMOSD?

[00:09:23] **Dr. Elena Grebenciucova:** I'll try to tackle this question, and then Grace, please follow up with any addition. So, pregnancy in women who live with neuromyelitis optica spectrum disorder should really be planned particularly because many of these medications are associated with potential effects on the fetus. And so, there are certain medications that are probably not recommended for sure in pregnancies. So, for example, satralizumab, Enspryng, continually do not utilize it in pregnancy. So if I had a patient on Enspryng, and I wanted her to plan pregnancy for her, I would suggest that she switches to a medication like rituximab, and we'll talk a little bit about it in just a moment how we do this safely, because obviously nobody wants to expose the baby to these medications, but there are certain ways in which we can still avoid much exposure to the baby, but also keep mom safe.

[00:10:26] So there are some differences between how people with multiple sclerosis, for example, versus neuromyelitis optica do. For people with multiple sclerosis, they generally can successfully go off of treatments during pregnancy with some exceptions and have very low risk pregnancies. In multiple sclerosis, the risk of relapse doesn't go up in pregnancy. It's actually very rare. In neuromyelitis optica, it's a little bit different particularly in those patients who are aquaporin-4 antibody positive, because we know that aquaporin-4 antibody is expressed on some of the tissue of our placenta. Women with aquaporin-4 antibody positive neuromyelitis optica, may actually have a slightly higher risk of disease activity or relapse during pregnancy and sometimes shortly after pregnancy. They also may at times have a slightly higher chance of miscarriage for that reason.

[00:11:24] So we consider being extremely cautious and do a lot of planning and discussions with women with neuromyelitis optica who are planning pregnancy. So, let's talk a little bit about medications. We do not believe that going off of medications completely and not having a plan for pregnancy is safe for people with NMO, specifically because of what I just stated that women with neuromyelitis optica who are aquaporin-4 antibody positive specifically may be at a somewhat higher risk of relapse during pregnancy if untreated, if they haven't had a good plan designed to protect them during pregnancy. And there are different ways of doing that to minimize the exposure to the baby, but at the same time, keep moms safe.

[00:12:16] So I would say that today studies show that pregnancies and neuromyelitis optica are perfectly possible and healthy and moms can have great outcomes and babies can have great outcomes, but it does have to be planned. So, as I mentioned, if a mom is on Enspryng, satralizumab, will have to be held and switched. So, let's talk about what do we do about those moms who are on rituximab on a B cell depleting treatment. So, we know that rituximab depletes B cells for about six months. And then we are trying to make sure they stay down. So, if a mom gets rituximab, for example, a month before she gets pregnant. So, let's just say - or let me rephrase this, let me backtrack and rephrase this.

[00:13:06] If a mom tells me, I would say to do the following. I would say to consider getting her - if she is on rituximab getting her rituximab and then three months later, it's actually out of her system. And then at that point, women can start trying to concede. So, there is very little exposure and then during pregnancy, we monitor their B cells for the emergence. And there are different types of treatments that can be considered

during pregnancy depending on your own disease type, depending on your safety concerns, your other health conditions, how the baby is doing. In some instances, tiny amounts of steroids can be given in some instances, IVIG, intravenous immunoglobulin can be used, but all of those treatments certainly have their own risks and side effects. So, there is a careful consideration and discussion with mom about her goals in protecting herself from neuromyelitis optica relapse and minimizing any risk to the baby as well.

[00:14:11] In terms of rituximab, rituximab is not FDA-approved for women who are pregnant but certainly there is already an accumulating experience of women whose pregnancies have been exposed to rituximab. And we have not been seeing any issues with any malformations or birth-defects. And that data, although limited, comes from patients exposed to rituximab who live with multiple sclerosis, or neuromyelitis optica, or other autoimmune conditions. And of course, we try to minimize that exposure, because babies born to moms, if they were exposed to rituximab, particularly later in pregnancy, if the rituximab was given during pregnancy, they had to give rituximab which in rare situations that may be the case. Sometimes babies are born with low B cell counts, but they will basically make those B cells back up in the next few weeks or sometimes a few months.

[00:15:10] And there is the consideration - not the consideration, but it needs to be communicated to the pediatrician that mom was exposed to rituximab and they should be monitoring babies' blood cell counts and some of the vaccines in the babies may have to be delayed, because otherwise these babies will not make the antibodies that they need. So, I think that there is no rule of how to treat women with NMOSD during pregnancy that fits all of us or each one of us. It's a discussion about risk versus benefits and it's about creating a unique plan that is suitable for mom and her goals and her understanding of how these medications work and what is her risk of relapse during pregnancy and how it can affect her and what are the safety considerations for her and for the baby. And we of course, have had many babies born. So, moms with neuromyelitis optica who have done wonderful and have had very successful pregnancies and their babies are doing well. And then there is another medication as you know Soliris which is eculizumab, which is again not approved by FDA for pregnancy, but some data may suggest a consideration of that in some instances. And Grace, I will let you expand on your opinion on some of the things that I mentioned.

