Avoiding a Misdiagnosis

Understanding the Differences Between MOGAD, MS, and NMOSD

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[00:00:00] **GG deFiebre, PhD:** Well, hello, everyone, and welcome to the SRNA Ask the Expert podcast series. This podcast is titled, "Misdiagnosis of NMOSD, MS, and MOGAD." My name is GG deFiebre, and I will be moderating this podcast. SRNA is a nonprofit focused on support, education, and research of rare neuroimmune disorders. You can learn more about us on our website at wearesrna.org. Our 2021 Ask the Expert Podcast series sponsored in part by Alexion - AstraZeneca Rare Disease, Genentech, and Horizon Therapeutics.

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[00:01:25] Horizon 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. Horizon believes science and compassion must work together to transform lives.

[00:01:46] For today's podcast, we are pleased to be joined by Dr. Geoffrey Eubank and Dr. Michael Levy. Dr. Eubank is an accomplished neurologist who specializes in multiple sclerosis and related disorders. He's currently System Chief of General Neurology at OhioHealth. Active as a volunteer physician for free clinics and for the National Multiple Sclerosis Society. Dr. Eubank has published research in several areas and is a member of several medical societies. He's also involved with research in multiple sclerosis and stroke. A native of Pompton Plains, New Jersey, he attended Pennsylvania State University and graduated from Muskingum College, majoring in chemistry and mathematics. He obtained his medical degree from The Ohio State University. He completed his preliminary medicine internship at Riverside Methodist Hospital and his neurology residency at the Cleveland Clinic Foundation where he was chief neurology resident.

[00:02:36] Dr. Michael Levy is an Associate Neurologist at Harvard Medical School. He is the Director of the Neuromyelitis Optica Clinic and Research Laboratory, and Research Director in the Division of Neuroimmunology and Neuroinfectious Disease at Massachusetts General Hospital. He specializes in taking care of patients with neuroimmunologic diseases, including multiple sclerosis, transverse myelitis, optic neuritis, and neuromyelitis optica. In the laboratory, one of his research goals is to develop neural stem cells for regenerative therapy

in these diseases. He uses rat and mouse models to test survival, differentiation, and functional capacity of human neural stem cells to improve neurologic function in post-inflammatory conditions. The goal of his laboratory and clinical effort is to translate the basic science stem cell work to a human trial in transverse myelitis and other neuroimmunologic diseases. Welcome and thank you both so much for joining us today.

[00:03:27] **Dr. Geoffrey Eubank:** Thank you for having us.

[00:03:30] **Dr. Michael Levy:** Thanks, GG.

[00:03:31] **GG deFiebre, PhD:** Thank you. So, to start, I mean, this topic, you know, I think is really important because, when people are first diagnosed there's often a lot of questions about, you know, whether their diagnosis is correct and kind of what these, you know, sometimes seemingly similar disorders, you know, if, if, if they've gotten the correct diagnosis. So, to start, Dr. Levy, do you mind just briefly explaining what each of these disorders are? So, MOG antibody disease, neuromyelitis optica spectrum disorder, and multiple sclerosis. So, just kind of a broad overview, and then we'll go into more of the details about the presentation and kind of diagnostic processes.

[00:04:10] **Dr. Michael Levy:** Sure. I think it's easier to think about them in their historical context. Multiple sclerosis has been known since the 1800s as the most common demyelinating disease. It's a recurring disease whereby the immune system periodically attacks the nervous system, either the optic nerve, the brain, or the spinal cord, causing small disruptions in the capacity of those nerves to transmit their signals. And this, these lesions accrue over time. And most patients, if they don't take any treatment over the course of the next 5, 10, 20 years, will eventually develop a progressive phase of disease that leads to increased disability and usually wheelchair requirement. That's multiple sclerosis.

[00:05:03] Then, we recognized, more recently, that some of these cases are more severe, have a distinct type of disease, they have different looking MRIs, and they have very different responses to treatment. And one of those is neuromyelitis optica, and an antibody to identify that one has been available since 2005. And then, in 2017, then we now have a antibody for MOG antibody disease. And MOG and NMO, neuromyelitis optica, are much, much, rarer than MS. MS is 100 times more common than them, than the others. But NMO and MOG have a distinct blood test that helps differentiate them. And MOG patients, which used to be under the NMO umbrella, are now emerging as their own.

[00:05:56] And so, each of these three conditions, what they have in common, is they're all immune-mediated. The immune system is attacking the nervous system. And what they are, how they are different is exactly what part of the nervous system the immune system is attacking. MOG is called MOG antibody disease because they have antibodies that attack the myelin oligodendrocyte glycoprotein. That's what MOG stands for. Whereas in neuromyelitis optica, the antibody is to aquaporin-4, because the immune system is attacking that protein which is expressed by astrocytes, not in myelin at all. And with multiple sclerosis, we don't know what the target of the immune response is. And so, as we continue to dissect down the, the, different multiple sclerosis patient populations, we might find future antibodies as well.

