Living with ADEM, AFM, MOGAD, NMOSD, ON and TM

You can view this presentation at: youtu.be/sZZK2OgY3rE

Krissy Dilger: [00:00:00] Thank you, all, for joining us today, and we're getting ready to hear from Dr. Michael Levy for a talk on living with ADEM, AFM, MOGAD, NMOSD, ON and TM. Dr. Michael Levy is an Associate Professor of Neurology and Research and Director of the Division of Neuroimmunology and Neuroinfectious Disease at Massachusetts General Hospital and Harvard Medical School.

[00:00:33] It can be frightening and stressful to deal with the unknown after being diagnosed with one of these disorders, including how these diagnoses impact life years after diagnosis. During this presentation, Dr. Michael Levy will address the long-term aspects of living with a rare neuroimmune disorder. Thanks so much, Dr. Levy, for joining us, and just as a reminder to everyone, you can submit questions in the Q and A. And there's also an option for closed captioning. If you have any questions just feel free to enter in the chat and one of us at SRNA will help you. Over to you, Dr. Levy.

Dr. Michael Levy: [00:01:09] Thanks, Krissy. Well, hello, everyone. My name is Michael Levy. I'm a neurologist at Massachusetts General Hospital, and I have a lab at Harvard Medical School where we develop new treatments for these diseases. And, what this small group presentation is about, this breakout session, is really what it's like to live with these conditions, two years or more out. So, you've had your onset of disease, two years ago. You've been dealing with the consequences, relapses, symptoms, doctor visits, everything, and we're going to pick up at the two-year mark and go forward from there.

[00:01:55] Now, for each of you, I think that there may be a particular individual circumstance, of course, that it doesn't necessarily apply to everyone else. I mean, if you just look at the title slide here, you'll see we're representing ADEM, flaccid myelitis, MOG, NMO, optic neuritis, transverse myelitis. So, there isn't going to be necessarily one key pathway for you and, similarly, I don't know how you're going to necessarily end up. But the purpose of this presentation is, I just have a few slides, is really just to get a conversation started. So, let me just jump in and, let's see here, I'm trying to figure out how I advance slides. Okay. Okay. I'm going to do it this way. Okay.

[00:03:01] So, the idea behind what happens in your future really depends on what disease you have. Okay. So, here I'm showing you examples from two diseases, multiple sclerosis and neuromyelitis optica. And, after I explain these two conditions, then we can apply them to MOGAD and other conditions.

[00:03:28] So, look on the left side, see the NMO chart there? What this represents is how disability accrues over time, where each red bar is an attack and the bar graphs above it represent the increasing disability. Let's say you have a transverse myelitis, develop some right leg weakness. You'll recover partially, hopefully, but your right leg is always going to be more vulnerable than your left. Then you have a second attack and a third attack, you're going to accrue these disabilities over time.

[00:04:07] What we think happens in NMO is that all of the disability accrues with each attack and that, in between attacks, you don't, you shouldn't really get any new disability, with exceptions for pain and spasticity, which is really part of the healing process, but can feel more disabling than the attacks even. So, that's NMO.

[00:04:31] And, if you look at the right side of the screen, you'll see the picture for MS, or multiple sclerosis, where these attacks also occur. They don't tend to be as severe and they don't tend to leave behind a severe disability, but there's also a background disabling process overlapping, which means that, even in between attacks, patients with MS might accrue more and more disability.

[00:04:58] Now, MOG seems to fit more of the NMO picture. And then, we have monophasic conditions like flaccid myelitis, or monophasic optic neuritis, or monophasic transverse myelitis, where one attack occurs and then that's supposed to be it. You make your recovery, which happens in the first 6, 12, 24 months, and then the expectation is that you're not really going to get a lot worse after that. That's the expectation.

[00:05:33] Some people continue to get better, there's a component of rehabilitation that tries to use the circuits that are still working to overcome the circuits that are damaged. So, there is a possibility to continue to improve, even well beyond the first 2 years. Get to the next slide here.