[00:16:35] **Dr. Grace Gombolay:** I think you did a wonderful job, and I will say that as a pediatric neuroimmunologist, this is not something that I encounter very frequently. One thing I do counsel my patients and families on is that there are risks like you were mentioning depending on what medication you're on. So really making sure that we talk about birth control and contraception and all these things. And then that way, we can make sure that everybody is safe.

[00:17:01] **Lydia Dubose:** Absolutely. Thank you. And we had a follow-up come in from our chat. I'm not going to say this correctly tocilizumab in pregnancy with a seronegative patient.

[00:17:18] **Dr. Elena Grebenciucova:** The same thing. So, some of these anti-interleukin 6 agents, they are not considered to be safe during pregnancy. So just like satralizumab, tocilizumab, likewise, you would have to discuss with your physician, essentially an alternative plan of coverage during pregnancy and while during conception so that the baby is not exposed. Just like I mentioned, some moms may be able to switch from tocilizumab or satralizumab which is Enspryng onto rituximab and then in three months, one is out of their system, but they're still protected from NMO attack, because the B cells are depleted, then mom can try to conceive, she's protected and there's no rituximab in her system, because rituximab half-life is about 16 days and it takes 5-6 half-lives to get it completely out of your system. Moreover, rituximab genuinely doesn't cross the placenta very well during the first trimester. And that's also important to know that even if there was a tiny exposure and there was a little medication in your body, it's unlikely to have crossed the placenta and done anything to the baby.

[00:18:27] **Lydia Dubose:** Thanks so much. We have a few questions related to treatments. First, what can a person who's not currently taking any treatments expect? And then for someone who is taking a medication like Rituxan is there any reason to switch to a different preventative?

[00:18:45] **Dr. Grace Gombolay:** Yeah, I can answer this and then have Elena add on anything that she would like to add. So, I think the thing about that we know about in particular for NMOSD is that more than 90% of the patients are going to relapse. And that's why even at the first episode, at the time of diagnosis, we recommend treatment, because we know there's a high risk for relapse and there's potentials for when you do relapse, you may not recover completely from it. So, we want to prevent that from happening.

[00:19:10] The other thing that we know about NMOSD, and this can happen in multiple sclerosis and other related disorders is that patients can also accrue progressive disability even without any evidence of relapses. And so, we just know that there's ongoing neuroinflammatory immune system is still attacking your nervous system. And so, we're trying to prevent all of those things from happening. And so, at the first time, when you first diagnose the patient, we're pretty aggressive about starting on treatment earlier rather than later, because we want to prevent those things, prevent relapses and prevent patients from occurring disability.

[00:19:45] For someone who is taking a medication like Rituxan, the reasons when I switch to something else are going to be a few options. One would be if it's not working. Number 1 is if the rituximab is not working, you have a relapse through it. You're starting to have worsening symptoms and disability and your B cells are still depleted, because like we were talking about earlier, most patients, B cells are depleted for about six months with rituximab, it's different for different people. I have some patients where their B cells will come back earlier. And if that happens, then I will give rituximab earlier or give a higher dose or that thing depending on the situation. But if your B cells are still depleted and you're having relapses or worsening symptoms, that's telling me that rituximab is not working, so I need to switch.

[00:20:28] For me personally, really serious side effects to the medication like rituximab, that would be another reason to switch. I'll be honest with you; I've had a couple of patients who we were worried about a severe allergic reaction. You check for anti-rituximab antibodies are negative and then you just do different management things usually slowing down the rituximab mitigates any of the side effects that people have. So, I haven't had to stop anybody yet on rituximab due to side effects. But those would be the two main reasons, either it's not working or if you have really bad side effects. Elena, anything that you'd like to add?

[00:21:03] **Dr. Elena Grebenciucova:** Well, I agree. I mean, the reasons to change with either if it's not working or there are major side effects and of course, the question always comes up is inebilizumab, Uplizna that is not FDA-approved, is it better than rituximab. And of course, while theoretically, it was designed indeed to be better to deplete these cells a little bit earlier, there have been no comparisons in head-to-head trials between rituximab and inebilizumab. So, we wouldn't be able to state definitively that inebilizumab, Uplizna is by so many percent better than rituximab. And in the absence of that data, sometimes I think if a patient desires to switch from rituximab to inebilizumab, Uplizna, it is absolutely fine by me. I think it's reasonable. It is an FDA-approved drug and I think it's a good drug that works really well.

