Open Q&A on Neuromyelitis Optica Spectrum Disorder (NMOSD)

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[00:00:02] **Krissy Dilger:** Hello, and welcome to the Siegel Rare Neuroimmune Association's "Ask the Expert" podcast series. This episode is titled "Open Q and A on Neuromyelitis Optica Spectrum Disorder (NMOSD)." My name is Krissy Dilger and I will moderate this episode. Today I am pleased to be joined by Dr. Elena Grebenciucova. Dr. Grebenciucova is an assistant professor of neurology and neurological infections at Northwestern University in Chicago, Illinois, where she also runs the Transverse Myelitis Center. You can view her full bio in the podcast description.

[00:00:42] SRNA is a non-profit focused on support, education, and research of rare neuroimmune disorders. You can learn more about us on our web site at wearesrna.org. This episode is made possible in part by the generous support of Amgen; Alexion, AstraZeneca Rare Disease; and Genentech.

[00:01:05] To start us off, Dr. G, can you begin by briefly explaining what neuromyelitis optica spectrum disorder is?

[00:01:13] **Dr. Elena Grebenciucova:** Yes, of course. Hi everyone and thank you so much for inviting me. So neuromyelitis optica is an autoimmune disease in which immune system makes a mistake and produces a protein called anti-antibody to an aquaporin-4 receptor. That receptor is ubiquitous in the central nervous system, in the optic nerves, the spinal cord, and throughout the brain. And so, when the immune system erroneously creates this protein this antibody, circulates by blood throughout the brain optic nerve and spinal cord.

[00:01:48] And it activates immune system to go and attack those areas where that receptor is expressed and people develop variable symptoms. Some people develop inflammation of the optic nerve, sometimes on both sides, sometimes on one side, which causes blurry vision that can be quite severe. Often with pain behind the eye, sometimes without pain or minimal pain.

[00:02:13] People can experience transverse myelitis or inflammation of the spinal cord in which people typically over a course of hours to several days lose strength sensation and often it affects their bladder and bowels as well and can also cause severe nerve related pain in the a. Including spasms.

[00:02:33] Other presentations include intractable hiccups or with nausea vomiting. So that is one of the key presentations of neuromyelitis optica that is sometimes being overlooked. So, if you are having intractable hiccups, not just something for. 20 or 30 minutes, that could be a sign of relapse, and your physician needs to know about it.

[00:02:53] Otherwise, things like what we call brainstem syndromes where a person develops trouble with speech or double vision or other cranial nerve deficits where their eyes don't move together or they develop

nystagmus. Some people with neuromyelitis optica also can have lesions in the cerebellum, in the balance center of the brain, and that is something that has been recently highlighted in the updates for the international criteria of neuromyelitis optica diagnosis.

[00:03:24] **Krissy Dilger:** Great. Thank you for that overview. So, you mentioned the immune system plays a big part in neuromyelitis optica spectrum disorder. But can you give us any more details on what exactly causes NMOSD?

[00:03:41] **Dr. Elena Grebenciucova:** Yeah. So clearly something triggers the immune system to make that mistake. All right. But to date, we do not know what is the inciting agent, right? There isn't a specific virus or a specific behavior that does that sort of a trigger. We know that people with a rheumatological disease a lupus, systemic lupus erythema ptosis seem to be more likely. To develop neuromyelitis optica, and we actually do not yet understand why that is.

[00:04:12] It is possible that genetically people who are more prone to develop a certain autoimmune disease cluster together, such as lupus and neuromyelitis optica. That's one. Mild something we noticed. The second thing is infections. They stimulate immune system. But all of us have infections since we are children.

[00:04:37] And not everybody develops immune autoimmune disease, but we do see that often people who present with neuromyelitis optica, they present shortly after some sort of an infection, maybe a viral infection or a urinary tract infection in some instances. And it's not to say that specific infections cause neuromyelitis optica, but it appears that for some people who are immune genetically predisposed to their immune system, make mistakes, sometimes an infection that activates immune system creates a canvas for the immune system to make that mistake.

[00:05:17] And that mistake arises and an antibody is formed and then it goes and activates immune system to do that damage. But to answer the question more directly, I would say one is that to date we do not have any evidence to suggest that neuromyelitis optica is definitively a genetic disorder.

[00:05:36] While there may be some propensities, there isn't such a thing as mom transmission of NMO to the child or so on. Then there isn't a specific virus that has been shown to definitively cause neuromyelitis optica, nor is there a certain bacterium or a vaccine to cause it.

[00:05:54] So we do believe that most of the immune diseases, just neuromyelitis optica, are multifactorial where immune system makes a mistake under a set of circumstances. And those circumstances could be a, somebody with a very specific immune type A, what we call phenotype, or a person who may be, whose immune system is a little bit more prone to making mistakes, right? So, we all have different propensities to the immunity.

[00:06:22] For example, women have higher propensity to autoimmune diseases than men for a lot of autoimmune diseases. So, our hormones have an effect on that as well. And two, there are. Likely environmental hits and some viral hits that contribute to dysregulation of the immune system. But we currently do not have data to suggest that one specific inciting agent, whether it with it is environmental, chemical, or a medication or a virus or a bacterium, that it is solely sufficient to cause the disease itself.

