The Transverse Myelitis Association 'Ask the Expert' Podcast Series
What is MOG antibody-associated disease?

The audio of this podcast is available at https://myelitis.org/resources/what-is-mog-antibody-associated-disease/

GG DeFiebre: 00:00:02 Hello everyone and welcome to the Ask the Expert Podcast Series. Today's podcast is entitled "What is MOG Antibody-Associated Disease?" My name is GG DeFiebre and I will be moderating this podcast with Kristina Lefelar.

Kristina Lefelar: 00:00:17 Hi, my name is Kristina Lefelar. I'm a recent Towson University graduate, majoring in psychology and communications. My mom and I are launching the MOG Project at the TMA to create a platform and greater understanding of MOG. So we're excited to learn more from both speakers today.

GG DeFiebre: 00:00:34 And just so everyone knows, the TMA is a nonprofit focused on support, education and research of rare neuroimmune disorders. You can learn more about us on our website at myelitis.org and this podcast is being recorded and will be made available on the TMA website for download and via iTunes. So, during the call, if you have any additional questions, you can send us a message through the chat option available with GotoWebinar. For today's podcast, we are pleased to be joined by Dr. Michael Levy and Dr. Ben Greenberg.

Kristina Lefelar: 00:01:07 Okay. Dr. Michael Levy is an Associate Professor of Neurology and the Medical Director of General Neurology at the Johns Hopkins Hospital in Baltimore, Maryland. Dr. Levy specializes in taking care of patients with neuro-immunologic diseases, including multiple sclerosis, transverse myelitis, optic neuritis, and neuromyelitis optica. In the laboratory, Dr. Levy's research focus is on the development of neural stems to regenerative therapy in these diseases. He uses rat and mouse models to test the survival, differentiation and functional capacity of human neuro-stem cells to improve neurologic function and 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.

GG DeFiebre: 00:01:57 And Dr. Benjamin Greenberg received his Bachelor of Arts degree from Johns Hopkins University and his Masters degree in Molecular Microbiology and Immunology from the Johns Hopkins School of Public Health in Baltimore, Maryland. He completed his residency in neurology at the Johns Hopkins Hospital and then joined the faculty within the Division of Neuroimmunology. In January of 2009, he was recruited to the

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faculty at the University of Texas Southwestern Medical Center where he was named Deputy Director of the Multiple Sclerosis Program and Director of the new Transverse Myelitis and Neuromyelitis Optica Program. Dr. Greenberg is recognized internationally as an expert in rare autoimmune disorders of the central nervous system. His research interests are in both the diagnosis and treatment of transverse myelitis, neuromyelitis optica, encephalitis, multiple sclerosis and infections of the central nervous system. He currently serves as the Director of Neurosciences Clinical Research Center and is a Cain Denius Foundation Scholar. Welcome and thank you both for joining us today.

Dr. Greenberg: Thanks. Happy to be here.

Dr. Levy: Thank you for hosting.

GG DeFiebre: Thank you. So, to start, can you just give an overview of what MOG antibody-associated disease is and how does it differ from NMO? Dr. Levy?

Dr. Levy: 00:03:21 Well, that is a loaded question because it's only been recently recognized to be a variant of NMO, per se. And the way this came about is that when patients test negative for the Aquaporin-4 antibody in NMO, we recognize that they have a similar type of diseases presentation with optic neuritis and transverse myelitis, that for all intents and purposes seemed to be very similar to those who tested positive for Aquaporin-4. But when we screened for new antibodies and this special population that does not have aquaporin-4, a large number, somewhere between about 25 to 40 percent, tested positive specifically for this MOG antibody. That's really where this disease came from. It was previously thought to be associated with ADEM, which kind of looks like NMO in some respects. There were some tests that were positive in MS patients and other neuroimmunological diseases, but when you really look back at them, they are most consistent with this NMO phenotype, NMO being optic neuritis and transverse myelitis. And so now we've kind of carved out this special group of patients who test positive for the MOG antibody and we're starting to recognize some unique features about them. So they are mostly like NMO in terms of predilection for optic neuritis and transverse myelitis, but they're different because they seem to have a different target within the nervous system. It

seems like the immune system is targeting myelin or myelin protein rather than astrocytes in NMO, and clinically they seem to be a little bit different because they seem to heal better after attacks and they also seem to respond slightly differently to different preventive medications, which we can talk about.

Kristina Lefelar: 00:05:32 Thank you. That was a really good overview and understanding of how the differences in those. So that brings me to the next question. What is the relationship between MOG and NMO Spectrum Disorder and ADEM?

Dr. Levy: 00:05:49 Well, we're still kind of sorting all of this out. We know that a lot of the ADEM kids will test positive for the MOG antibody. It doesn't necessarily mean they're going to develop MOG antibody disease with relapses of optic neuritis and so on. There are some kids who have just ADEM, are positive for MOG but then never have another attack again. And then there are some kids who test positive for the MOG antibody and do have relapses in the future and they can look a little bit like recurrent ADEM or they can look more like NMO. And then there's some kids with ADEM who were never tested or may test negative for MOG antibody, who relapse in the future and then they test positive for the MOG antibody disease and have more of that NMO phenotype. So it's really a spectrum right now. We don't know why some kids develop a relapsing disease and why some kids with ADEM don't. But we think that that MOG antibody is a marker if it persists. So if six to 12 months after your kid has ADEM, if they still test positive for the MOG antibody, that tends to be a little bit more concerning for relapsing disease.