[00:22:00] But I think there are certainly all of us physicians and scientists, we would like to read the data to show that it does definitively work better than the rituximab. Theoretically it should, but we certainly yet have to have to see more data to prove that. But in other words, if my patient has been on rituximab long term and they're doing wonderful, I never tell them you must switch to the inebilizumab. I always tell my patients about their options and let them decide. And I think that's really our responsibility as physicians to have that ability to communicate all the updates about new drugs that are coming out, their safety concerns, what we know, what we don't know and make that joint decision in your care. Help you decide. Maybe if that decision

is not today, maybe it's in six months or a year. But it's a journey. It's a journey of understanding what is the best drug, and we are on this journey with you together.

[00:23:02] **Lydia Dubose:** Great. Thank you so much. Next, we have a question about what is step therapy and how can patients advocate for themselves when insurance is requiring that they try one treatment before offering them the opportunity to take another?

[00:23:24] **Dr. Grace Gombolay:** I can start with this. So, step therapy is - I think of this more in the MS world than they do in the NMOSD world, because NMOSD, we have some really well-proven treatments. And so usually for me, it's rituximab first line that I usually use. I find the step therapy and I usually don't have issues getting that covered by insurance. Step therapy I find and more of my patients who have MS, I've had a lot of insurance companies come back. And the other thing is I'm seeing children with MS and so a lot of the medications we have available for MS are not FDA-approved, we just have one FDA-approved medication for MS which is fingolimod, and everything else is not. And so, I have a lot of insurance companies - this happened to me yesterday, actually, they came back and said, oh, you have to try these injectables, which are the "traditional first-line therapies in MS" or one of the oral agents before you can recommend an infusion like rituximab.

[00:23:38] And I think for me is that what I do is - and then the other things they ask about teriflunomide, I that they also have to fill teriflunomide. And so, I write this - I see Elena shaking her head. So, I write this letter and I put this in my notes, and I put the children with MS are at high risk for relapses. They're at high risk for disability, they cannot do injectables, because injectables are not as effective. We only know they're 30% to 40% effective compared to 80% to 90% for like rituximab or Gilenya. On top of that teriflunomide is a category pregnancy X. Most of my MS patients are women or young ladies who are of pregnancy age. So, I am not giving them teriflunomide and it doesn't work as well as the other agents too. So, I'm not going to give them teriflunomide when it's category pregnancy X.

[00:25:06] And I do have patients who have trouble adhering to daily oral medications. And I find that once I explain all of that to the insurance company, they'll come back and say, okay, we will approve this medication. So, you have to decide what medication is, what your personal situation is also. And then I find that if I can put this article, I send them articles about all of these things and then explanations of why I do not recommend these particular medications, that can help. I do have patients who also call up their insurance company to help the physicians in the office side of things with him. But oftentimes if I write a long letter, put this in my clinic note that gets sent to the insurance company that can help. It still is a battle though. Elena, what's your experience with this?

[00:25:49] **Dr. Elena Grebenciucova:** I agree. Most of the time, it's actually up to us physicians to advocate for you guys. And that's certainly something that we do virtually every single day when insurance is declining medication or tries to take care inappropriately. When discussing medications with my patients, I never take into account the step therapy as what is meant in this question. Meaning that at the end of the day, we will apply for the medication that you and I jointly have decided is right for you. And then we will take the steps if medication is declined to do a peer-to-peer phone call with medical director of the insurance company and try to explain to them why it is that you specifically need this medication versus another.

[00:26:35] A lot of times, for example, if the patient is really afraid of needles, they may not be able to inject satralizumab, Enspryng, or maybe the patient is not going to be able to get Soliris every two weeks because they are traveling for work every month. So, there are certain considerations that we certainly document in

the notes of why other options are not a good choice. And most importantly, we also explain why we believe this medication will be the correct one, the right one specifically for you. Maybe it's because you have certain other medical problems, for example, high risk of infection, what kind of infection, some of these medications may be theoretically much safer for you than the others, or maybe you have really bad asthma. So maybe I don't want to use a medication A versus B versus C.

[00:27:28] So there are certain things that we document in our thinking or when we choose these medications and then if it's declined, we usually will do a peer-to-peer phone conversation. And if that doesn't help, then we write a letter of medical necessity where we attach scientific papers to show why we are recommending this medication and an extremely rare case that's extremely rare when, where it's still not approved, then the patient has a right to basically for an appeal through an outside party for an additional review. That said, all of that certainly can delay care. And that is something that we take very seriously. And so, we push very hard to make sure these things are done and are done as quickly as possible.