[00:06:56] **Krissy Dilger:** Got it. That's very interesting. And hopefully in the future we can learn more about this, but that's a great explanation. So, moving on, one thing that I know has hopefully improved over the years, but it still seems to be a concern is diagnosis of NMOSD. And some people it takes a really long time to get diagnosed and some people it's right away the first day that they're admitted.

[00:07:26] But can you talk about how NMOSD is diagnosed from someone coming into the hospital presenting with certain symptoms and how that kind of process goes along and what, what kind of doctors see them and what kind of tests they're run?

[00:07:44] **Dr. Elena Grebenciucova:** Oh, sure. For sure. Yes, indeed. Over the years so many patients were initially misdiagnosed historically as multiple sclerosis and then later it became evident that they are. Anti-aquaporin-4 antibody positive, and they actually have neuromyelitis optica. So historically, that was an issue for several decades, essentially. But I do think that these has improved dramatically because now when a patient presents with symptoms such as blurry vision or transverse myelitis, so they have weakness in the arms or legs, or both numbness, tingling, et cetera.

[00:08:22] They present with intractable hiccups. People are thinking more about the differential diagnosis. They're now not thinking about MS alone, but they're thinking about mimics such as neuromyelitis optica, MOG associated demyelination, also known as MOGAD. There is very specific, highly specific testing that's available for that.

[00:08:42] So the typical diagnosis occurs when a patient presents with symptoms that are concerning for demyelinating disease or astro cyto in the instance of a neuromyelitis optica. So maybe they have blurry vision or double vision, or they have transverse myelitis, or they have intractable hi. So, the next stage is that doctors get an MRI and they evaluate to see if there's a lesion on the MRI that is compatible with what we see in neuromyelitis optica.

[00:09:11] And lesions in neuromyelitis optica often are very different than what they look like in multiple sclerosis. So, for example, lesions in the spinal cord and neuromyelitis optica are typically what we call longitudinal leaks. Extensive spanning three segments of the spinal cord or even longer, sometimes lighting up the entire spinal cord.

[00:09:29] Although a small percentage of patients can also have short patchy lesions, about 10 to 15% of people with NMO. And that represents a big caveat to actually physicians to say that we still need to look for neuromyelitis optica even when those lesions are small in the spinal cord. Optic nerve is often affected in a more longitudinal matter on the MRIs.

[00:09:52] And sometimes it's actually both optic nerves and there are certain types of configurations to the lesions that we see in the brain that are very different than what we see in multiple sclerosis. So, MRI with contrast ideally is critical for the diagnosis of neuromyelitis optica.

[00:10:09] But the diagnosis relies not only on clinical and radiological findings, but most importantly on finding the anti-aquaporin-4 antibody. And where we look for that antibody is actually the blood. So, what, where we do see misdiagnosis quite often is a patient who presented to say some outside hospital and their workup was done and aquaporin-4 antibody was sent, and it was negative.

[00:10:38] But it was sent in the cerebrospinal fluid on the lumbar puncture, not in the blood where it needs to be sent. So that is one of the very common errors that happen still unfortunately. And that's how the diagnosis gets delayed. The compartment that needs to be tested is the blood specifically.

[00:10:58] And it needs to be ideally tested before the high dose steroids, plasma exchanges are given because if we test after, then it diminishes the ability of the test to pick it up. So, if you got tested after you received high dose steroids and or plasma exchange, your doctors should be retesting you subsequently, maybe a month or a couple of months later to see if you are indeed aquaporin-4 antibody positive.

[00:11:25] And most importantly if you are somebody who were tested and you were a negative, you would have to ask what type of test did they use? Okay, so they tested me in the blood, but was it cell-based assay, live cell-based assay, or was it fixed based assay versus ELISA? So, it's a lot of technical words that of course nobody expects everybody to like, remember.

[00:11:53] This is really more for physicians to know the subtle differences. But I would say that if you were tested with ELISA test you should be retested via the best standard of care test, which is a live or, at minimum, fixed cell-based assay. So, if you are a negative retesting on an ELISA, retesting with a better, higher sensitivity test, which is a standard of care, is really critical.

[00:12:22] So knowing and talking to your physician what test was sent is important. And unfortunately, not all physicians are aware. Of these differences and sometimes that leads to the delay of the diagnosis or misdiagnosis. And then of course the important thing is to rule out other conditions, right?

[00:12:43] So when people are presenting, we don't always think just about NMO or a mass. We think about what else could this be, right? Could this be an infection? Could this be cancerous? Could this. Be something else. So, the workup a lot of times is, particularly when we do the spinal tap lumbar puncture, we really are making sure there isn't an infection that's causing optic neuritis or causing transverse myelitis.

[00:13:07] So infections absolutely can do that. For example, chicken pox or like shingles can affect the optic nerve, can affect spinal cord. Herpes viruses can do the same thing. Certainly, there's a plenty, a plethora of different infectious agents that can affect brain, spinal cord and optic nerves.

[00:13:25] Excluding infections is one of the first things that we do because it's so critical, because next we have to give a patient high dose intravenous steroids, right? Generally, plasma exchange in most cases of NMO. We want to make sure there is no infection happening at the same time, or that it could be the culprit because certainly we would not want to give intravenous steroids to a person who is ac acutely infected.