GG DeFiebre: 00:07:07 Okay. Thank you. And, you know, I know we've talked kind of broadly about the relationship between NMO and the MOG antibody, but can a patient test positive for both the NMO, the aquaporin-4, antibody and the MOG antibody? Dr. Greenberg?

Dr. Greenberg: 00:07:25 So that is not something we've observed. So in general, patients test positive for one or the other. While the anti-aquaporin-4 antibody has been identified in patients who have other auto-antibodies, that and anti-MOG have not been co-associated. And if it's worth mentioning, I agree with everything Michael said in terms of the diagnoses and how we separate these out. I think it's important just as a background for everyone to understand how we got to this point because this is very confusing both for clinicians and for families and we're just one

thing to remember is for hundreds of years, all of neurologic diagnosis has been based on symptoms and phenotypes. We see a certain pattern of symptoms, a certain pattern of weakness, a certain pattern of tremors, a certain pattern of walking changes. And we would figure out which part of the nervous system was affected. And that's how we would diagnose a condition. With the explosion in our capabilities to molecularly diagnose a patient, we are realizing that there are multiple biologies that can lead to the exact same symptoms. And so our nomenclature of ADEM, our nomenclature of neuromyelitis optica, our nomenclature of multiple sclerosis is rooted in a history of observation and not biology. And now the two are merging and we are forced with having to improve our language and improve the names and categories we assigned to patients based on their biology, not just based on their symptoms. So while a person with an anti-aquaporin-4 antibody and a person with an anti-MOG antibody can have almost identical symptoms, they have very distinct biologic causes of those symptoms.

Kristina Lefelar: 00:09:34 I see. And so this is really interesting because my mom tested positive for MOG back in November, but she initially was diagnosed with NMOSD. So that brings me to the next question. If a person has NMOSD, but they do not test positive for NMO, what symptoms and criteria should lead a neurologists to test a person for MOG.

Dr. Greenberg: 00:10:06 So, I can come in on what we're doing here in Dallas, and I'm very curious to hear Dr. Levy's thoughts on this, but for anybody who has evidence of central nervous system inflammation, whether it be optic neuritis, brain based events or spinal cord based events, we are screening patients for both antibodies. And the reason for this is back to the phenotype issues I discussed. There is such an overlap between the signs, symptoms and MRI findings between these various conditions that we think in our center the safest thing is to test for both antibodies in all patients. Now, if somebody tests positive for one, we have not been routinely testing for the other because we don't think they coexist. Although an argument can be made we should be screening everyone, but at the outset, we're testing everyone and if somebody has carried the diagnosis of neuromyelitis optica but has tested negative for the anti-aquaporin-4 antibody, we are testing all of those patients for the anti-MOG antibody. And indeed we've been testing patients

who have previously been diagnosed with multiple sclerosis, for both antibodies. And the reason for it is I don't trust the infallibility of our phenotypic diagnosis. I don't trust that just signs and symptoms will be accurate enough for us to know that somebody is negative for an antibody. And so while there are classic presentations of the conditions associated with these antibodies where if somebody calls us and described signs or symptoms Dr Levy or myself or others could have a better than 80 percent accuracy of predicting somebody would have one of these antibodies if we heard a certain history. It's still not perfect. So we're testing almost everybody, if we haven't gotten an answer in the past. Michael. How are you guys approaching this?

Dr. Levy: We are taking a very similar approach. We prefer to err on the side of testing rather than to wait. But I know that there are ophthalmologists at very high profile institutions who say that we are over-testing and yeah, patients with optic neuritis for example, have less than a 1 in 100 chance of being an NMO or MOG patient. And so it may not, you know, it may not be that useful to test every single patient with optic neuritis. That changes if they have a relapsing condition. If they have two optic neuritis attacks or something like that, it's certainly worth it. But then I've encountered a lot of my colleagues who say, well, if their brain MRI is perfect for MS, we're going to treat them for MS. Why should we test all of these patients? We've been treating these patients for a long time and there's no indication that we need to test them, especially if they're doing well. And my response to them is we're still learning about MOG for example, and we know a lot of patients have MRI's that look like MS. So my approach, and I think your approach, Dr. Greenberg, is maybe a little bit more on the modern side of things where our approach is to test as many patients as we can to see the different varied phenotypes clinically that have been out there as we understand more about this antibody and more about this disease. But I would say that a lot of doctors in the community are still relying on their clinical acumen and clinical diagnoses, just like you talked about. And more often than not, they'll make a diagnosis of MS. And it's only when they do poorly, when the patients do poorly on MS medications, they end up in my clinic and then we commence the workup for antibody screening.

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GG DeFiebre: 00:14:10 That's a nice transition to the next question because we've talked about the relationship between MOG and NMO, but I've talked a little less about MS. So does testing positive for the antibodies rule out a diagnosis of MS? Dr Levy?