[00:06:46] **GG deFiebre, PhD:** Great. Thank you so much for that overview. And so then, in terms of presentation or what the kind of potential symptoms are that someone might have before being diagnosed with one of these conditions, what are the similarities between the disorders and what are the differences? Dr. Eubank?

[00:07:03] **Dr. Geoffrey Eubank:** Sure. One of the more common ways that someone presents with any of these disorders is something called optic neuritis, or inflammation of the optic nerve. And that's where, that's what gets us started here. Now, in the setting of MS, we're, we're used to seeing that. And in that scenario,

they usually have a pretty decent recovery. And as compared to neuromyelitis optica, they also have optic neuritis, but quite frequently they have significant damage, and they can go blind after a single attack. So, it can be a much more severe attack. And lastly, we have MOG antibody disease, and they can also have optic neuritis, but they tend to respond pretty well to steroids. They also can have bilateral optic neuritis at the same time. And so, on the one hand, it's like they can all have optic neuritis, but there's a little bit of difference there.

[00:08:03] Additionally, a lot of, all three of these diseases can have what we call transverse myelitis, or inflammation of the spinal cord. Once again, with neuromyelitis optica, it tends to be more severe, and they cannot recover nearly as well as the other two can. So, it's, it, there's a, a, a definite difference there. But sometimes we have people with NMO that just have a milder attack. The parts of the nervous system that frequently are, are involved with all three of these are the optic nerve and the spinal cord. So, that's a fair about, about the similarities.

[00:08:42] The differences, I think I highlighted some of those, which is neuromyelitis optica tends to have incomplete recovery. The other thing is there's, oftentimes, presentations with multiple sclerosis in other parts of the central nervous system, brain stem, and other areas that tend not to be impacted by MOG and NMO. So, I think that's clinically how they differ, just from talking to a patient and dealing with them. I think you have some other questions later about the diagnostic processes and the treatments. But from the clinical presentation, that's, that's some of the highlights.

[00:09:18] **GG deFiebre, PhD:** Great. Thank you. And then, just to, to follow up on that, are there any differences in the way that potentially the optic neuritis might present? So, you know, one eye versus two being affected, or the way the inflammation in the spinal cord might look, so, like a long lesion versus a short lesion? Are there any sort of differences there, Dr. Eubank?

[00:09:38] **Dr. Geoffrey Eubank:** Yeah, I think, you, you highlighted one of those. If you get bilateral optic neuritis, that's something that we strongly would consider MOG antibody disease. So, that's one of the differences, if it happens in both eyes at the same time. The severity tends to be more severe with neuromyelitis optica. And then, when you look at the optic nerve itself, if you are able to see the inflammation, with MS it might be a small little area of inflammation, whereas with neuromyelitis optica and oftentimes with MOG, you'll see a longer segment of inflammation as well.

[00:10:14] And that same thought process kind of extends to the spinal cord as well. In MS, you might have a small area of the spinal cord, really just maybe a what we call, one segment, kind of, you know, the length of a vertebrae. Whereas, with neuromyelitis optica, especially, it can be several segments, three, four, sometimes the large portion of the spinal cord. And MOG itself also has these longer lesions within the spinal cord. And once again, in the spinal cord with neuromyelitis optica, the recovery oftentimes is incomplete, whereas the recoveries with MS and MOG tend to be at least a bit better, not always complete, but certainly can be better.

[00:10:56] **GG deFiebre, PhD:** Great, thank you. And then, so, we talked about the presentation, and so, the, in terms of the diagnostic process, how is, how is this done when someone is assessed for one of these disorders? Do they maybe come in with transverse myelitis and optic neuritis or just, you know, one or the other? What is the diagnostic process that's used to assess which one of these conditions they might have? Dr. Levy?

[00:11:21] **Dr. Michael Levy:** The initial process is basically doing what Dr. Eubank did, which was to help, to look for features that help distinguish among these conditions, and then to test for them specifically. So, first you come up with your list of all the things it could be based on the appearance on the MRI, based on the description from the patient, based on the examination that you get in the clinic room. And then, you go,

you start thinking through, "Well, if I think it's this disorder, then what tests would help confirm that?" Could be another MRI, it could be optical coherence tomography, photographs of the eye. It might be blood tests. Certainly, if you're suspicious for neuromyelitis optica spectrum disorder, there's nothing better than the aquaporin-4 antibody. The one that is resulted at the Mayo Clinic, which is a cell-based assay, is extremely specific. And that means that if you test positive it's very, very, very likely to be neuromyelitis optica spectrum disorder, especially if your doctor thought that that's what it could be, and then sent for the test.