[00:28:18] **Lydia Dubose:** Thank you so much. And we did have a follow up. Somebody was asking why FDA-approved therapies here in the United States tend to be given to seropositive patients, but rarely to seronegative ones?

[00:28:37] **Dr. Elena Grebenciucova:** Because these treatments went through clinical trials and the adult population. Grace, I'll handle that question. So, I think it has to do with the fact that most of these medications were designed to address the underlying mechanisms as we know it when NMO is caused by aquaporin-4 antibody. So, if we have that aquaporin-4 antibody, we know several things. We know that depleting B cells is important because we get rid of those B cells that can produce extra aquaporin-4 antibody. We know that blocking interleukin 6 via tocilizumab or satralizumab is important, because that cytokine or hormone of the immune system feeds and drives both B cells and T cells. And we know that eculizumab or Soliris blocks the terminal damage that aquaporin-4 antibody does when it binds complement and a lot of inflammation and damage to the tissue ensues.

[00:29:44] So aquaporin-4 antibody mediates its damage, is very well studied today. But when it comes to what we group onto neuromyelitis optica spectrum disorder, that is negative for the antibody. Look, over the past six years, what did we learn? We learned that a subset of those people who were called neuromyelitis optica spectrum disorder turns out the subset of them have MOG antibody with a completely different mechanism of how it does the damage. So, there is no full consensus on understanding the underlying mechanisms in all of those people who are called neuromyelitis optica spectrum disorder, because most of these people don't have an antibody that is found.

[00:30:30] So yes, neuromyelitis optica spectrum disorder can behave very similarly to aquaporin-4 positive neuromyelitis optica. And that's why we use rituximab for a second. But we don't have to prove that there is also - in all of these cases that there's complement activation. So, we must use Soliris or in all of these cases, these benefit from anti-interleukin-6 agents like satralizumab. And this is actually precisely why for a subset of those patients who were previously diagnosed with neuromyelitis optica spectrum disorder negative for aquaporin-4, once we find MOG antibody, what are we learning? We are now learning which treatments are effective, which treatments are not effective. And that may be a little different than aquaporin-4 antibody positive people.

[00:31:18] So this is like a historical lesson of how science groups diagnosis and then over time advances and finds novel antibodies, novel explanations that pave the way to very focused specific treatments in clinical

trials. And absolutely more research needs to be done in antibody negative neuromyelitis optica spectrum disorder. And most definitely, all of these clinical trials need to include these groups of people. But then of course, the interpretation of that data becomes a little bit challenging, because we don't really know. Are they all truly the same? Do they truly all have the same underlying mechanism? And how reliable is that data? And those are the major challenges that I think need more research.

[00:32:09] **Lydia Dubose:** Thank you. We've talked a lot about treatments - we've talked a lot about treatments just now, and we had some questions about natural or holistic or different words that people will use for helping with managing neuropathy or pain. So, they asked specifically about CBD, hemp oils, or creams, and if those are helpful.

[00:32:33] **Dr. Grace Gombolay:** I can start this Elena and I'd love to hear your experience with this too, because I get this a lot. I think for me, the first thing I also want to make sure is that because neuropathy and pain is a huge component of a lot of these neuroinflammatory disorders and can be quite challenging to treat. And so, one of the things that I will actually start with is I will check vitamin levels, because there we know certain vitamins can affect your nerves. And so, if you have - and it's very easy to give you back those vitamins with different B vitamins, for example, can do this. So, I'll check that just to make sure that your levels are at a good place and if they are not, then we can replete those.

[00:33:07] I think the thing about the CBD, I know there's a lot of interest in it and I think there's a lot of hope in CBD and how it can help. And there's a lot of good bio mechanism data, data in different cells and all of this scientific research looking at CBD and how it can help in pain specifically. And I think that's very exciting. I think the challenge is, is that a lot of these CBD products are bought over the counter, and they're not really regulated. So, it's hard to know what's in them. And unfortunately, because it's not regulated, a company can claim that there's CBD in there even if there isn't. And so, I think that's the challenge is that even though I'm hopeful about CBD actually having an effect and actually helping pain, I think the question is how you actually get the CBD, because it's not available because there's no prescription CBD cream for right now. And then when you buy this product over the counter, are you actually getting what's listed on the bottle. Elena, what's your take on this?