Dr. Levy: 00:14:29 Well, we're sort of overlapping MS and MOG antibody disease in some respects because we don't know exactly what the immunological target in MS is. We think there may be a myelin component to it. MOG is a protein on myelin, so there may be overlap, a very legitimate overlap biologically and clinically, between MS and MOG. And so, I don't necessarily exclude MS, but what I say is you have a MOG antibody-associated disease. It doesn't necessarily mean that you won't respond to MS medications or have a progressive course like MS. You might because we don't know enough about MOG antibody disease. Now that's in contrast to the aquaporin-4 antibodies where we know that there's a very clinical separation between aquaporin-4 NMO and MS. We know prognostically what that means. We know what treatments you're going to respond to, but with MOG it's a little bit more vague right now. There may be more that we learn in the future where we'll be able to draw stricter lines between MS and MOG. But for now, there is a little bit of overlap in my mind.

Kristina Lefelar: 00:15:49 Okay. So kind of just getting a better understanding of how MOG compares to other diseases. How are the symptoms of MOG antibody-associated disease different from the symptoms of other demyelinating diseases? So, do MOG patients usually fair better or worse after an attack than other diseases?

Dr. Greenberg: 00:16:12 So embedded in your question is actually two separate questions, because on the one hand we're talking about symptoms and on the other we're talking about outcomes and prognosis and I think it's important to separate the two. The symptoms can be basically identical to symptoms seen in multiple sclerosis or anti-aquaporin-4 associated disease Because when inflammation affects the optic nerve, whether it's being triggered by an antibody to aquaporin-4 or an antibody to MOG or whatever the trigger is in multiple sclerosis, which we don't know, the symptom basically looks the same. An inflamed optic nerve is an inflamed optic nerve from the patient experience in the moment of an acute event. So there can be pain in the eye, blurred vision, loss of vision. And so the challenge is recognizing that there are multiple biologies that

		can give the exact same symptom because the symptom is only mediated by what part of the nervous system has been affected. Now the second part of your question is around prognosis, recovery, outcomes and response to therapies; all of the aspects that would be related to the underlying biology. So the initial symptom is only related to what part of the nervous system is affected regardless of biology for the most part. The response to therapy and the outcome is very dependent on the cause of the event. And in general, what we're seeing in our clinic and what I think is borne out in some of the literature is when there is inflammation in the nervous system triggered by an anti-MOG antibody as compared to an aquaporin-4 antibody, the recoveries seem to be better than an equal amount of inflammation caused by an anti-aquaporin-4 antibody. For people who are persistently positive for the anti-MOG antibody, such that they're in a category at risk for relapses, the number of relapses over time appear to be less or more spaced out than individuals with an anti-aquaporin-4 antibody. And I'm very cautious about those conclusions because I think they are very, very preliminary. We're still trying to sort that out. But in general, we think, I think the MOG antibody, has a better prognosis relative to frequency and severity of attacks then somebody's persistently positive for an aquaporin-4 antibody. In terms of response to therapies, the approach to treatment of the two diseases are at this point almost indistinguishable, very similar, both in the acute setting and the long term setting.
GG DeFiebre:	00:19:20	Okay. Thank you. That transitions to the next kind of set of questions which are about treatments. So, I know you briefly mentioned that there are similar to it to NMO, but what if you go in a little bit more detail Dr. Greenberg about what the treatments are and what's the decision process for determining the best course of treatment for someone with MOG antibody-associated disease.
Dr. Greenberg:	00:19:46	So I'll separate it into the two categories. The acute setting a versus the preventative setting and this is where anti-MOG does differ from aquaporin-4 mediated disease. So, in the acute setting, if somebody comes in with acute disseminated encephalomyelitis, meaning brain inflammation, transverse myelitis, meaning spinal cord inflammation, or optic neuritis, meaning optic nerve inflammation, the treatment is the standard treatment we use in immune mediated attacks of those areas which is high dose steroids and often coupled with

plasmapheresis. Some centers will use IVIG, and most studies and guidelines probably place a preference on steroids and plasma exchange over IVIG, but we don't have good head to head data. And so the treatment regardless of cause of antibody is basically the same in the acute setting. After the acute setting, things diverged significantly because there are a group of patients, and Dr Levy mentioned this, who will have an anti-MOG antibody present in the acute setting, but then it goes away and six months later, a year later, they're negative for the antibody. And so far it seems as though those patients are not at risk for the relapses that we see either in patients with an anti-aquaporin-4 antibody or in patients who are persistently positive for the anti-MOG antibody. So, after the acute setting, what we're doing in our clinic is retesting patients 6 to 12 months later to see if they are persistently positive for the anti-MOG antibody. And if somebody is persistently positive for the anti-MOG antibody, then we are having a conversation with them about whether or not they should go on a preventative therapy. Now, the preventative therapies we use in our clinic are somewhat identical to what's used in anti-aquaporin-4 mediated diseases. They're immunosuppressants, although there is data out of the UK to suggest that IVIG might be helpful for prevention. We have not seen that to be the case with anti-aquaporin-4 mediated disease. And so, if somebody's persistently positive, we are offering therapy. Now, the interesting part about this biologically, and the part that I have been unable to get a good answer for from folks is to my knowledge, patients with an anti-aquaporin-4 antibody who come in with optic neuritis or any other symptoms outside of the setting of treatment, they don't revert to a negative status. We don't know of this phenomenon or at least to the degree we see it in anti-MOG where people have the antibody transiently and then it just goes away. They seem as though they're persistently positive and yet there's a group of anti-MOG patients who will have the acute event and then the antibody goes away. And so if somebody comes in with a single event and aquaporin-4 positive, we don't wait to retest them. We recommend going on preventative therapy at that moment.