[00:05:57] Most of my data, you'll find, comes from NMO, and why is that? It's because that's where the data is, that's what data has been, that's what studies have been funded to do. But, again, they are applicable. This is a picture of where we are with NMO, for example, regarding mortality rate. We all know that these diseases can be fatal at their onset and with each relapse, there's always a concern that the disease is going to hit a breathing center or swallowing center which is vital for life.

[00:06:34] Then, we have about 18 percent of our patients have a permanent visual disability, meaning 20/200 or worse in that eye. 23 percent are wheelchair bound and can still transfer, in some situations, but I just want to emphasize with these numbers that even a single attack can be disabling or the disability over time can be disabling. It really just depends on what your, the course of your disease looks like.

[00:07:09] Then beyond motor and visual disability for all of you, there's also the psychological trauma of having to deal with relapses, having to deal with doctor visits, with the uncertainty, with what it's like to live with these conditions. So, here I have an example of levels of anxiety, pain, disability with usual activities, problems with self-care and mobility. And for NMO, it far exceeds the numbers that general Americans are dealing with, with their everyday lives, on average. So, NMO is much worse than the average.

[00:07:54] And then, mortality rates, I mentioned, are mostly related to attacks in the brain stem and the upper cervical spine. Now, for most of you who are on this, in this small group session, where you've already been dealing with your disease for at least 2 years, most of you should be on a stable therapy that will prevent any more attacks and hopefully prevent any future morbidity and mortality.

[00:08:25] For those of you who've had attacks in the past and you're wondering, "What are my changes for

recovering from each individual attack?" The numbers aren't great. Okay. MOG is the one exception to this rule. This is what, this is probably, on the slide here you'll see the numbers for NMO, which are the worst, okay? NMO has the hardest hit relapses, and the recovery is the least. If you have transverse myelitis, which is the pie on the left, your chance for complete recovery with best therapy back to where you were before is only 17 percent. And with optic neuritis, the chance of recovery is 32 percent back to where you were at baseline.

[00:09:12] Now, there's partial recovery, that's what the blue part of the pie is indicating, and so it's not like you're going to get any recovery. For MOG, the interesting thing is a lot of people tend to recover. It's not totally completely, it's partial, but it's much better than NMO. And then for AFM, there tends to be a very severe phenotype and the problem with AFM is the poor recovery process. Now, it tends to be monophasic, so there's only one severe attack, but that attack can be very disabling.

[00:09:50] ADEM is on that sort of MOG spectrum where there's a very severe event that happens at the onset with seizures and change in mental status. It's very frightening in kids. Can be vision loss, certainly mobility problems, and bowel and bladder dysfunction, but ADEM tends to recover well. Not totally back to normal, but 2 years out, what you'll find is that they're walking and talking and seeing, but they may still have problems in school, problems concentrating, problems focusing and getting good grades again, maybe some emotional problems as well.

[00:10:31] So, those are the only slides I have and, really, I just wanted to set the stage for people to send in their questions and see if, especially if your question is relevant to everyone regarding how you expect to live with these disabilities in the long-term. I mean, there are many issues relating to bowel and bladder function, and pain, and mobility and, again, relapses, that I'm sure everyone has individual questions about. So, I'm opening the floor now to people to send in their questions. And, if you don't send me any questions, then I'm going to just start talking off the top of my head.

Krissy Dilger: [00:11:25] Hi, Dr. Levy. Someone did ask, can someone have a reoccurrence of optic neuritis in the same eye with an NMOSD diagnosed after transverse myelitis?

Dr. Michael Levy: [00:11:38] Yes. So, the question as I'm interpreting it is, if you've had optic neuritis related to NMO, let's say it was in the left eye, can you have a relapse of optic neuritis in that left eye again? The answer is yes. In fact, there was an interesting study out of South Korea that looked at what are the chances after optic neuritis that it's going to be the left eye or the right eye, and is there some sort of explanation for that? And, the only thing they could come up with was it was more likely to be in the same eye on the second attack.