[00:12:32] And the MOG antibody test is also, it's under, it, it's being researched right now. It may have a very similar specificity compared to aquaporin-4. We do think very highly of it. There are issues with the titer, the level of antibody. We'll get to those issues later in this podcast. But there's no blood test for MS. There is a spinal fluid test that we use for helping make the diagnosis of MS, but it's not specific, meaning that MOG and NMO patients may also test positive, as may people with other conditions. So, it's really putting together all the different clues that are based on your initial hypothesis that comes from just thinking through the clinical case scenario.

[00:13:18] **GG deFiebre, PhD:** Okay, great. So, you mentioned the, the blood tests, and then, you know, the, the spinal tap or lumbar puncture results. Do you also, in terms of looking at an MRI, do you look for differences there as well, Dr. Levy?

[00:13:30] **Dr. Michael Levy:** Yeah. As, as Dr. Eubank was saying, the lesions with MS tend to be small, whereas the lesions with NMO tend to be long. In MOG, it can be both. And another thing with MOG that I've noticed in particular is the remyelination and the recovery that's apparent with MOG. So, it, when I have patients who have even long lesions on their MRI, but then they get much better over the course of just a few months, that makes me think more MOG compared to NMO. MOG patients just tend to heal better. And sometimes, it's even resulted in some cases where the MRI is done so late after the, after the onset of a relapse, that it's already healed. And patients are coming in with symptoms that they insist are new, but the MRI doesn't show it. And that's kind of something that we've seen with MOG more recently.

[00:14:27] **GG deFiebre, PhD:** Great, thank you. And so, what are the common reasons people might be misdiagnosed with these conditions, when, you know, if they have one but they get misdiagnosed with MS, but they actually have NMOSD? What are, what are kind of the, the reasons why this might happen? Dr. Eubank?

[00:14:45] **Dr. Geoffrey Eubank:** There's a lot of reasons. I mean, one of the bigger reasons is experience. You, you, as... if, if you're seeing a neurologist, a neurologist comes out. If it's a general neurologist, there's a lot of things to keep track of. And most cases that, of optic neuritis and spinal cord disease, the first place you're going is MS. And for the longest time, we didn't have these excellent biomarkers or the laboratory studies that helped us with that. And while we have classic cases of NMO and MOG antibody disease, there's some cases that kind of fall in between. And so, first of all, you have to think about these other disorders. And then, you also have to know to, to run the, the right test.

[00:15:31] And there's a lot of people that say, "Hey, I think I know what this is." You stick with the diagnosis. There's something called this anchor bias. So, if you diagnose somebody with something early on and you say, "Geeze, the, the MRI scan of the brain doesn't show too much, but I think it's MS," and then, sometimes people forget that sometimes you can be incorrect in your diagnosis. I've made that mistake a few times over my career. And you have to look back, and I said was I sure about this and do I need to look back at it, either based on how the patient is progressing or how they respond to therapy.

[00:16:04] So, I think the first thing is, is, is not just going with the most obvious diagnosis but making yourself... if you're going to diagnose something like MS, at least pause and rethink to think about these other disorders.

I don't think it means we're always supposed to order these laboratory studies on everybody we think has MS. I think there's a little bit of a risk in probably over-testing with that. But we at least want to think through it clinically and critically as we look over their history and their MRI.

[00:16:34] **GG deFiebre, PhD:** Great, thank you. And then, what are the consequences of receiving a wrong diagnosis? Dr. Levy?

[00:16:42] **Dr. Michael Levy:** That, it depends on which diagnosis was given and what was done about it. So, for example, if a diagnosis of MS is given to someone with neuromyelitis optica, and they use a medication that we know is useful in MS but not in neuromyelitis optica, it, it can actually make neuromyelitis optica worse, like the injectables, then you'd have a bad outcome. That would be consequential. But there are some treatments for MS that are also useful in NMO. For example, B cell depleting therapies. So, in cases where I'm unsure of what the diagnosis is, I will often look for a treatment that covers both just in case, rather than a treatment that would necessarily make one worse at the expense of, make one better at the expense of the other. That way, you're, you're double covered.

[00:17:44] Now, there, as I, I'll echo what Dr. Eubank was saying. Usually, patients are misdiagnosed with MS. It's just much, much, more common. Prevalence is almost one in a thousand now. Most people know somebody with MS. Whereas, with NMO and MOG, we're talking about one, or two, or three per 100,000 people. And so, it's just much rarer. It really takes a lot of thought to consider the diagnoses, and you have to know to test for it. And while many academic centers are prime to do it, because we're teaching residents and fellows how to do it, I would say that there is still many places that are not even considering NMO or MOG on their, on their differential.

[00:18:29] **GG deFiebre, PhD:** Thank you. And then, so you mentioned how the drug use for MS can make NMO worse. Is this also the case with MOG? And why does this happen? And is the alternate true as well for the drugs used for NMO or MOG? Can they make MS worse?