Kristina Lefelar: 00:23:04 So we got a question about treatment, and it is, "What evidence is there that people who have failed on a disease modifying drug are unlikely to get much benefit from staying on it?" Dr. Levy?

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Dr. Levy: 00:23:22 A lot of that comes from our experience in NMO, aquaporin-4 NMO, where we tracked patient outcomes after attacks and recognized that if a patient relapses on CellCept or Rituximab, that they're likely to relapse again on the same therapy. So that history comes from the aquaporin-4 seropositive patients. We don't know if that's the case for MOG. We're hesitant to find out. We are nervous. With each relapse, the damage is being done. So our tendency is to say, "Well okay, if you have MOG antibody disease and you relapsed on Rituxan, we have other options available, let's utilize those". But if a patient said, "Well this attack was so minor, I was stable for so long on whatever medication it was, I'd like to give it a second chance". I think there are some situations where it is reasonable to stay on the medication. I think our tendency is just to not take the chance and if there are other available options, probably use them.

GG DeFiebre: 00:24:34 Okay. Thank you. Dr. Levy, do you know of any stem cell treatments are being considered for MOG patients like they are for MS patients?

Dr. Levy: 00:24:46 Well, there's a lot of different types of stem cell treatments that are being considered for MS. There are some that intend to impact the immune system, so it's another preventive therapy. I think the question you're asking is, "Is stem cell therapy as a regenerative option to try to improve neurological disability after attacks and damage in central nervous system". And those, that stem cell approach, uses neural stem cells, either directly injected or delivered in another way to try to regenerate or restore function. MS studies like this, with stem cells, are not being done in the US right now. There's a one private clinic in New York I know that are doing them the sort of deeper service option, but there are a lot of trials like that going on worldwide. I think my last count, there were 10 studies in MS with a stem cells, mostly in China and India and a lot of other countries. And so if we're going to learn from them, and there's also one going on in China for NMO. We're going to learn from that as well. There aren't, as far as I know, any stem cell studies being done for MOG antibody disease. But I would say that most likely around the world MOG antibody patients are being diagnosed with MS anyway. So it's certainly possible some of those patients could get mixed up in the trial for MS.

Kristina Lefelar: 00:26:21 Thank you. So, we get a lot of questions about insurance for the treatments. So, the next question is how should the doctors

diagnosed and code the treatment for insurance approval so that the patient could get the quickest possible approval? Now my mom says that the way that they code at Hopkins where she gets the treatment is really excellent. So, do you just want to kind of talk about that and what that process looks like?

Dr. Levy: 00:26:53 Yeah. I wouldn't say I'm the expert at this. Maybe if I code it, there's an office here, an office staff that maybe re-codes it and figures out ways to get treatments that your mom needs. I don't know exactly. I would say I've heard that if you prefer to use Rituximab that you code for NMO, and that if you prefer to use something like IVIG, then you would code for ADEM where it's more likely to be used, and if you're gonna use CellCept, then it doesn't really matter. There are always MS options. I think there's no diagnosis code for MOG. So if you give a diagnosis code for MS, you have access to MS medications like B-cell depleting therapies. So I think there are kind of ways around the issue for MOG antibody patients, but they take a little bit of, you know, office help from people who have experience with insurance companies.

GG DeFiebre: 00:27:57 Okay. And Dr Greenberg, do you have anything to add to that?

Dr. Greenberg: 00:28:02 Yeah, I think in general what we've been doing is still using the diagnosis of neuromyelitis optica spectrum disorder, because I think it's fair to use while the field figures out the best title to give this. And since the therapy is that we use in neuromyelitis optica are pretty much synonymous with the anti-MOG syndrome, we have not been running into issues with getting things covered.

GG DeFiebre: 00:28:33 And then we've talked a little bit about the significance of antibody levels over time. So if we could just go into a little bit more detail, we have a few questions about it, then I'll try to kind of summarize together. So one, is it possible that someone can lose the presence of the antibody in their systems with or without treatment? How often should someone be tested to see whether the disease is going into remission and then, you know, how long after an initial tack can you test positive for MOG? Dr Greenberg?