[00:12:16] So, if your first one was left optic neuritis, your second one is more likely to be, slightly more likely, to be left optic neuritis again, rather than right-sided optic neuritis. But it seems to be almost random, I think, when you look at the larger population and you try to make predictions. You can't really predict accurately in any individual, and so, but, yeah, if you've had one attack, it doesn't preclude you from having another attack in the same spot.

Krissy Dilger: [00:12:48] Another question we got is, is it best to go to a center or doctor specializing specifically in one's condition? This person goes to an MS center, but they have TM, and is wondering if it is worthwhile to see a TM specialist in hopes of improvement?

Dr. Michael Levy: [00:13:07] I think that depends on what you're trying to achieve. So, let's say you've had transverse myelitis and you really want to focus on rehab. Well, I think the MS rehab centers are wonderful.

MS patients have mobility issues as well, and sometimes have more resources for good physical therapists that are focused on MS, and they may be able to really help you get back on your feet, or strength training, or whatever you need.

[00:13:37] Now, there may be other issues related to TM that you want to see a TM specialist about. For example, if you are worried about recurrence, MS specialists may just throw you on the latest MS drug, but maybe there's something specific to your condition that you want to discuss with a TM expert. For that, I would definitely recommend going to see an expert.

Krissy Dilger: [00:14:07] We also had a question, what are the therapies for MOG antibody disease? A big question, but.

Dr. Michael Levy: [00:14:18] It is a big question, but I'll give you the short answer. That there are no FDA-approved treatments for MOG. And, what we're doing is basically just trying different things until something seems to work. And, what we've hit on, a couple of ideas so far, IVIG, intravenous immunoglobulin, which works well for ADEM, and so, by extension, we think it should also work for MOG, does seem to work. And we have data mostly in children, but in some grown-ups as well, that IVIG could be useful not just as a preventive agent, but also as an acute treatment agent, and so that's something that we're developing.

[00:15:02] Now, there are other treatments like CellCept that also seem to help. CellCept and azathioprine, or Imuran, are drugs that are always thrown at an autoimmune disease in the hopes of just suppressing the immune system. And in the case of MOG, it does seem to be, those drugs do seem to be helpful, but I don't have numbers to quote you in terms of the chance of remission or how effective it will be.

[00:15:28] One thing I do want to point out is that last Friday we did launch the first clinical trial in MOG antibody disease. It's a drug called rozanolixizumab, short name is rozimab, and you can Google this or go to clinicaltrials.gov, and read about the eligibility criteria. Our hope is that we can prevent relapses with this drug, which comes in a patch form, it goes in your, on your body, it diffuses in 15 minutes under the skin, and then you just take the patch off. And it's weekly, it's done every week. We're hoping that that prevents relapses in MOG.

Krissy Dilger: [00:16:02] Thank you so much. Unfortunately, I think we might be, oh, wait. We're not at the end of our time. Sorry about that. Okay. We have a question from someone who's asking, if someone has been diagnosed with TM or ON, how should they be thinking about their diagnosis over time? Specifically, is transverse myelitis always a one-time event? Should one keep getting MRIs, and how often?

Dr. Michael Levy: [00:16:37] The way we think about it is it's either a one-time event or it's a relapsing condition. So, if you have one attack of transverse myelitis and, say, 5 years pass and you've never had another attack, and you're not on any immune suppressing therapy, the thinking is that that was most likely a one-time event. The immune system made a mistake. It may have been in reaction to a vaccine, or a virus, or other infection, or some sort of immune stimulus that triggered the attack and the immune system apologized after the damage was done, apologized and left, and said, "Okay, we're not going to do this again." That's the monophasic, one-time transverse myelitis or the monophasic, one-time optic neuritis.

[00:17:23] Then, if it's not that, and if you've demonstrated that you have a relapsing disease, you will have an attack again. And most likely, it will happen within the first 3 years. If it's multiple sclerosis, the average is once every year or two, and NMO, as well, once every 12 to 13 months. So, we expect that if you have one of those diseases, it will relapse. And so, that's really how we, that's the first division is, one-time attack

or relapsing disease. If it's relapsing, we want to know what it is because MOG seems to respond to some treatments and NMO to others. MS is a whole different category. So, then you have to go about trying to figure out what you actually have.