[00:18:46] **Dr. Michael Levy:** That is a good question. We think that the reason that some MS treatments make NMO and MOG worse is because if you use the medications... some medications for MS activate a part of the immune system, and the activation of that part of the immune system is intended to outmaneuver a different part of the immune system. So, it's like restoring a balance that was thought to be upset in the first place. But with NMO and MOG, the thought is you don't want to activate any part of the immune system, because that could activate the rogue element that then leads to an attack. All of the injectables used in MS, except for Copaxone, are probably harmful in NMO. And we don't know about MOG. There are small studies. In kids, for example, 10 out of 10 kids who had MOG who were using injectables for MS had bad outcomes. Whether they were worse than if they did nothing, we're not exactly sure. It takes a lot of, a lot of trial and error to learn these kinds of things, and we don't, we don't really want those errors.

[00:19:57] So, for the most part, what we're trying to do with NMO and MOG is suppress the immune system, whereas with MS, we're at the point where we're really trying to modulate the immune system. And that's why they're really different therapies with few overlaps. But for the most part, we want to know which diagnosis you have, so that we can institute the right treatment.

[00:20:21] **GG deFiebre, PhD:** Got it. Thank you. And then, under what circumstances might someone want to get a second opinion with one of these diagnoses? Dr. Eubank?

[00:20:31] **Dr. Geoffrey Eubank:** That, that's a tricky question. It, it probably depends what physician you're seeing. If you're at a well-known center that deals a lot with multiple sclerosis, I think there's going to be a

wide breadth of experience and understanding, which things are MS and what cousins might be available. But, you know, I think, you know, if, you know, the most likely circumstances we talked before was, somebody was diagnosed with MS, and is it really MS?

[00:21:02] And I suppose, if somebody's listening to this and has MS, you know, there's nothing wrong with saying, "Hey, I heard there's these other diseases that are like MS." And if you have a conversation with your physician and they walk through the reasons why it wouldn't be, or isn't, or maybe they say, "Geeze, I hadn't thought about that." But I think, if you get the confidence and you have a good conversation with your physician that you've kind of, that you have, they have thought about and excluded the others, I think that's good. I think if you're getting an answer that's, you know, less than satisfactory, then that would be at least one circumstance to do that.

[00:21:42] I also think that NMO and MOG are rare enough that sometimes if you're not at a place where that's seen a lot, you really want people that have both the expertise in diagnosis, and even more importantly, the expertise in knowing what the best treatment options are to choose.

[00:21:59] **GG deFiebre, PhD:** Great, thank you. And so, we often get questions from people who either were originally diagnosed with transverse myelitis or they thought it was, you know, idiopathic transverse myelitis and monophasic, had another attack, and were diagnosed with NMO or MOG, and so, you know, they often ask like, "Did my TM turn into MS, or MOG, or NMO?" So, similarly, can MOG or NMO develop into MS? Or how are these kind of related to one another in that way? Dr. Levy?

[00:22:32] **Dr. Michael Levy:** Transverse myelitis and optic neuritis can develop into relapsing conditions, but they can also be monophasic. And I think, GG, when you ask the next question about, "Why can it sometimes take so long to get the correct diagnosis?", it's really in those cases where we're not sure if this was just the first and only attack or if it's going to be a relapsing condition. That's what takes so long to present itself sometimes. If the antibodies are all negative, and if there's evidence of a relapsing disease, I will honestly tell my patients, I'll say, "Look, this might be a one-time attack, and it may never occur again, but I won't know that until three, four, five years from now. And then, I'll be able to look back and tell you, oh yeah, this was a one-time event."

[00:23:25] On the other hand, a lot of people with MS, for example, have optic neuritis. About 40% will start with optic neuritis and then develop MS symptoms, and, and, signs, and MRI findings later on. And so, we have to repeat MRIs on a regular basis to rule that out or rule it in. These things evolve over time. And there's no blood test for MS. It's a clinical diagnosis, so we have to just wait until these things happen. With NMO and MOG, we'd like to make the diagnosis as soon as we can, ideally with the confirmation of the antibody, so that we can prevent any additional damage from future attacks.

[00:24:09] **GG deFiebre, PhD:** Great, thank you. And so, you did talk a bit about, you know, why it can sometimes take so long to get to the correct diagnosis. But Dr. Eubank, do you have anything to add to, to that?

[00:24:18] **Dr. Geoffrey Eubank:** Yeah, I, just to maybe echo some things, you know, patients don't come with just a textbook version of what we're looking for. So, we can have something and be a bit uncertain. You know, each, each year, five years, 10 years, we get better and better, because we have better tools. We understand things better. We have experts that can teach us, you know, what, what oddities to look for on the MRI and these blood tests. You know, like, even the MOG antibody really wasn't available up until a few years ago. So, we used to call MOG sometimes something else. It was just chronic relapsing inflammatory optic neuropathy that we didn't know what else do with. And probably, you know, a lot of those, or most of those, were, were

MOG. So, sometimes it's just we haven't developed the tools at the right time. And sometimes the patient just doesn't have enough things that happen to allow us to be certain about a diagnosis.