Dr. Greenberg: 00:29:12 Well, so this gets to this phenomenon of being transiently positive. So what we know is that in an acute setting, people can be positive for the antibodies and then it naturally

disappears or disappears because of the therapy they got in the acute setting. Either way, as long as they remain negative, to my knowledge, we are not seeing relapses in those patients or to any significant degree. Which is different than the individuals who 6 to 12 months or more after an acute event test positive for an antibody, those individuals seem to have a significant risk of relapse in the future. Now it may be years before the relapse, but there is a significant risk of a relapse. And so, what we do, that the key data point for us is whether or not there's an anti-MOG antibody 6 to 12 months or more after the initial event. So, if somebody comes to me and they had an event two years ago and I test them now and they're positive, that's a significant data point to us. If they were positive two years ago and now without any therapy, they're not on immunosuppression, they're now negative, then we presume it was a transient positive at the beginning. Once somebody is in the category of a persistent positivity, meaning they're positive 6 to 12 months or more out from their event - they have a single reliable, positive test - then the decision to treat or not treat or the monitoring of a treatment is no longer dependent on the antibody tests in our clinic, because if I put somebody who's been persistently positive for the antibody on immunosuppression and they revert to a negative status, I assume that's just because of the treatment and we keep the treatment going. Likewise, we have not yet associated a change in amount of the antibody circulating with a response to therapy and so repeating the test over and over again isn't changing how we're managing those patients, so we're really just looking for a test 6 to 12 months out from the acute or longer that's positive and then discussing risk of relapse and need for possible therapy.

GG DeFiebre: 00:31:39 Thank you. And Dr Levy, do you have anything to add about that?

Dr. Levy: 00:31:45 Yeah, there was one observation that we made when we first started testing MOG antibody in our lab and that is that when we test the patients who were physically in the hospital with a relapse, you seem to have a lot more antibodies. Then when patients came into the clinic and remission doing well and we tested them there, they seem to have lower levels on average and we don't see that with aquaporin-4, but we seem to find that phenomena true with MOG. And so that brought up the question, "Well, what does that mean? Is it true that the

antibody level goes up with the attack? Does it happen after the attack starts? Does the antibody level go up first? What was the implication? Can it go up without an attack?" And so now we're very curious about that because it's not true in aquaporin-4 NMO. And it seems to be different in MOG. Does this indicate something that's different about this disease immunologically? It would be great if we had, you know, every MOG patient out there getting an antibody level done every month. I'm just throwing a number out there in terms of how often we would like to see the antibody level and how it changes over time. And we'd love to be able to see a level right before an attack and during an attack and after an attack to really understand what those levels mean because I think it would shed light on the immunological process.

Kristina Lefelar: 00:33:18 So, if a neurologist has a new MOG patient, what should they know about the disease that will help them better care for their patients?

Dr. Levy: 00:33:35 I think it's probably wise to consult with one of our centers that manages a patient actively because the field is changing so quickly. We're just really learning, still learning a lot about the disease that it's worth every neurologist out there who makes the diagnosis by blood test or however else they make it, to just reach out, maybe get one consultation, maybe a phone call with us, get caught up on the basics. I think if the doctor is comfortable for treating MS then they can quickly learn about the unique features of MOG and know what to look out for and so I think it's just worth the least a phone call to one of us. It's not a referral.

Kristina Lefelar: 00:34:25 Okay. And Dr Greenberg, do you have anything to add to that?

Dr. Greenberg: 00:34:29 No, I think Mike's right. I think this is an evolving area. I think we're going to be handling some of this differently a year from than we are now. And we haven't mentioned one part of the history here that's interesting and potentially important. We have known about the anti-MOG antibodies for 30 years. So they were identified in patients with ADEM and optic neuritis and transverse myelitis 30 years ago. The issue was the assay that was used to identify the antibodies was very unreliable and inconsistent. We were getting different results from different labs on the same blood sample. So I'd send my blood to lab 1 and it would say positive and lab 2 would say negative and back

and forth and back and forth. So the field didn't know what to do with the antibody and it wasn't until just a couple of years ago that a group in the UK essentially fixed the assay and sorted out why we were getting inconsistent results. And now that the blood test works, all of a sudden, things are starting to make sense in terms of, what's happening to patients over time and how they respond to therapy. And so it's an example of how as the science improves and technology advances our ability to care for patients improves and our ability to advise patient improves, but we're going to be better at this a year from now than we are now. And so for practitioners who are just having their first patients with these antibodies, checking in with a specialty center and then remaining in contact is probably a worthwhile thing because, this podcast next year might be different.

GG DeFiebre: 00:36:16 Right, okay. Thank you. And then kind of flipping that question to the patient side, if someone has tested positive for what should they know about the course of their disease that will better help them be able to advocate for their own health, especially during this attack? So, you know, if someone is worried that they're having a relapse at the time, what's the best way for them to avoid permanent, new damage if they suspect that they're currently having an attack? Dr Greenberg?