[00:13:54] **Krissy Dilger:** Got it. That's very interesting. And it does lead me to my next question, which you already, answered. But I guess if you could give me a little more detail about the acute treatments that are used during an NMOSD attack. You mentioned the intravenous steroids and plasma exchange, but can you explain what each of those are and how it's decided what, treatments a patient would get?

[00:14:20] **Dr. Elena Grebenciucova:** Absolutely. Because neuromyelitis optic attacks can be so severe and so life altering, the treatment needs to be initiated as soon as possible. So, if you are a patient who has neuromyelitis optica and you think that you are having a relapse, it is critical not to, to just call your doctor and see if you can be seen in the next couple of days, but to actually speak to your doctor on the phone urgently.

[00:14:48] And if they're unable for some reason or unavailable to take care of you immediately, or guide you to the emergency department, then you would. Come to the emergency department, right? Because delaying initiation of acute treatment can mean worse outcomes. So, the faster we give you the treatment.

[00:15:09] The better people do long term, the higher at their chances of recovery. So typically a patient presenting with acute neuromyelitis optica attack, meaning they have a new inflammatory lesion in the brain or optic nerve, or the spinal cord, which is contrast enhancing, would receive intravenous steroids, typically methylprednisolone, and they would do so for five days with subsequent, typically a taper of oral steroids by mouth ranging from weeks to sometimes months, depending on some specifics.

[00:15:42] We typically highly recommend plasma exchange. That's a filtration of your, blood to get rid of the pathogenic anti-aquaporin-4 antibody and what we know is that there's a difference in outcomes for those people who get plasma exchange versus those who don't. And also. There's a difference in outcomes when it comes to timing of the plasma exchange.

[00:16:07] So, the sooner plasma exchange is given, the better people typically do and the better are their chances of recovery. When plasma exchange is delayed by weeks or sometimes months it certainly has a lower chance of. Being effective. It can still be done but it doesn't have the same high effectiveness as it does when it's initiated quickly in the setting of an acute relapse.

[00:16:33] Now, historically there have been people with neuromyelitis optica who present with an attack, and their symptoms are actually relatively mild. And doctors give them steroids, and while they get steroids, those patients recover it dramatically, nearly back to baseline or baseline. And in some of those instances, doctors historically may have bypassed plasma exchange, but the reality is that for a person who has neuromyelitis optic eye attack, who has moderate to severe death neurological deficits, typically both steroids and plasma exchange should be given to give them the. Best chance of recovering or improving over time as quickly as possible.

[00:17:16] **Krissy Dilger:** That's good to know. And are there any adverse, I guess effects or just side effects of either like the intravenous steroids or plasma exchange that someone should be aware of?

[00:17:29] **Dr. Elena Grebenciucova:** Yeah. When we read about steroids, when patients read about steroids, people o often ask what about the side effects? What about increased risk of infections? What about weight gain or bloating, water retention, mood swings or sleep? And so, it is true that a high dose steroid intravenously can cause some side effects. But most of them are minor and transient, and so you know, it's always risk versus benefit when risk is small, but the benefit is large in terms of benefit of actually treating NMO.

[00:18:03] The risk is considered to be very small. So, the typical side effects that people could experience while getting intravenous. Steroids. Some people can get flushing. They can get a little bit of heart racing. So, we hydrate them, we help them calm down. Sometimes even if, somebody feels extremely anxious, doing steroids, using a little bit of a benzodiazepine can be helpful.

[00:18:25] But people can bloat for a week or two, so retain some water. It's not necessarily real weight gain. So just about three to five days of steroids are not gonna make you gain 10 pounds. Most of it, if you did gain five or 10 pounds, it's probably, most of it is gonna be water retention. Steroids certainly increase the risk of infection.

[00:18:48] Certainly around that time if somebody is getting intravenous steroids, most of the time they're in the hospital, right? So, they're not going out and out and out and about. Getting infected. But even after intravenous steroids were given and say the patient is discharged, they're typically on some oral steroid taper for at least a couple of more weeks.

[00:19:09] In most cases, those steroids are much better tolerated because they are lower doses, but they can still spike the blood sugar. So, for those people who have diabetes or pre-diabetes, the blood sugar needs to be monitored. There needs to be a communication with the primary care doctor and endocrinologist that you're on steroids and what's the taper doing because chronic steroids chronic steroids, meaning for more than six weeks, which really shouldn't be the case for people with NMO.

[00:19:38] But chronic steroids can also really thin out the bones and cause an osteoporosis. Short bursts of steroids typically do not have high risk of doing so, so they're pretty safe. When you get intravenous steroids, you should avoid any alive or attenuated vaccines afterwards for at least a month after steroids and generally avoid other vaccines because they're not gonna be highly effective after you've just gotten the intravenous steroids, you're just not gonna get a good immune response.

[00:20:09] What else? There are rare complications of intravenous steroids. Something called avascular hip necrosis. This is typically for people on massive doses of steroids and that involves pain in the hip. But that is extraordinarily rare in 10 years of. Treating people with autoimmune conditions and neuromyelitis optica have may be seen it once or twice in among thousands of patients.

[00:20:35] So it is very rare. Yeah. So those are the main side effects. Oh, and actually effects on mood and sleep, right? So, when you are getting high dose IVIG steroids, it's very common to feel really anxious or to feel very energetic. Some people can feel nearly hypomanic where they have so much energy they're crawling out of their skin.