Krissy Dilger: [00:18:08] Thank you. So, we are getting a lot of questions. So, I'll do my best to hopefully get to as many as we can. Okay. The next question is, what are the chances of having optic neuritis if I've only had four TM relapses over 28 years?

Dr. Michael Levy: [00:18:28] That's a good question. It depends on the disease. If you have multiple sclerosis, your chance of having optic neuritis is somewhere around the order of 40 to 50 percent, even if all of the previous attacks that you've noticed are in the spinal cord. If you have NMO, it's probably age dependent. The younger you are, the more likely you are to have optic neuritis. The older you are, the more likely you are to only have transverse myelitis.

[00:18:55] And, if you have a recurrent transverse myelitis, those conditions seem to be confined to the spinal cord, almost by definition and not really involved in other parts of the central nervous system. And so, it really depends on what your disease is. And, another thing I will say about the 28 year question, is that, while the average is once every year, once every 2 years, if you're on therapy to suppress the immune system, then we expect that to prolong the interval between attacks or, ideally, stop attacks all together.

Krissy Dilger: [00:19:34] Yeah. Thank you. Someone asked, how many people are diagnosed with TM that later end up having NMOSD or how often does that occur, or what are the chances?

Dr. Michael Levy: [00:19:47] That's an evolving question, okay? So, when I started training with Dr. Kerr, the answer was only one out of five are going to have NMO or something like that. Now the numbers are creeping up. The better we are at testing people, the better the tests are, the more we're finding out that people have relapsing diseases. So, the chance of a monophasic disease course is going down, and the chance of a relapsing disease course seems to be going up with improved testing.

[00:20:20] But, it really still depends and there are other clues that give us some sort of prognostic ability. For example, we can tell that NMO is more common in non-Caucasians, and MOG and monophasic disease is more common in Caucasians, and so race helps us predict. The age of onset, a 7-year-old is more likely to have ADEM or MOG, rather than aquaporin-4 NMO. Whereas a 70-year-old with a new transverse myelitis, it's almost always aquaporin-4 NMO. So, there are other clues that can help us. But, the chances of having a relapsing disease does depend on all of your workup, the testing, blood testing, even MRI features are helpful, and so it's really an individual question nowadays.

Krissy Dilger: [00:21:17] We also got a question regarding children who are diagnosed, or people who are diagnosed as children. What information is there, if any, about these children and what their disorder will look like 10, 20, 30 plus years out?

Dr. Michael Levy: [00:21:35] I'm sorry, Krissy, did you say these were MOG, or any children?

Krissy Dilger: [00:21:39] I think, they didn't indicate specifically, but just I guess any of these disorders or if there is any information on any specific disorder. Whatever you have.

Dr. Michael Levy: [00:21:51] I would say that the vast majority of children who come to our attention have either AFM, depending on the season, that's acute flaccid myelitis, thought to be related to an echovirus

infection that happens once every other year, but this year it didn't happen. Maybe because of COVID. So, it's either AFM, ADEM, a lot of kids with acute disseminated encephalomyelitis, and MOG. Those are basically the three conditions we see most in kids.

[00:22:23] Now, after the initial ADEM and MOG event, we'll see the optic neuritis emerge later. Then around teenage years, we start to see more monophasic transverse myelitis. We definitely see a blip on the demographics peak. There seems to be a lot of cases that happen in the teenage years. We're not sure why. And with MOG, those cases tend to present as seizures. So, they'll have a brain lesion that causes seizures, and then as you progress into adulthood, it manifests as more classic MOG presentations, like optic neuritis, or with aquaporin-4, it will be the classic longitudinal extensive transverse myelitis.

Krissy Dilger: [00:23:09] Thank you. I think this is a follow-up question to when we were talking about therapies for MOG antibody disease. Someone asked if it was steroid dependent?

Dr. Michael Levy: [00:23:22] It is. MOG is very steroid dependent for good and for bad. So, what happens with MOG attacks is, if you start to treat with steroids, the inflammation will subside and it feels great and when the inflammation goes away, neurological function is restored. It's a great treatment. The problem is coming off of steroids, that's the challenge, and the longer a patient is on steroids, the harder it is to withdraw them. And, I'm talking about 6-12 months later people are still stuck on the dose of steroids that they can't decrease from.