Dr. Greenberg: 00:36:48 So, it's always important to be in touch with your healthcare providers. If you're ever having new symptoms that you're worried might be an attack, in the setting of symptoms what healthcare providers will do is trying to determine whether in fact there is new inflammation or if we're dealing with, what's referred to as a pseudo-exacerbation, whether we're having symptoms without new inflammation. Sometimes it's easy, sometimes it's hard. But if a healthcare provider and you both determined that this is indeed new inflammation, then we recommend a intervening with high dose steroids. Whether they're administered through an IV or through pill isn't as important as the dose and making sure it's a high dose. And then from there, the big decision is whether or not the attack, based on its severity and/or response to steroids would require further treatment, specifically plasmapheresis. And so there is no one answer on whether or not, we should plasmapherese. It depends on not just what symptom of person is having. It depends on how severe it is, it depends on response to steroids and it depends on what their history was. So for example, if a

patient has had prior attacks such that their left eye is basically blind and they're coming with right eye symptoms, I will do plasmapheresis sooner and earlier in the course without waiting than I would if the left eye was normal because we can't afford a damage at all to the right eye. And so it is a case by case decision, but there needs to be a discussion with healthcare providers on why or why not certain therapies are being used.

Kristina Lefelar: 00:38:44 Okay. So a lot of patients want to find resources online or research that will kind of help them be able to advocate for their own health and take matters into their own hands and just get a better understanding. So, are there any research studies targeting MOG antibody-associated disease? And how do patients find out about these studies? Dr Levy?

Dr. Levy: 00:39:09 There are no studies that I know of currently for any treatment, but we're always looking for MOG patients to enroll in biorepository so we can follow them over time and learn more at the natural history of the disease. I think as an advocacy group, the TMA has a great opportunity here to sort of be the home for MOG antibody disease, to put stuff on the web and in print that can help patients and family members understand more about the disease certainly with our help. But it's kind of a new phenomenon right now and you know, we're always looking for help - volunteers - a couple of patients of mine who've offered to help put things together for other patients and I think that's the right approach.

GG DeFiebre: 00:40:00 Okay. Thank you. And then we've gotten some questions about, alternative therapies like changes in diet or supplements or something like CBD oil or medical marijuana. Is there any sort of research or information about, these sort of alternative therapies in the context of MOG? Dr. Greenberg?

Dr. Greenberg: 00:40:29 Unfortunately, no. The literature around diet and nutritional supplements for all of these conditions is a completely lacking and while we - with one exception, I think it is still safe to say that the data around vitamin D and autoimmunity suggests that maintaining an adequate vitamin D level reduces the risk of recurrent autoimmune attacks. Outside of that, I think the literature is scant at best. We are launching - we have launched a study here looking at the microbiome of patients with these conditions including anti-MOG, as a way to set the stage for future diet and supplements intervention studies to see if as

		you change your diet, do you change the bacteria living in your gut? And in turn, does that change the course of the disease? But it's in just the initial stages of getting launched
Kristina Lefelar:	00:41:33	In terms of the research, there was a Harvard study where there was evidence that there had been gut flora linked with MS. So, is this a possible area of study that will be explored with MOG and other demyelinating diseases?
Dr. Greenberg:	00:41:51	Yes. And we're not the only ones. We're doing it here in Dallas, but there are multiple groups looking at a gut bacteria, the San Francisco group years ago, published on certain bacterial species relative to patients with anti-aquaporin-4 antibodies. This is an area that is going to expand significantly over these couple of years as a way to try and understand what drives these various autoimmune disorders.
GG DeFiebre:	00:42:26	Okay. Thank you. We've gotten a few questions in during the podcast itself, so one person asked, "If someone has MOG-positive optic neuritis, are they likely to develop transverse myelitis later?" Dr Levy?
Dr. Levy:	00:42:48	It's certainly possible. What we've noticed about MOG patients is that about two-thirds of attacks are optic neuritis, and the other one-third is everything else and that includes transverse myelitis. So yes, there is a chance of that happening. The transverse myelitis can be long just like in aquaporin-4 positive NMO. It can also be short, and so there's a little bit more evidence that MOG transverse myelitis tends to affect the lower part of the spinal cord which innervate things like the pelvis, bowel, bladder, sexual function as compared to aquaporin-4 NMO, but I think that there's still significant enough risk that a patient with MOG antibody disease who has numbness or weakness or tingling or any symptom that can look like to the spinal cord, definitely get checked for transverse myelitis.
Kristina Lefelar:	00:43:48	Okay. So another question that we got in is "My 19 year old was diagnosed with ADEM and August of 2017 and was not tested for MOG. I recently asked for this test and the doctor told me they only test it if the patient is present with NMO. She's willing to test him but thinks it's unnecessary". So what are your thoughts on this situation?

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Dr. Levy: 00:44:15 Well, I think it's kind of like the situation where you have an MS patient or an optic neuritis patient where there's no clear indication yet have a relapse. So, you know, that links back to what Dr. Greenberg was saying about doctors really depending on their clinical judgment than the phenotype of the disease to make a diagnosis rather than the molecular, the antibody and biochemical testing. And, I think there's no right answer. I think there's just different ways of practicing. If I had an ADEM patient or an ADEM child, I'd still want to know if there was a MOG antibody. Not that I wouldn't necessarily act on it. If there's a persistent MOG antibody that's present and the, you know, if a patient has a MOG antibody that's diagnosed and tested positive at the time of ADEM and again later, that would indicate to me some concern. Maybe closer observation would be warranted to make sure that if the patient relapses, we're right on top of it, and we treat it. And I do have some patients who tested positive for the MOG antibody and said, "I want to start treatment. I don't even want to risk having MOG antibody disease. I'd rather be treated right now even without knowing for sure". And that's a conversation I'd be willing to have as well. So I think there are a lot of different ways of practicing and approaching this issue and I think a lot of it just depends on what your experience treating ADEM and MOG and NMO.