[00:20:55] This is transient. If it is to the point of severe anxiety, you should talk to your physician. They can give you some medications to help you calm during this period of time. But these effects are transient. Now, if the patient has a history of bipolar disease or severe depression that should be verbalized to the treating physician and those symptoms should be monitored and treated accordingly if exacerbations of depression or bipolar disease occur.

[00:21:23] That's why people who do have a history of bipolar disease or depression, if they do need steroids, really should be done in the hospital setting ideally. So, they are supervised for any worsening of their mental health types of symptoms and otherwise effects on sleep. So, steroids are ideally given in the morning.

[00:21:41] Because if given in the afternoon or in the evening, which sometimes happens because say patient arrives to the emergency department at 4:00 PM and we got to give steroids as soon as possible so a sleepless night can happen. So, you would just have to mention to the physician that you're having difficulty sleeping and a sleeping pill can be provided for that period of time. But this is a short-term side effect of steroids that clears once you stop steroids.

[00:22:10] **Krissy Dilger:** Got it. Thank you so much for, going through those side effects and potential side effects I should say. What are so moving on from the acute setting we know that NMOSD can potentially cause long-term effects and relapses. What are the currently available long-term therapies for NMOSD? And does this differ by location, for example, the United States versus Europe or Asia?

[00:22:44] **Dr. Elena Grebenciucova:** Yeah. In the United States we have several FDA-approved medications. So, you have Soliris, which are co terminal complement inhibitors. You have Alisa, which is an anti-CD 19, a B-cell depleting agent, and you also have SPR, also known as satralizumab, which is a self-injectable once a month. So, these are the, highly effective, what we call disease modifying treatments that are available to people living in the United States.

[00:23:19] Albeit they're not available in every country elsewhere. And it gets very specific in terms of like specific countries where these things are available. But in other countries the older mother drug, so to say of vasa if I may call it that, rituximab. Typically, available. So, rituximab is available, and this is also a B-cell depleting agent that is certainly available here in the United States, and many patients are still on it, and some of them have transitioned to FDA-approved medications.

[00:23:51] But in Europe, in Asian countries, European countries in Canada virtually on every continent, rituximab is available for the treatment of neuromyelitis optica. Although it isn't, doesn't have a specific FDA approval here for NMO, it is certainly used off label for decades and actually is effective drug as well.

[00:24:12] Are there medications that are available in other countries? In most countries? I would say tocilizumab. So, tocilizumab is anti-interleukin six agent. It's similar to ENSPRYNG (satralizumab). So, in some countries, and again, like there's such a long list that I would be worried about. Saying something is available in a specific region and it may not truly be available but in, in many countries, tocilizumab because it's an older drug, is available and it's an infusion and it's a drug very similar to satralizumab, which is ENSPRYNG.

[00:24:48] And then eculizumab, which is SOLIRIS is available in Europe and in some other I, I believe I may, I believe it's available in Canada. I may be wrong, but I believe so. Yeah, so most of these medications are available widely. Certainly, all what comes into question is the insurance coverage. So that gets really tricky, particularly in European countries who also have very strict sort of preferences for what medication needs to be initiated first.

[00:25:19] **Krissy Dilger:** Great. Thank you so much. So, we had a question from a community member. They ask I have a lesion on the thoracic level of my spine from NMO affecting my whole lower body will levels, will high levels of vitamin B12 help heal my myelin? An aid in nerve regeneration. They said someone suggested B12 supplements two times a day with levels 125,000% RDA, they say they are not on rituximab treatment.

[00:25:59] **Dr. Elena Grebenciucova:** Certainly, B12 is critical for myelin, so is folate. But currently there are no data to suggest that high dose vitamin B12 would be helpful in remyelination. Specifically, however, what I would say is that it is, for me, it is the standard of care. When I. Have patients with neuromyelitis optica or other diseases that affect brain spinal cord optic nerves. I typically always check B12 because some people are actually at the very low level. And so, when you are at the very low level, then yes, you do need to take a supplement.

[00:26:40] So we typically want the levels of B12 to be above 300 because if you are below true deficiency is below 180, but below 300. That's, we consider it insufficient. So, if you're insufficient or deficient, yes. That's not gonna help. Remyelinate, right? So, we actually do want more vitamin B12 on board, but vitamin B12 is also one of those vitamins that is water solubles.

[00:27:05] So that means that your body can only use what it needs. And if you give massive amounts of B12 to your body, you're just gonna basically lose it through the urine, so you're gonna pee it out. But, to summarize while B12 supplementation has a role particularly for those people who are deficient or insufficient in vitamin B12 really super high doses of vitamin B12 do not seem to have significant amount of data to suggest that they ate in remyelination.

[00:27:37] **Krissy Dilger:** Great. Thank you for answering that. We had another person write in they, I'm not sure that they have NMO, but chronic optic neuritis. They ask if there have been any breakthrough treatments for chronic optic neuritis.

[00:27:56] **Dr. Elena Grebenciucova:** Yeah, I'm not sure what is meant by chronic optic neuritis because in neuromyelitis optica, optic neuritis is typically not chronic. It's acute, and then inflammation goes away. In some instances, we know that enhancement or, basically leakiness of the contrast on the MR. I can persist in some people with optic neuritis even though their symptoms have resolved or are stable and we actually do not call it chronic optic neuritis.