[00:34:07] **Dr. Elena Grebenciucova:** I agree with you, Grace. While I have heard some positive feedback from some patients have utilized that, certainly it hasn't worked for everyone, and I share your concern that this is not FDA controlled or regulated and any company can manufacture it and put whatever they want on the label without any specific high responsibility for the quality control and what else is in it. And so, I also worry about potential long-term effect or what's in it actually and doesn't actually have what it says it has. And so that is definitely my concern as well. But yes, I hear from time to time that it worked for some people who tried it, for others, it doesn't. And I agree, Grace, beyond checking vitamins, particularly B-12, sometimes I also want to make sure my patients are not over supplementing B6, because too much B6 can actually be toxic to your nerves, and it can cause painful burning neuropathy and can even worsen the pain. And sometimes people chronically try to take too many vitamins B complexes where it's like B6 is one of them and they can get themselves into trouble.

[00:35:19] Also, there have been a lot of people who during the pandemic have been taking a lot of zinc and zinc in a lot of supplements that's like Elderberry plus zinc or vitamin D plus zinc. The trouble with zinc is that zinc can deplete copper from the body and copper is necessary for maintaining healthy function of the nerves and the brain. So, when you take zinc so much day every day for months and months, it actually can cause burning painful neuropathy and balance issues and can mimic NMO related neuropathic pain. So, I would always welcome people who are taking supplements with zinc to review it and discuss with their physician for safety of long-term use.

[00:36:09] Also thyroid disorders that are common in adults can also cause a lot of neuropathy type of symptoms. People who suffer from poor sleep, a lot of times if sleep is poor, the threshold for pain perception becomes lower. So, you experience pain of a higher degree. So, I know that many of people who live with neuromyelitis optica have trouble sleeping because they're in pain. But then of course, lack of sleep also worsens the perception of pain. So, I always encourage my patients to work with primary care doctor or us in neurology or best with sleep medicine doctor. Sleep neurology is best to come up with a plan of managing sleep while trying to work on pain. And sometimes managing pain and managing sleep may also have to employ some biofeedback, cognitive behavioral therapy, working on sleep hygiene, which is also more of natural ways of addressing what's happening in your body.

[00:37:17] And of course, good nutrition is super critical. There are many vegetables and fruits that are filled with plenty of anti-inflammatory agents and agents that help us fight infections and a lot of herbs like thyme and basil and sage and rosemary actually have antiviral and antibacterial, antifungal properties. And a lot of them also actually fight inflammation. So really having a very healthy diet that is filled with antioxidants, anti-inflammatory substances can also help you feel better, reduce fatigue, and reduce at least a small percentage of that pain that you may be experiencing.

[00:38:02] **Lydia Dubose:** Thank you. And we had a very similar question as well. Is there anything besides pain meds that have been proven to help with TM issues like pain, spine curvature or the MS hug experience? And what doctor who should they be seeing to help with these issues?

[00:38:24] **Dr. Grace Gombolay:** I think Elena touched on a lot of these things. So I think we work very closely with our pain colleagues too and what they focus on, they don't focus on just giving pain medications, they focus on other things like the biofeedback, cognitive behavioral therapy, having a psychologist who's working with you to help you manage the pain and then just making sure that some of those lifestyle factors like Elena talked about the diet, exercise also, which I know can be challenging if you're fatigued or having pain. But doing some of those things can help with managing with a lot of these symptoms that people have.

[00:39:05] **Lydia Dubose:** Thank you. And we had a question about Lion's Mane and if that is safe.

[00:39:15] **Dr. Elena Grebenciucova:** Lion's Mane has never - so there's a couple of things that go into this. Some of the mushrooms and some of the herbals actually are immune stimulants. And Lion Mane, while it has some nice properties and positive things to it as many herbs do, and many plants do, many mushrooms do, there are some concerns about its effect on the immune system and being pro basically stimulating the immune system. And that is certainly a concern in that person who lives with autoimmune condition. And because it hasn't really been studied well for safety in neuromyelitis optica, I certainly would never be able to say, oh, it's definitively to be okay to take that.

[00:39:57] And second, which is what Grace already mentioned, these supplements are not FDA controlled, so how they are grown, what heavy metals or chemicals or pesticides are used in manufacturing processes and what actually goes into those bottles, we have no idea. And there's very little true quality control that goes into it. It's not FDA regulated per se. And, of course, the concern naturally would be as a physician, I would say, what is it that you're taking on a daily basis, because nobody is testing it for heavy metals and we know that, if you look at baby food what do they find all the time? They find that in this spice or in this grain there is arsenic or there is lead or this. So, the same goes for virtually any herb, any supplement, is anybody actually testing them for what are the levels? Nobody is because it's not FDA regulated. So that would be my major concern. So, I would say, I suppose if somebody occasionally took that, I wouldn't be totally against it, but I don't have enough data to say that it's safe for you to take on a daily basis.