GG DeFiebre: 00:46:04 Okay, thank you. And we have another question that's a very kind of specific question, but maybe will apply to some of the listeners. So this person's daughter was diagnosed with ADEM and PREES on May 5th. She was in the hospital 21 days, had seizures and went blind. She's home and still on steroids and is positive for MOG. Once she gets off the steroids, her mom is very worried that this is going to happen again. Are there any, you know, what should be done to kind of prevent these future attacks? Dr Greenberg?

Dr. Greenberg: 00:46:43 So, we're really sorry to hear about kids who are going through severe events with this, and I completely understand the concern. In general, in our experience for patients who have had acute disseminated encephalomyelitis, kids who had it, who are treated with steroids and are then on a taper, as the taper slowly goes down, we are not seeing significant numbers of early relapses. And what we do in this setting is we focus on rehabilitation and recovery with a plan to repeat the MOG antibody tests in any child who has had ADEM and had a positive antibody. We repeat it six to 12 months later to see if

it's still positive. If it is not still positive, we feel as though those children are at a low risk for recurrences. If we find a child who is persistently positive, then we have a discussion of a long-term preventative therapy or not. It is worth noting this is a controversial area in terms of should we put every child with a persistently positive antibody on a long term treatment and different practitioners have different points of view on this. I do not think the field has conclusively answered it.

Kristina Lefelar: 00:48:06 Okay thank you. And another question from someone: "My son is MOG positive. He had his first optic neuritis attack in September of 2017. He is still positive for MOG 10 months after his initial diagnosis. He is not on any preventative medications. Is that something we should be looking into or should we just wait and see"? Dr Levy?

Dr. Levy: 00:48:27 That's exactly what we've been talking about. These are cases that we don't know the answer to. There is some indication out there that a persistently MOG positive patient will relapse. I think some of it depends on their age. We know that kids turnover their immune system, so to speak, a little bit better than an older patient. So if an older person has an ADEM event and then is persistently positive for MOG, that might be a different conversation from a kid who had ADEM and is positive for MOG for a year or two. But actually we don't have the answer and it's a discussion between parents and the practitioners about that cost and the benefits of using preventive medication and how long we would use it for. There is some indication that even patients who have relapsing MOG disease who were treated for for a significant period of time who go into a really long-term remission can actually lose the antibodies over time. And maybe that means that the whole disease turns over as well. We just don't know the answers to these kind of questions. They're more like conversations and at the end of it, patients, they have different wishes and may come out of the clinic sometimes on therapy, sometimes just with close observation,

GG DeFiebre: 00:50:03 Thank you. And then, is there any information on the risk of developing epilepsy for MOG patients who have seizures and encephalitis? Dr Greenberg?

Dr. Greenberg: 00:50:14 So, we have seen patients in a setting of their MOG antibodies both present with seizures or have seizures as a complicating

feature of their event. In general, if somebody has not had seizures or recurrent seizures, we do not put them on seizure medications just because they have the MOG antibody and indeed the rates of seizures is still quite low. But it is one of the known events that can happen early in the course of the disease with inflammation. But if somebody just has had an optic neuritis or transverse myelitis and their anti-MOG positive, we do not see a concern with developing epilepsy, we just monitor.

Kristina Lefelar: 00:51:02 So is an MRI always necessary for diagnosis of relapse? Dr Levy?

Dr. Levy: 00:51:11 It's not necessary per se. There are some clues that either with optic neuritis and transverse myelitis that we can bank on. For example, if a patient has never had a transverse myelitis attack and they come in with weakness in the arms and legs. I wouldn't withhold treatment to get an MRI. I think that's pretty obvious attack. Similarly if the patient had optic neuritis only in the right eye with MOG antibody and then has vision loss in the left eye, in the opposite eye, I don't think you necessarily need an MRI to start treatment. We usually get an MRI anyway just to see what we're dealing with to follow long term. But the cases where we get MRIs are where we're not quite sure the patient's having a relapse or a pseudo relapse and we want to see more objective evidence. And so that's when we usually get the MRI's.

GG DeFiebre: 00:52:08 Got It. And then just to go into kind of more specifics about treatment. What's the standard timeframe or schedule for treatments that someone can expect with medications like Rituxan and CellCept and IVIG or even steroids? Dr Greenberg?

Dr. Greenberg: 00:52:29 I'm sorry, in the middle, I didn't hear. The expected time course for response - is that it?

GG DeFiebre: 00:52:34 No. Just like the schedule of treatment. So how often does someone get a Rituxan infusion or CellCept or how often does someone get IVIG treatments?