[00:28:26] But if the person means chronic optic neuritis as recurrent optic neuritis, the best strategies are still preventing prevention. Now there are some people who truly have chronic optic neuritis who, and that's generally not neuromyelitis optica. So chronic optic neuritis or smoldering ongoing inflammation of optic nerve.

[00:28:47] Most of the time we have to think about diseases like neurosarcoidosis or IgG four related disease or some perine neoplastic disorders. But neuromyelitis optica, per se, should not. Have an ongoing chronic inflammation along optic nerve over months or years. When it happens, it typically resolves and then there's a static period in between unless there's another attack on the o optic nerve again.

[00:29:17] **Krissy Dilger:** Okay. Thank you so much. Another person asked how they can successfully appeal insurance to continue physical and occupational therapies with for a patient with significant de deficits due to NMOSD relapses.

[00:29:36] **Dr. Elena Grebenciucova:** Yeah, the, this is certainly very challenging. And there isn't a one specific way to do it, but I think that your doctor, your neurologist should be your best advocate because what they're able to do, and what I do for my patients is basically collect all the data on the importance of physical and occupational therapy for people with neuromyelitis optica copy make a copy of those papers, look at the statistics.

[00:30:06] I highlight them and I send it to the insurance company saying that, "Hey, my patient needs it. They could benefit from it." And when it's denied going through an appeal and escalating to the medical director and then sometimes even escalating to the external appeal. So, this is more on your it's on your physician to advocate for you and utilize the research, articles that show benefit and fight for you.

[00:30:37] **Krissy Dilger:** Thank you so much, and I know this is a big issue that many of our community members do face, unfortunately at least here in the United States. So, I appreciate your perspective and encourage everyone who is, needing their neurologist to be their support in, something like insurance appeals to really to really advocate for yourself in that setting. And also, if it's not working out with your neurologist to, try and see if you can find a better fit with someone who is willing to fight for you.

[00:31:19] So thank you for that answer. We have someone ask that they feel they're exhibiting symptoms such as a ring of stiffness and pain around the waist and lower back, as if someone has carried you off the floor, holding you at the waist. What kind of symptom would you describe that as, and what kind of medication is usually prescribed for that kind of symptom?

[00:31:48] **Dr. Elena Grebenciucova:** When I hear stiffness and pain around the lower back, I always want to make sure that it's truly related to neuromyelitis optica. Certainly, if the patient had a lesion, transverse myelitis in that area, in the lower thoracic spinal cord, and that's their typical symptoms that they have a lot of pain and stiffness there.

[00:32:13] We will use medications like muscle relaxants for stiffness. So, things like baclofen, tizanidine for nerve related pain. We will use medications like Pregabalin, Lyrica, Gabapentin, which is Neurontin, and also duloxetine, Cymbalta. But there are some other medications that can be utilized as well.

[00:32:35] In cases where the pain does not respond to medication management certainly sometimes acupuncture can be helpful. But in severe cases we employ pain management doctors to step up on the medication management and were. All medication management fails. If it does, then spinal cord stimulators for pain control can be done via a neurosurgical consultation.

[00:33:01] But as a neurologist, when I hear a patient tell me about a low back pain and stiffness, I also wanna make sure that it's not the lumbar. Bin that there isn't like a badly slipped disc or stenosis narrowing in the low back pain. Because the truth is for people with neuromyelitis optic eye and for people with MS, when people who are having symptoms, a lot of times it just gets attributed to their disease without sometimes investigating for what else could this be?

[00:33:30] So if somebody had low back pain and it was worsening, I would say, sure. I'll, check the MRI spinal cord in terms of neuromyelitis optica, but I'm also gonna take a look at your lumbar spine. There is no spinal cord there. There are nerve roots going into your legs, but low back pain often comes from the lumbar spine because of degenerative disc disease or a narrowing in the lumbar spine, and that can cause a lot of chronic pain and stiffness as well.

[00:34:00] **Krissy Dilger:** Great. Thank you. Someone asked what considerations should someone diagnosed with NMOSD have who is thinking of family planning?

[00:34:14] **Dr. Elena Grebenciucova:** This is a very important questions question. I think that what I. I will tell you what I tell my patients in general because neuromyelitis optica tends to be so active during the first couple of years of diagnosis.

[00:34:31] I tell my patients to try and stabilize your disease for at least two years before trying to conceive. And in terms of medications. Not all medications can be continued during pregnancy, so you would have to talk to your physician about your specific medication that you are on and how to time it around the pregnancy so that your baby's not exposed.

[00:34:59] And then how quickly should you get back on the medicine after you have the baby? And discuss the considerations about breastfeeding. So, on some of these medications, breastfeeding should not be done on at least one of them. It can be done. And also have a discussion with your physician about pregnancy, the actual pregnancy planning.

[00:35:22] So if there was a relapse during pregnancy what would be the treatment? Would it be steroids? Can, what else can be done for older medications like rituximab there certainly have been cases and for many physicians, some patients, had rituximab and then shortly after became pregnant and had their baby safely.