[00:25:11] And while we want to get a diagnosis as soon as we can, we don't want to get too far in front of it without being certain. If we get too far in front we're... Once we, once we get to a diagnosis, most of the time we're committing to lifelong therapy. And that's especially true with MS, when we don't have a definitive marker. With something like NMO, I think, we, it's a little bit easier. We, we can be more certain early on and make sure we get on therapy. If it might be MS, I need to make sure it is MS before I commit somebody.

[00:25:46] **GG deFiebre, PhD:** Got it. Thank you. And then, what can be done to not only test for MS but NMO and MOG at the same time?

[00:25:54] **Dr. Geoffrey Eubank:** So, you know, we're doing that with our history. Our, our, our same history and our same exam works the same for each patient. So, I guess the thing where there's the overlap is really, how do we testing for it? When, when we're looking at the MRI scan, both patients are going to have similar studies. They're both going to have an MRI scan of their brain and the vast majority of the time their entire spine, when we first diagnose people. So, really, it's, there's not a lot of different testing with a couple of exceptions that we, like we mentioned with the laboratory studies. But it's really just critically looking at the tests that we have available. So, with the MRIs, we're looking for the differences between NMO, MOG, and MS is certainly one thing. We've already alluded to the two antibodies that we have. That's probably the main thing.

[00:26:49] Another thing, I guess I would say, is the spinal fluid studies. It tends to be abnormal in a, in, with MS in a particular way, but it's not absolute. And you, you can have spinal fluid abnormalities that might suggest MS, but it doesn't mean that you've ruled in or ruled out the other two conditions or, or vice versa.

[00:27:11] **GG deFiebre, PhD:** Great, thank you. And so, what are, what are those abnormalities that can be seen in the, the spinal fluid?

[00:27:16] **Dr. Geoffrey Eubank:** We see something called oligoclonal bands, which is a fancy way of s-... and there's something called an IgG synthesis rate. And effectively, what those things are is an excess antibody production that seems to be mostly focused within the central nervous system or spinal fluid. And when you look at the serum, what's circulating in the bloodstream, you don't see that same level of inflammation. So, effectively, you're seeing inflammation that seems to be focused in on the central nervous system while relatively sparing what's going on in the rest of the body.

[00:27:52] **GG deFiebre, PhD:** Great, thank you. And then, Dr. Levy, are there different levels of severity for each of these diagnoses? I know Dr. Eubank talked a little bit about it, but are there different levels of severity in terms of the optic neuritis or the, you know, inflammation in the spinal cord that might occur, or how people present?

[00:28:10] **Dr. Michael Levy:** There are some differences, yes. So, the... Each attack in NMO and MOG can be severe. Sometimes, when I don't know which antibody patients will test positive for, I, I... You know, a patient can be blind in one or both eyes, and I won't know if that's going to be MOG or NMO yet. The, the initial severity can be about the same. But when a patient comes back into clinic three, four, five, six months later after treatment, MOG patients tend to heal better. So, the initial severity was worse, but the final severity is better for MOG. NMO patients don't tend to make as good of a recovery each time. And then, MS patients rarely have severe attacks. They do, but not as often as NMO and MOG. But with MS, although each attack is less severe, there is a progressive course to the disease that tends to cause more and more disability

over time, even in the absence of, of inflammation. And so, in the end, the, the disability may be higher in MS compared to NMO or MOG.

[00:29:22] **GG deFiebre, PhD:** Okay, thank you. And we often get questions about, someone might test positive for the MOG antibody but then test negative later, and same with the aquaporin-4 antibody. So, if that happens with MOG, for example, does someone still have MOG antibody disease? And then, what about for aquaporin-4, do they still have neuromyelitis optica spectrum disorder even if they test negative at a later time? Dr. Eubank?

[00:29:52] **Dr. Geoffrey Eubank:** I think with the aquaporin-4 antibody, especially if it's a cell-based assay, we have quite a bit of confidence. And I can't remember too many times when somebody tested positive for that and then tested negative later for that cell-based assay for aquaporin-4. On the other hand, I have had patients test positive for MOG, especially the low titers. And I think that's the one we have to be careful with. We're not sure that everybody that tests a low positive actually has that disorder. I've seen patients that really seem like they fit much better with MS.

[00:30:30] The, one of the good news is, even if they do have MOG antibody disease, and they test positive and maybe they test negative later, those patients actually seem to have a more benign course. And sometimes that gives us the opportunity to watch them closely and maybe not put them on lifelong therapy. So, I think it is important. But I have seen MOG go positive to negative. It's usually in the low titers. And it makes me question whether MOG antibody disease is right or not. It depends on everything else that's going on.