[00:41:09] **Lydia Dubose:** Great. Thank you. There is a question about spasms. Can you explain what's happening when there's a spasm with NMOSD and what somebody should do after they have this spasm?

[00:41:22] **Dr. Grace Gombolay:** So, I've seen patients with a few different types of spasms and so a lot of times what happens with them is that there's a couple of kinds I've seen. I've seen where patients have what's called tonic spasms. Well, they'll have this painful. It's a muscle contraction. It can occur in the arms, or the legs and they'll just freeze up. It'll last for a few seconds, and it'll go away. But it can happen multiple times a day actually. And sometimes people will say, oh, is that a seizure or not? And then they'll get an EEG, a brain wave test to look if there's a seizure and it's actually not seizure related. And I find it more often if you have certain areas of your brain affected, especially the deep part of your brain or in your cervical spinal cord, the part in your neck.

[00:42:08] And so there's been some studies looking at, it happens to be a seizure medicine, although we're not using it for seizures, but something like oxcarbazepine or Trileptal works very nicely in those patients. And you don't have to use the same dose that you do for seizures, much lower dose, that thing. And so, I've seen that. I've also seen other patients who have spasms in that where their arms or their legs just start shaking uncontrollably. Sometimes it's triggered by movement. If they move in a certain way, if they are positioned in some way, just start shaking. And then what you can do is that when that happens is to take your hands and something else just to touch to your leg just to see if you can calm it down. And that usually helps with that. And we have a lot of treatments for that. The first line that I usually use is something like Baclofen. There's a lot of other medications that we can use for those things. Elena, what's your experience with spasms in NMO?

[00:41:58] **Dr. Elena Grebenciucova:** I agree. Exactly. So, the same thing. So, for those very painful tonic spasms that you just described that we commonly see in adult population, but people have spinal cord lesions, particularly cervical spinal cord lesion. And those can involve just one arm and one side of the body and where it just freezes up and then there's this excruciating pain and it's lingering. So, medications like carbamazepine or oxcarbazepine really do work and they often work at rather low doses. And in some patients over time, we are able to decrease the doses and even get rid of these medications long term. And so, some people may need a low dose long term.

[00:43:43] And doses of, for example, carbamazepine have been helpful even at low doses of 100 milligram twice a day or 200 milligram twice a day. That is something of course to discuss with your physician, but essentially occasionally very low doses of this medication can actually be very helpful. And then of course, if this is more of muscle spasms and cramps here and there, for example, in lower extremities, we also utilize muscle relaxants like baclofen, tizanidine. A good hydration regimen is critical in preventing muscle spasms, making sure that you have adequate magnesium. Some people even take a small supplementation of magnesium over the counter and it's safe. Unless you have that kidney disease, then that would be something to discuss with your doctor which of course you should always discuss any new medication that you're about to take or supplement with your physician to ensure it's safe and the dose is correct for you.

[00:44:41] But magnesium supplementation can be helpful, appropriate hydration and most important if possible, some level of active or passive stretching several times a day to decrease the spasticity, decrease the propensity to muscle spasms and stiffness. And sometimes it's really stress reduction. So if somebody is really struggling with anxiety or depression, or somebody is having some family related difficulties where maybe there is some fighting happening with a loved one, trying to make steps to help those issues, going to a therapist or talking to a social worker or talking to a primary care doctor about it, can also be helpful in preventing some of these stress driven spasms, because as we know, stress and continuous stress can

certainly lower your threshold of pain perception, so you will perceive pain at a higher level and can definitely in many patients provoke some of these spasms if they are really stressed or tired.

[00:45:54] Another thing is sleep deprivation. So poor sleep and I always go back to sleep. I think all the roads lead to Rome and sleep, because say if sleep is less than perfect, if your body and your brain are not getting adequate rest, there's a lot of things that happen, people certainly have more inflammation in their body, their pain threshold becomes lower, they become more anxious, more depressed, they experience more fatigue and a lot of those symptoms that people with neuromyelitis optica already struggle with a baseline. So, fixing sleep a lot of times goes a long way in keeping yourself healthy. And important point about sleep is also if you're snoring, if you're somebody who snores, and if you're somebody particularly who have some brainstem lesions, or generally, if you snore and you feel like you wake up and refresh, it is really critical that there is a consideration of a sleep study to make sure that there is not an apnea, whether it's obstructive or central sleep apnea, where at night, your body from time to time, just makes these pauses in breathing. And some people wake up gasping for air, but they don't realize why they woke up, they just woke up multiple times a night.