[00:35:49] And we never have seen any kind of birth defects or issues on babies exposed to rituximab. But babies exposed to rituximab, particularly if the exposure was later in the pregnancy, sometimes can have low white blood cell counts that self-resolve over the next couple of months. Sometimes their neutrophils can become low.

[00:36:08] That's a subset of immune cells. And so those things become important for babies, vaccines. So, in some instances. For a patient who has highly active neuromyelitis optica, and the doctors are really concerned about potential relapses during pregnancy, some doctors historically have that rituximab shortly prior to the pregnancy and sometimes even during pregnancy.

[00:36:36] This has been done. There are there's some medical literature on that in virtually every. Person who treats neuromyelitis optica has some experience with that. Having said that, certainly there is no FDA approval for this medication or any medication for the use in pregnancy. So, these decisions are tough ones, and they have to be discussed with your physician based on you know how well you have done in terms of controlling your neuromyelitis optica.

[00:37:03] Have you had any recent relapses? And that's why I say that ideally you should stabilize your disease for at least two years, no relapses for at least two years before you try to conceive. And we do that as to minimize the risk of relapse during pregnancy.

[00:37:22] **Krissy Dilger:** Great. Thank you. Those are important considerations. And I think anyone who's considering, family planning should definitely have a conversation with their neurologist to start off and start having those conversations. Is there an ever a time when a long-term therapy can be weaned off? If I haven't had an attack in several years, should I come off treatment? Also, are there negatives to staying on a treatment long-term? 10 plus years.

[00:37:57] **Dr. Elena Grebenciucova:** Yeah. Yeah. Thank you. This is such an important question. What we know is that the vast majority of people with neuromyelitis optica have a relapsing disease. And the ephemeral concept of monophasic and ammo disease is. Barely existence. So, most people do require long-term treatment to prevent attacks, and absolutely we see people that have been stable for 10, 15 years and then can still have an attack. We see sometimes I will cite an example, a person who is on CellCept or Mycophenolate mofetil stable for 10, 12 years.

[00:38:40] Let's say that the physician has a difficult time convincing them to go onto an FDA-approved medication that is actually better in in controlling the disease and preventing relapses, say, PLES not, or SPR or cell or Ultomiris. That person on CellCept, even when their sixties or seventies can still have a relapse.

[00:39:04] So in real world. We all have had patients, including myself where we've seen a relapse in somebody who was already so much older, sometimes in their sixties or seventies, who has been stable for 10 or 15 years, particularly in some of those non-FDA lower efficacy drugs, and then they relapse on that drug.

[00:39:23] So unfortunately, people can continue to have relapses, even at the extremes of the age group. So, we do see it sometimes even in 70-year-olds. So, I would stay on the treatment. And then the second part of the question, forgive me, I didn't answer it. What are the long-term side effects? Every medication has side effects, and it's always about risk versus benefit if the risk is small, but the benefit is keeping you neurologically intact and preventing severe optic neuritis.

[00:39:53] So transverse myelitis, or even rare, more severe complications like becoming a ventilator dependent, which is. Something that certainly everybody is afraid of with neuromyelitis optica. Small side effects or low risk side effects are typically tolerated well. So, for most of these medications slightly increased risk of infections or modestly increased risk of infections for some is an issue.

[00:40:23] So that's why we there are several medications available. So, if one if the person is not doing well on one of the medications and is having frequent infections, perhaps a switch is warranted right after a discussion with your physician to a different medication. But for most of these medications, risk of infections is the one key side effect that we think about.

[00:40:49] Certainly some of them are safer in terms of risk of infections than the others. But then in terms of long-term side effects, so none of these medications that are FDA-approved are really known to cause major long-term side effects, such as increased cancer rates, for example. That's generally not the sort of the risk of things like B-cell depleting agents or anti-interleukin six agents or complement inhibition, that is not the typical risk, right?

[00:41:20] Because some of these medications have been used for a long time for other disorders with hundreds of thousands of people and similar drugs around the world. So, typically increased risk of cancers is not a

concern with the FDA-approved medications for NMO, the older medications like CellCept Mycophenolate mofetil are a trine that are actually less effective and they're non-FDA-approved. They're used off-label, were used off-label before better medications became available on those medications. They do have carry a warning of slight increased risk of malignancies over the long term of immunosuppression.

[00:41:59] But otherwise the medications like SOLIRIS, ULTOMIRIS, UPLIZNA, ENSPRYNG, while on some of them you may, we monitor the liver enzymes, right? While you may see some liver enzyme elevations on one or two of them, typically these are not the drugs that are hepatotoxic or really toxic to the liver.

[00:42:19] So occasionally we see liver enzyme elevations on some of them, and we basically see if it just self resolves on its own. For most, of the time that's the case, or sometimes it has actually nothing to do with a drug. It's. It may be an autoimmune liver disease, or it may be a fatty liver disease, or we find something else that's causing it.

[00:42:37] But generally speaking, for most f FDA-approved treatments, risk of infections would be the side effect that your physicians hopefully is discussing with you and preventive, strategies for the infections and the importance of investigating infectious symptoms and treating infections quickly as to prevent more severe disease.

[00:43:01] **Krissy Dilger:** Great. Thank you so much. We got two kind of similar questions or on the same topic I should say, about behavioral and psychological changes after diagnosis or, personality changes. So, can you shed light on, like the timeline of is, that behavior normal to experience right after diagnosis, but what's the prognosis? Will someone return back to they were the way they were before their attack? And what kind of behavioral and psychological changes are associated with NMOSD?