[00:31:02] Now, if they showed up with bilateral optic neuritis and a longitudinal extensive legion within their spinal cord, I think they still have MOG antibody disease. But if they happen to show up just with optic neuritis and a low titer MOG, and then it went away and nothing ever showed up on another scan, I think we'd watch them to see what would happen.

[00:31:23] **GG deFiebre, PhD:** Got it. Thank you. And then, we did get a question, you know, related to these kinds of titers of, of the MOG antibody. This person had a one to 20 titer after having two distinct relapses. But, you know, they were told that, potentially, a low titer can be a false positive. So, they're wondering whether people with low titers are, you know, definitely positive for having MOG antibody disease or not, or if it's a, a false positive potentially. Dr. Levy?

[00:31:51] **Dr. Michael Levy:** So, the first thing to recognize here is that this person has a relapsing condition, and that takes them out of the monophasic condition. So, this is not just a one-time optic neuritis but a relapsing condition. And, and among relapsing conditions, we have multiple sclerosis by far the most common. And then, also MOG, NMO, CRION, as, as Dr. Eubank mentioned. So, there are other conditions, neurosarcoidosis.

[00:32:19] Now, you, you look for all of these conditions or you consider which ones you're going to test for, and a positive MOG antibody comes back. If it's one to 20, that is the lowest level that Mayo tests. Quest goes all the way down to one to 10. And these lower titers have been associated with false positive conditions, especially confusing them for MS. So, about half are thought to not be a true positive, half are. So, there's a 50/50 chance, right off the bat, that a person with low MOG titer, in the context of recurrent optic neuritis, is in fact MOG antibody disease. Then, the other half could be false positive, most often confused with MS.

[00:33:06] And more recently, we're starting to describe series of patients who appear to have both MS and MOG. That is an overlap that we've noticed more often with MOG and MS especially, where patients can have brain MRIs and even those oligoclonal bands Dr. Eubank mentioned, that's consistent with MS but also test positive for low titer MOG antibodies consistently. And so, we're recognizing that maybe these people

have an overlap condition and might actually have the good clinical outcomes of MOG patients but may also respond to, to treatments that are effective for MS. So, that's something that we need to look deeper into.

[00:33:52] And then, one more thing that I would men-, I would echo is what Dr. Eubank mentioned about people who have a monophasic condition, a single attack, usually optic neuritis, with a low positive MOG titer. If that tends, if that goes away on repeat testing six or 12 months later, there's a good chance that person is going to be monophasic, not relapsing condition. Sometimes, it takes a relapse to convince us that it's a relapsing condition. But many doctors won't start treating a person with MOG antibody to prevent a future relapse if they are not convinced that it is actually a relapsing condition. So, that's something sometimes patients just have to convince us, either with recurring disease or with increasing antibody titers, that it's worth treating for MOG antibody disease.

[00:34:46] **GG deFiebre, PhD:** Okay. And then, so, in terms of MOG titers, are there any kind of recommendations on how often these should be tested? Dr. Eubank?

[00:34:55] **Dr. Geoffrey Eubank:** I think, you know, certainly if somebody has a low titer, I think it's something to be, to be worth repeating down the road. Really, you're trying to get to when you're as certain and comfortable about the diagnosis. And I think, sometimes we just simply are. And, you know, repeat testing for, at least for my practice, I don't do just to do it. And again, with NMO I have a, a bit more confidence. If I have a positive NMO antibody and I have the right clinical syndrome, I may not repeat.

[00:35:27] Now, on the other hand, sometimes the very first time you test for somebody, they can test negative. And so, I do keep in mind that it sometimes bears repeating 6, 12 months down the road to ensure that that is not a false negative. But I think, with MOG, I think it just depends on the clinical situation. If you have somebody that consistently tests low positive and you're not sure, probably depends on what they're doing clinically and what their MRI's doing. So, I could see a situation where you might check it a number of times. But I think the majority of the time, it's repeating it maybe a second time, generally, is all that usually is required.

[00:36:10] **Dr. Michael Levy:** GG, can I add one quick thing about the aquaporin-4 antibody?

[00:36:14] **GG deFiebre, PhD:** Yeah, go ahead.

[00:36:15] **Dr. Michael Levy:** It seems, it seems that the benefit that we see with MOG when the antibody goes away is not something that we see with aquaporin-4. The experience of patients who have, whose antibodies have gone away over time, does not seem to be that beneficial. It's not like you can come off of immunotherapy and the disease has gone away. We do see that with MOG. We don't, we do not seem to see that with the aquaporin-4 NMO.

[00:36:44] **Dr. Geoffrey Eubank:** That's a great point.