Dr. Greenberg: 00:52:43 So I think the course for this is basically the same as for others. For people who are taking CellCept for prevention, it's an oral medication that we dose twice a day, and the targeted dose in adults, the average is a thousand milligrams twice a day. In children it can be a little different. In Rituximab, the treatment protocol is the same in anti-MOG as it would be in other

conditions. Although it's worth noting there was some variability around the country and how people dose it. In our center, for adult size children and adults, we use a thousand milligrams every six months. Then we looked to make sure that it's been successful at depleting B-cells and that a person remains B-cell-penic, meaning their B-cells remain absent for the six month duration. For some people we have to dose at five months instead of six because the cells start to grow back. IVIG gets trickier if you're using it for a long-term prevention. If you look at other autoimmune diseases, whether they be of the brain and spinal cord or of the peripheral nervous system, there's a lot of different regimens that are used. Most of them use either a monthly, or sometimes spaced out to every eight or every 12 week dosing. But in the setting of autoimmune diseases that affect the central nervous system, most groups will use a monthly dose of IVIG as a preventative, and that single dose can be split up over multiple days in order to avoid side effects like headaches, nausea or vomiting. And so, that dosing has a lot of variability around the country.

Kristina Lefelar: 00:54:37 Okay thank you. And our next question is, "I was diagnosed with anti-MOG last summer. My second cousin on my mother's side was recently diagnosed with NMO. So is there a family connection there?" Dr Levy?

Dr. Levy: 00:54:54 Actually, I'll let Dr Greenberg take this one because maybe he can talk about his recent genetic finding in aquaporin-4 as well.

Dr. Greenberg: Okay. Well, so we can approach this one together because between your, the genetic study of the TM side and the NMO side, I think what we're all learning is that there are genetic risk factors for autoimmune disease in general. And so we will see in families where somebody has one autoimmune disease that there may be others, but of different kinds. And then what we found in our study for neuromyelitis optica was for patients who have the aquaporin-4 antibody, there were two genes that if there were certain alterations in them, increased the risk significantly and like most conditions where genetics are a risk for the disease, but the disease isn't caused by a genetic mutation, we find lots of patients who have the condition, whose genes look totally normal. And then we find a proportion of the population that have certain changes in them that are statistically different than the general population, meaning this variant of a gene just happens to be much more common in

		individuals who develop the disease. And so when we see families where one person has one diagnosis, but whether it be multiple sclerosis or neuromyelitis optica, and then somebody else gets a diagnosis of an autoimmune disease affecting the central nervous system, our theory is that they just share a general risk for autoimmune disease. But we always, at least in our clinic, like to investigate the accuracy of the diagnoses to make sure that, somebody who was told that have neuromyelitis optica has been screened appropriately because we are always on the lookout to see if there are families where any of these conditions with the same auto-antibody run together. And today for aquaporin-4 there've only been a few families with multiple members affected by the aquaporin-4 antibody. To my knowledge, and Mike, I don't know if you know of an exception, I am not aware of a family described yet with multiple individuals having the anti-MOG antibody. I haven't seen one and I haven't heard of one. I don't know if you have.
Dr. Levy:		No, that's about accurate then. I'd be very interested to hear. And anybody on the phone listening in has family members with both people having MOG antibodies, we'd be very interested in studying that family.
GG DeFiebre:	00:57:46	Okay thank you. And we are almost at the end of our time, so I just wanted to end with a question about research and kind of hope for the future. So how has the discovery of MOG in patients changed the roadmap of research not just for MOG, but that being conducted for demyelinating diseases in general? Dr Levy and Dr Greenberg as well?
Dr. Levy:	00:58:08	I'll go back to what Dr Greenberg was saying about using molecular markers to identify diseases. These are antibodies and other things that we can use to really understand what the immune system is targeting so that we can then go back and try to fix, really upstream, so we can go to the immune system and say, "Okay, why are you attacking that protein specifically?" And then try to correct that problem. And that I think has a lot of implication for diseases where we think that there's one or two targets that we can re-educate the immune system on. This phenomenon is called tolerization. And I think that's really where the future of modern immune neurology is going.
GG DeFiebre:	00:58:52	Dr Greenberg, do you have anything to add?

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Dr. Greenberg:	00:58:54	And what I would add is I think Dr. Levy is right. I think as we understand the biologies, we can start to target patients biology without global immunosuppression. We published a paper here recently with a mechanism to clear the anti-MOG antibody from a mouse while leaving the rest of the immune system intact and so these technologies are in development, but they're only helpful if we know the actual antibody causing the disease. So, in multiple sclerosis, we don't know it. But as we find patients with these very specific syndromes and very specific antibodies, we will get to a place where we can prescribe a very selective therapies that leave the normal part of the immune system perfectly functioning and provide a much safer a treatment option to patients.
Kristina Lefelar:	00:59:50	Alright. Well thank you both so much for being here. This podcast is recorded and will be on the TMA website in the resource library.
GG DeFiebre:		Yes. And we hope to you know, as you both mentioned, we're still learning about this condition. So, I'm sure we will do a podcast in the near future as we learned more. So thank you both so much and thank you Kristina as well.
Dr. Greenberg:		Yes, thank you.
Dr. Levy:	01:00:21	Thank you.