[00:43:47] **Dr. Elena Grebenciucova:** Sure. I think this is an important question. I think that generally people experience psychologically experience the concept of disease very differently for some people. When they have their first attack on the diagnosis, there appears to be no strong association with depression or anxiety. For others, they may experience depressive symptoms. Severe anxiety, trouble sleeping. And that, of course, can cause changes in the personality. So, the disease itself, the inflammation itself really shouldn't be causing changes in personality.

[00:44:32] But the perception of what. You as a human being are going through and the concept of the disease and the diagnosis and the stress of healthcare and the stress of learning about the disease and the medications while you are trying to recover while you are trying to go through physical therapy.

[00:44:52] That is an incredible amount of stress that can take a huge toll on people's emotional health and does affect the behavior. It is very common that we see people that go through what we call adjustment disorder due to medical illness. This is adjustment disorder due to medical illness is usually feelings of depression.

[00:45:16] Due to their diagnosis or their neurological issues that happened secondary to disease. Also, anxiety about what does the future hold for me? How will I do, will I have another attack? Will this medication work? What are the side effects I'm reading and I'm so scared. So, depression, anxiety are very, common. Typically, they're short-lived and we call them adjustment disorder due to medical illness. But absolutely, they can cause personality changes by disrupting sleep, by robbing you of the energy. And because depression alone can rob somebody of energy, not just neuromyelitis optica and inflammation can cause fatigue as well.

[00:45:59] Absolutely. But it's almost liked a vicious. Cycle of fatigue due to the inflammation. But also, if you're feeling down and depressed, that can also cause more fatigue. And if that person is having trouble

sleeping, that's going to worsen the fatigue. That can create a lot of brain fog, particularly if you're not sleeping or, your sleep is interrupted.

[00:46:20] So for those people who suffer from nerve pain for those people who suffer from bladder issues with emptying the bladder or having to use the bathroom nonstop, that affects. The sleep. And when the sleep is affected, the mood is going to be affected. When the mood and sleep are affected, personality changes.

[00:46:39] People can become more depressed or more irritable. Also, when we think about depression, and depression manifests itself very differently in different people. Some people may have low appetite; some people can basically stop eating. Some people can't sleep at all. Some people, all they wanna do is sleep.

[00:46:56] Some people. Just sad and they have cried spells and some people become more hostile or more irritable and really sometimes even can go into rage. So, there are differences in how depression is experienced sometimes between individuals and sometimes between different genders.

[00:47:14] So I think that at the time of the diagnosis of neuromyelitis it is common to see this and the key to this is to make sure that the neuroimmunology doctor who is treating for you, for neuromyelitis optica is somebody who you connect with, who can explain, who can provide reassurance and answers. In the language that you understand that you feel that the doctor is available if you have more questions.

[00:47:48] A lot of times we'll tell our patients to grab a video appointment with us if you have more questions, because having neuromyelitis optica is a very lonely place because it is so rare and there are very few people that have it. As much support from your physician that you can get, you really need it.

[00:48:08] A lot of support comes through just education about the neuromyelitis optica. Joining support community with through we are SRNA or Sumaira Foundation can be helpful as well. But then also making sure that your physician is talking to you about your sleep and your emotional health. And there are certainly psychotherapy and medications at least transiently for depressive symptoms and anxiety that can be utilized.

[00:48:38] So sometimes setting up with a neuropsychiatrist can be helpful. Setting up an appointment with neuropsychiatrist can be also helpful as well. Meanwhile, many neurologists will prescribe medications to help manage anxiety and depression. And then have you set up with neuropsychiatry colleagues as well?

[00:48:57] Clinical psychologists can be very helpful as well as support groups. Most important is your relationship with your treating physician because you in this disease, it is particularly critical to have a physician who hears you, who understands you, who explains well who provides resources and who advocates for you.

[00:49:22] **Krissy Dilger:** Great. Thank you so much and that's great advice. Appreciate your sharing. So, we do have 10 minutes left, so I'm gonna try and get through a few more questions. If anyone who's joining us live right now has a last-minute question for Dr. G, please feel free to put it in the chat or in the q and a and we'll try and get to it. So, someone did ask if there are any trials available for aquaporin-4 negative patients.

[00:49:56] **Dr. Elena Grebenciucova:** This is something that I think the entire research community is working towards because aquaporin-4 negative neuromyelitis optica spectrum disorder previously, and now we are gonna be calling it neuromyelitis optica clinical syndromes.

[00:50:16] Based on the updated neuromyelitis optica criteria diagnostic criteria, it's gonna be called double seronegative neuromyelitis optica clinical syndrome, and it recognizes people who have had symptoms or attacks similar to people who are aquaporin-4 antibody positive neuromyelitis optica.

[00:50:38] But there is also a more and more recognition of the fact that these two diseases are very distinctly different. So, the biomarkers between those people who are seronegative, neuromyelitis optica, or a clinical syndrome versus aquaporin-4 positive, they are different. Their outcomes are different when it comes to clinical trials as well.