[00:36:47] **GG deFiebre, PhD:** Got it. Thank you. And so, and then, someone submitted a question about a paper that they had read where they were talking about agents that selectively eliminated MOG-specific antibodies without affecting the levels of other antibodies in the, in the body. Is this something that is planned for commercialization or for a treatment or something for MOG? Dr. Levy?

[00:37:11] **Dr. Michael Levy:** You know, if, for MOG, I think this is a nice proof of concept that you can remove specific antibodies. In the case of MOG antibody disease, though, those antibodies are probably not the problem. And so, it's not going to help much to, to get rid of them. You still have all of the immune cells that made them, that are involved farther upstream in deciding when and where to attack the nervous system,

and it may be that the antibody contributes a little bit to that process. But even without the antibodies, the disease can progress. So, in this case, it's not that helpful.

[00:37:51] However, this is something that can be used for other conditions where the antibody is more intimately involved, in, in conditions especially that cause blood clots due to some antibodies, or platelet disorders, or some other autoimmune conditions in which the antibody is much more involved, and if we can get rid of that antibody without getting rid of the other ones, that would be very useful.

[00:38:20] **GG deFiebre, PhD:** Got it. Thank you.

[00:38:21] **Dr. Michael Levy:** Same with aquaporin-4 antibodies. Getting rid of them would not do the job.

[00:38:26] **GG deFiebre, PhD:** Okay. Okay. And then, so we got a question from someone who is diagnosed with MOG in February of this year, but they currently have tested negative for the antibody, and they don't have any additional lesions but have experienced, you know, an increase in numbness.

[00:38:42] Is this, you know, something that is, sometimes happens as a result of MOG? You know, is this potentially an... People talk about having a relapse versus a pseudo-relapse or kind of a worsening of symptoms without new lesions. Would you mind just speaking a bit about that, Dr. Eubank?

[00:38:59] **Dr. Geoffrey Eubank:** It's always difficult for somebody's specific situation. Most of the time, when we're dealing with NMO and MOG, we tend to get specific attacks rather than slowly developing symptoms. I suppose anything's possible. But usually, we get something more suddenly. So, that's, that's what we're looking for to change our opinion. I guess you'd have to keep an open mind. It would depend, in part, upon what their examination looked like. If I'm seeing changes on their exam, whether they're having new weakness or reflex abnormalities, or if we did additional imaging and everything looked good, I think you'd have to kind of keep an open mind and make sure you're not missing something else, a vitamin deficiency, or, or some other process like that. But I think if their exam and their MRIs were stable, it's one of those situations where you're uncomfortably just watching to see what happens next.

[00:39:57] **GG deFiebre, PhD:** Thank you. And then, we did get a question from someone who says that they have great neurologists in the clinic setting. So, I guess the, likely the neurologist that they see kind of to manage their care. But they'd like to know how to handle neurologists who haven't heard of MOG or downplays presenting symptoms when active lesions don't show up. So, for example, in an ER, if they're going there, are there any kind of suggestions on how to chat with someone who might not know as much about MOG as, as, both of you do? Dr. Levy?

[00:40:29] **Dr. Michael Levy:** Well, I think that listening to podcasts is good for your own education. I think neurologists are busy these days. It's hard to get them to pay attention to your condition. Maybe it, another way to do this would be to establish care with an expert neurologist somewhere else, not on a regular basis, to maintain your relationship with your local neurologist who's going to be there for you in case anything goes wrong. But for specific issues that are, that, where you're lacking expertise in your area, it might be worth getting that second opinion from, from the larger academic center nearby that... And then, those two doctors may be able to communicate. That may be one way around it that I can think of.

[00:41:19] **GG deFiebre, PhD:** Great, thank you. And so, another question that we got was that someone's daughter was MOG positive, had one attack in February of this year, so at this point monophasic. You know, are there things that, you know, things that are looked for to see if it might be potentially recurring, or is it just kind of a, a wait and see? Dr. Eubank?

[00:41:46] **Dr. Geoffrey Eubank:** I think it's a bit of a wait and see. As we already alluded to before, those low positive titers seem to be something that would be in our favor for a possible monophasic course. But I still think, regardless of the titer, for something like MOG, I think, you know, waiting to see what the next step is, you know, it's always uncomfortable to wait for the next step. But what we really want is to wait uncomfortably for a really long time. That would be the, the ideal situation, and that's kind of how we try to explain it. It's like, we don't know what's going to happen. And I think with, with this condition, it, it's, it bears waiting out to make sure a second thing comes, because we don't want to put people on long-term therapy when we know some of those patients simply won't need that.

[00:42:34] **GG deFiebre, PhD:** Great, thank you. And then, Dr. Levy, I know you've done some research on familial transverse myelitis. We got a question from someone, someone who their daughter was diagnosed with MOG and had optic neuritis three times. Do they need to test other children or parents for, for MOG as well?