[00:47:18] So that is treatable and the evaluation for that start with a sleep medicine doctor or a neurologist or a sleep neurologist. And then of course, bladder. If somebody is having severe urgency, and they can't sleep, because they have to use the bathroom every couple of hours and their sleep is chronically impaired and that really prevents adequate rest for the brain and for the entire body. And those people also often feel not only worsening of fatigue and anxiety and depression and headaches and brain fog, but they also feel more pain and sometimes more spasms and more spasticity and more stiffness. So, talking to your neurologist about managing bladder symptoms or seeing a urologist also can help improve your sleep and through improving sleep, improve your quality of life outside of adding more medications for the management of A, B, and C, and D.

[00:48:19] **Lydia Dubose:** Great. Thank you. And we had another question that was coming in about if there are any foods that can help for the myelin sheath to regenerate. Is there anything you can eat that can help with that?

[00:48:36] **Dr. Grace Gombolay:** I wish there were. But at this point, we haven't found any. But I think just going back to what we've talked about earlier, healthy diet as much as possible, trying to limit processed foods, trying to limit too much sugar intake, because we know that there's some high fat, high sugar diets that can be pro-inflammatory. I think those are the best practices. And then there's some animal model data, we can't really study as in humans as well. But if you do exercise, there's some thoughts about repairing of the nervous system. It helps your cells regenerate and grow. But again, there's not a lot of good data in humans, because there's not a good way to study it. But in animal models, there's some suggestion of that.

[00:49:19] **Dr. Elena Grebenciucova:** And I would add that there's some data about olive oil and remyelination. So, olive oil and virtually essentially Mediterranean style diet, have more protective factors for brain health and spinal cord health and myelin protection and it really from both angles. One is olive oil is excellent for your brain health and your myelin. But also, the antioxidants that a lot of these fruits and vegetables and herbs like basil and rosemary, etc., offer. Because when you remyelinate and you're trying to repair, you also want to protect the same cells from the damage from all the free radicals and oxidated damage. This is why we focus also on those protective substances that are found in blueberries and garlic and strawberries and basil and rosemary. So, a lot of those antioxidants that have come into our diets from fruits and vegetables and different herbs that we use in cooking. And also, as we mentioned, making sure your B-12 is within normal range. So, it would be very difficult to remyelinate something if your B-12 is efficient. In fact, that's

what's going to be causing more harm to myelinate if your B-12 is low. And as I mentioned, if somebody is taking a lot of zinc that's actually working potentially against you, particularly if it's depleting your copper. So, something to review and discuss with your physician.

[00:50:41] **Lydia Dubose:** Great. Thank you so much. Now, this is a question that's come up a lot over the past now, three years, just about what have you been seeing related to TM and other conditions tied to COVID infections? And before you answer, I'll also say we do have a handful of podcasts and discussions from Dr. Greenberg and others who are listed on our website as well. So that's another resource. I'll point y'all too outside of this conversation. But whoever wants to take a stab at that.

[00:51:19] **Dr. Grace Gombolay:** I can talk about my experience in children if Elena wants to talk about the experience in adults. So, I've seen - I actually haven't seen TM related to COVID. And again, we're going to talk about tie too. We don't know if COVID itself it's caused it. We're just saying that, it happened around the same time. So, they're linked together, but we don't know for sure if it's causing it. I wouldn't be surprised because we know other infections can trigger neuroinflammatory events like TM. So, I wouldn't be surprised. I haven't seen any increase in these conditions actually in my experience. But I've definitely had one new MOGAD patient and then a couple of "new diagnosis of MS", but what we know about those patients that they have evidence of inflammation before they actually came to us. So even though it's possible that the new COVID infection triggered that particular event that caused him to come to the hospital to get diagnosed with MS, they had evidence of stuff going on beforehand. So, I can't say that COVID caused the MS, because there's other stuff happening beforehand. But I've definitely seen a few cases where the child was also COVID positive.

[00:52:37] **Dr. Elena Grebenciucova:** Grace, I agree with you. So, I mean, historically, what do we know about transverse myelitis? We know that there are cases of transverse myelitis that occur shortly after an infection. So, we call them post infectious transverse myelitis. And it could be any infection, it could be a cold virus like rhinovirus or influenza or COVID virus or any virus known to humankind. And because all viruses and all bacteria, they activate immune systems, so immune system can make a mistake shortly after. So, I think there is a set of post infectious cases that transverse myelitis and COVID would fall nicely into that group.