[00:51:05] So the challenges of designing clinical trials for people who are seronegative, who are neuromyelitis optica clinical syndromes is based on the fact That That term is an umbrella for people who may have very different underlying pathologists or actual diseases. That's why they don't respond to treatments equally as well.

[00:51:28] As, people who are coopering for antibody positive. So those clinical trials are challenging because they encompass people with variable disease pathologists. Until we have better biomarkers to understand the more unique features of the people who are aquaporin-4 negative and more negative, but neuromyelitis optica spectrum clinical syndromes, it is difficult truly to design trials that provide really good definitive information.

[00:52:06] **Krissy Dilger:** Okay. Thank you for that explanation. And just a note on the, the, revised clinical guidelines that you mentioned. We will have more information about that hopefully in the coming month or two so that we could share more about those new guidelines all of you in more detail. We have a question. Do chances of relapse increase with age?

[00:52:40] **Dr. Elena Grebenciucova:** No not that we are seeing in general population in people who are stable on a medication. There is no data to suggest that getting older increases your risk of relapse.

[00:52:53] **Krissy Dilger:** Great, thank you. How often should I see my neurologist after diagnosis and initial treatment?

[00:53:05] **Dr. Elena Grebenciucova:** Typically for patients who are taking chronic medications, let, maybe they're on UPLIZNA or ENSPRYNG or on SOLIRIS or ULTOMIRIS, the standard of care is that patients should be seen every six months. But how often you specifically should be seen also depends on what's going on so for a person who had their attack, received IVIG, steroids, and plasma exchange, and they actually had a very nice recovery with minimal residual symptoms, that person certainly can just see their physician every six months and otherwise is needed.

[00:53:41] But there are patients who have incomplete or poor recovery, and they are still suffering from a lot of nerve related pain or a, lot of muscle spasms or stiffness, spasticity, bladder issues. Those patients should be seeing the physician ideally more frequently. typically, after you've been discharged from the hospital, the expectation is that you should be seen within a month.

[00:54:05] And then based on that assessment, say if your physician is still trying to get your pain under control and. Stiffness or muscle spasms under control. A lot of times we'll have a short follow up within three to four weeks or within six weeks and then go from there depending on how well your symptoms are controlled.

[00:54:24] So there isn't like a specific guideline as to how often you should be seen. It's really guided by how well you are doing and if the symptoms are under control. So, for some of my patients who, whose symptoms are not under good control, I might be seeing them every month.

[00:54:39] For the first couple of for the first three to four months, there are also patients that are struggling with, the concept of the diagnosis and the fear of what's to come. So, for those patients, we do suggest that they actually see us during the first couple of months more frequently so that we can be there to support them and answer questions and help calm, hopefully calm some of those fears.

[00:55:05] But otherwise if, somebody is stable, we typically see them every six months and in between as needed by them. And that's really just driven by the patient if they have some sort of questions or they are concerned about something.

[00:55:19] **Krissy Dilger:** Great. Thank you. I think we have time for probably one, maybe two more questions. We got a few different questions about relapses, so I'll try and. Summarize them into one. Are effects from a relapse permanent such as vision loss or those acute symptoms someone experiences during the relapse. Are they permanent? And what are the chances of fully recovering after a relapse?

[00:55:54] **Dr. Elena Grebenciucova:** I think that this is. A question of statistics, but I think that statistics are unfair when it comes to a specific individual because of affects everybody differently and people have different severity of the disease and the treatment that's initiated is initiated at different points. Some people get treatment very quickly, like intravenous steroids and plasma exchange.

[00:56:21] Some people get treatment with a delay of many days or hopefully not weeks. Some people may have never received plasma exchange, right? So, there's a lot of variables and also variables such as age, right? So, we know that younger people, for example, tend to recover better than older. And it's most people when they are recovering, most of the recovery is typically seen within the first three months or so, or with more recovery that can be seen slowly up to a full year. But the degree of the recovery really depends, number one, on the severity of the attack. So, people with severe attacks, with complete loss of vision at times have more poor recovery.

[00:57:13] People with milder loss of vision often have better recovery simply because the damage that was done clearly is not as severe as in those people who have had more severe vision. And but definitely the timing to the medication and the timing to the plasma exchange is, very meaningful in these instances.

[00:57:35] And so the faster people get treatment and particularly plasma exchange for severe attack, the better they tend to do. But the first three months is. The sort of the time when we see most of the people recover to, to, most of the recovery. But some more recovery at a slower pace can occur up to a full year typically.

[00:58:00] **Krissy Dilger:** Great. Thank you so much. And I think that's placed to land on to end this conversation. But I do appreciate you spending the time with us today and answering so many of our questions. And I'm hoping to continue the conversation again. I know we; we can always keep learning and keep doing more of these info sessions. Thank you so much Dr. G.

[00:58:26] **Dr. Elena Grebenciucova:** Thank you so much for having me. Thank you. Bye.

[00:58:32] **Krissy Dilger:** Thank you to our "Ask the Expert" sponsors, Amgen; Alexion, AstraZeneca Rare Disease; and Genentech. Amgen is focused on the discovery, development, and commercialization of medicines that address critical needs for people impacted by rare, autoimmune, and severe inflammatory diseases. They apply scientific expertise and courage to bring clinically meaningful therapies to patients. Amgen believes science and compassion must work together to transform lives.

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