[00:42:55] **Dr. Michael Levy:** MOG, it does not appear to run in families. The very first family with two or more affected, with two affected people, is being published as we speak. It's a family out of Australia. But beyond that, it does not seem to run in families. And also, MOG patients don't tend to have a lot of autoimmune disease in the family, and that's compared to neuromyelitis optica. You ask them, is there any autoimmunity in the family? "Oh, my mother has lupus, and my sister has Sjogren's, and you know, I also have some psoriasis." You don't hear that with MOG. It does not seem to be a typical kind of autoimmune predisposition. We don't really know why it happens.

[00:43:43] But interestingly, it, in, in different animal models, you can break immunity to MOG. And what that looks like in those models, including the rats that we're doing stem cell treatments on, is exactly the same as humans. It's an inflammatory attack of the optic nerves and spinal cord, and sometimes the brain. And it can happen in monkeys and dogs, and in cats, and rats, and mice. And it's all against MOG. And so, it's, and it really doesn't depend on the genetic background. There are, the genetic background makes it, can tweak the phenotype, what it looks like. But the susceptibility of the MOG seems to be universal. So, we need to understand why that happens, and maybe we'll understand why it happens in people as well.

[00:44:34] **GG deFiebre, PhD:** Great, thank you. And then, why are... So, Dr. Eubank, you talked about oligoclonal bands that might be present in someone through the spinal fluid. Why are they more likely to be positive in MS compared to the other two conditions we've been talking about?

[00:44:51] **Dr. Geoffrey Eubank:** That's actually a, a very good question. So good that I'm actually going to lean on Dr. Levy's expertise, if he happens to have that answer. Because I don't have a great answer.

[00:45:00] **Dr. Michael Levy:** I have a theory.

[00:45:02] **Dr. Geoffrey Eubank:** Okay. [laughs].

[00:45:03] **Dr. Michael Levy:** So, you know, I think MS is a condition that, it probably lives in the central nervous system and leaks these findings, these markers, into the central, into the spinal fluid, whereas NMO and MOG probably live in the peripheral circulation, in the blood, in the lymph nodes, in the spleen. And then, MOG and NMO will periodically attack the nervous system. Whereas, with MS, while there are attacks that occur periodically, there's also that smoldering inflammation that leads to progressive disease. And that may be because MS is just constantly there, constantly causing inflammation in the central nervous system.

[00:45:51] **GG deFiebre, PhD:** Great, thank you. And so, we've talked a lot about how important it is to get to the correct diagnosis, you know, partially because treatments used for one condition might not work

well for others or may even cause harm. Is there any kind of research that's currently happening to improve diagnostics or kind of help this process? Dr. Levy?

[00:46:12] **Dr. Michael Levy:** Well, I can tell you that there are trials that are being launched, specifically in MOG. These are carefully designed trials that will limit the, the bias, and therefore limit any false positive or false negative results. And what they're intended to do is to determine whether or not these treatments are, are, are effective in preventing relapses, specifically in MOG. And that we have that with NMO. We have 22 approved drugs in MS. So, I think we are getting better at picking specific therapies for specific people. The, the category that's still being left out are the ones that don't test positive for anything and don't have a clear-cut MS condition that's easily diagnosed. For those people, there is ongoing research to further identify new diseases based on blood biomarkers, MRI biomarkers, spinal fluid biomarkers, and so on.

[00:47:14] **GG deFiebre, PhD:** Got it. Thank you. And then, Dr. Eubank, do you have anything to add to that?

[00:47:18] **Dr. Geoffrey Eubank:** No, I think that was well summarized.

[00:47:21] **GG deFiebre, PhD:** Great. And so, we are actually at the end of our time. So, I just wanted to open up and see if you had anything else you wanted to mention that we haven't talked about, about, you know, how to avoid a, potentially avoid a misdiagnosis or kind of the similarities and differences between these conditions. Dr. Levy?

[00:47:38] **Dr. Michael Levy:** I think we were pretty thorough. Yeah. I, if people are interested in clinical trials for MOG, the first one just launched, and there will be two more coming out very soon. So, I hope we'll cover those in future podcasts.

[00:47:55] **GG deFiebre, PhD:** Yep, that'd be great. And Dr. Eubank, anything to, any last thoughts?

[00:48:00] **Dr. Geoffrey Eubank:** No, I just, I really appreciate the fact that you guys are getting this information out there. I, I think it's really important as we described before. People need the right diagnosis so they can get the right treatment. I'm just happy to be part of this and hopefully, the people that are listening to this get some good information.

[00:48:22] **GG deFiebre, PhD:** Yes. Thank you both so much. We really appreciate taking the time to do this and all your expertise and, and answering questions from our community. We, we really appreciate it. So, thank you so much.

[00:48:33] **Dr. Michael Levy:** Thank you, GG.