[00:53:18] In reality, among adult patients, I have not during the pandemic seen an increased number of transverse myelitis cases shortly after COVID. Now just like after any infection, whether it's flu or COVID or some bacterial infection, people with autoimmune conditions often present to us for the first time, shortly after an infection. Why does that happen? Well, let's say a good example would be somebody with multiple sclerosis. People with multiple sclerosis can have silent lesions in the brain for many years before they actually develop symptoms. So, imagine there is a young man with multiple lesions in the brain. He has no symptoms. He has no idea he's got lesions in the brain, but then he gets this infection. He gets really sick, and that infection stimulates his immune system while the immune system is fighting infection, it also is erroneously going and attacking his optic nerve. And now he presents with optic neuritis or transverse myelitis.

[00:54:21] And at that moment, we do an MRI, and we say, oh, he is transverse myelitis. Is it COVID caused transverse myelitis? Not really because we see evidence of old scars in the brain that leads to the diagnosis of multiple sclerosis. So, we see a lot of that, but I would not say that we have seen an increased number of transverse myelitis cases shortly after COVID. And that's reassuring. And I would even second this, I remember even during the first couple of years of the COVID pandemic, searching every article ever written trying to see, are we seeing cases of transverse myelitis post COVID and it was an absolute positive, very few here and there. And the way it goes is that it's difficult to actually truly attribute it to the virus, because, like I said, transverse myelitis can happen after any infection pretty randomly, but luckily, very rare. And then when it comes to vaccines, again, this is an extraordinarily rare complication. And we have not seen isolated cases of transverse myelitis at my clinic after any specific COVID vaccine.

[00:55:34] **Dr. Grace Gombolay:** I agree with that and piggybacking on that, I will say I have a lot of my patients who have neuroinflammatory disease, especially those who are on treatment. I do recommend it just because we know, especially if you're on certain agents like CD20, like rituximab, you're at increased risk for getting severe COVID. And all of my patients so far, I mean, they had the usual symptoms. They have body aches or maybe like low-grade fever or feeling fatigue after the vaccine, but no one's had a relapse so far after having vaccines.

[00:56:03] **Dr. Elena Grebenciucova:** I second that. I mean, virtually the majority of my patients, I can't say all, because I don't keep a track of it, but the majority of my patients have been vaccinated. And multiple times vaccinated those that are - my patients are on treatments that are working for them. So, in the treatments they have been vaccinated and none of my patients have had attacks that relapses. And I think it's so important to get vaccinated, because a lot of these medications increase your risk of severe disease.

[00:56:34] **Lydia Dubose:** Great. Thank you so much. And we're coming close to the end of our time here together. So, I think this will be our final question. Folks were wanting to know about tolerization and what is it, and are there trials, in progress for bringing medications to NMOSD and MOGAD patients?

[00:57:00] **Dr. Grace Gombolay:** Elena, you want to take this one or do you want me to?

[00:57:03] **Dr. Elena Grebenciucova:** Either one.

[00:57:05] **Dr. Grace Gombolay:** Go ahead.

[00:57:06] **Dr. Elena Grebenciucova:** So, in terms of tolerization and tolerization basically employs the ability of the immune system to be exposed to small antigens in small amounts when it's combined with another molecule to start ignoring it a little bit and lose the desire to attack that specific protein. So, you could try to tolerize immune system or autoreactive cells through the aquaporin-4 specifically. So, I think that right now we do not have any immediate medications that are coming down the pipe, but I know that there is definitely some research and in animal models including at Northwestern, that's being done to potentially address that route of treating neuromyelitis optica.

[00:57:57] **Dr. Grace Gombolay:** My understanding is that they're actually giving more like you eat the protein, that's how it's working. Like some of what they've done with peanut allergy trials in kids is that you eat small amounts with the medication to calm down the immune system to retrain it from attacking.

[00:58:17] **Lydia Dubose:** Thank you so much. Well, I think that is everything unless we have any last questions slide in here in the last moment. But I really appreciate you both for being here and being our experts for today. We're really excited for NMO awareness month, NMOSD awareness month and hopefully raising more awareness, hoping that people can get to their diagnosis and treatment even faster in the future. And thank you for all that you're doing each day with patients in your own communities. So, thanks again for being a part of it. And I guess we have one minute left if either of you have any last words.

[00:59:06] **Dr. Grace Gombolay:** I just want to say thank you for the opportunity to speak. Thank you for all who's joined, because I think like Elena said, we're as your physicians, but we're partnering with you to help you with your care and to really work with you on this journey. And so, the fact that you're here, that you're learning more to take ownership of your care, I think is really wonderful.

[00:59:26] **Dr. Elena Grebenciucova:** Thank you so much for having us today, Lydia and thank you everyone for joining us. I hope everybody stays safe and I hope to see you in our future webinars. Bye.