[00:24:01] So, one of the pathognomonic features of MOG, the distinguishing features of MOG, is that steroid dependence, but it's also exquisitely steroid responsive, so it's sort of like a double-edged sword. We use it to suppress inflammation, but then we have a hard time getting people off of it. And, we do recommend prolonged tapers. So, a taper is when you decrease your dose over time, maybe over 3 to 6 months, but the most likely time for a MOG patient to relapse is in the first month after stopping steroids, and that's a true fact, and that's a really difficult part about using steroids in MOG.

Krissy Dilger: [00:24:50] Thank you. Lots of questions about MOG here. So, someone is basically saying that they tested positive for MOG antibodies, but their doctor said that they may be not actually having MOG antibody disease, possibly because their titer level is low. Can you just explain why that might be?

Dr. Michael Levy: [00:25:14] Yeah.

Krissy Dilger: [00:25:14] Or what the titer level might indicate?

Dr. Michael Levy: [00:25:19] Titers are amounts of antibody. And the titer for MOG is really helpful in helping make the diagnosis, in the sense that false positive, low titer MOG antibodies have confounded the picture. It's most important when you're trying to figure out if this is MS or MOG. That's really the best way to use the titer levels. So, let's say you've had optic neuritis and your brain MRI is most consistent with multiple sclerosis, and you've had a lumbar puncture, and you have oligoclonal bands, and everybody's saying, "You have MS, you have MS, you have MS." And then you get a MOG test, and it comes back one to 20, which is the lowest titer level. Then what do you have? And, the answer is, we're not quite sure.

[00:26:15] In some people, according to some experts, you still have MS with a false positive MOG antibody. And, the Mayo recently published a paper saying that that false positive rate could be as high as 50 percent, and so a lot of people with that low titer MOG will have features consistent with MS. What do you do with these patients? What's the best treatment for them? What does their prognosis look like? We don't know.

We're just beginning to profile these patients because we think that they are a special form of either MOG or MS, or an overlap disease that's not MOG classic or MS classic. And so, that group of people need to be studied, I think, separately. If you have a high titer MOG, that means one to 100 or higher, which means you have a lot of MOG antibody, then that's more consistent with a MOG antibody disease picture. And, even if you have features of MS, we're thinking you belong more in the MOG group then. So, that's how the titer helps to distinguish.

[00:27:23] Now, if you have optic neuritis and a low titer, but you don't have any features of MS, well then, that false positive is not likely to be a false positive. It means that you do have an immunity to MOG and that there is a risk of recurrence, especially if that MOG antibody is still positive six, 12, 18 months later. That means your immune system is still sensitive to MOG, still surveilling for it, looking for it, and ready to attack it, and that will manifest as a relapse at some point in the future, in about 80 percent of cases.

Krissy Dilger: [00:28:04] Thank you. We have a question about someone who was diagnosed with transverse myelitis and they're wondering if it's, it was 13 years ago, and they're wondering if it's too long from the time of diagnosis to find out if they actually had a spinal cord stroke instead of transverse myelitis?

Dr. Michael Levy: [00:28:28] Thirteen years is a long time to try to go back and re-adjudicate what happened. It could be a spinal cord stroke. They look very similar on the MRI. They look very similar clinically. They're really, really hard to distinguish. When we have a patient in front of us, where we're trying to sort out TM versus spinal cord stroke, we wring our hands a lot. At this point, 13 years later, you're not going to be able to find a test that can distinguish between those two. The damage was done. The immune system is gone if it was TM. The blood flow has been restored in some other way, if it was a stroke, and so you're never going to be able to figure it out.

Krissy Dilger: [00:29:14] Thank you. Someone did ask, "How can I find an immunologist that will meet via televisit to manage IVIG and look into genetic testing for selective IgA deficiency?"

Dr. Michael Levy: [00:29:31] Okay. So, there's two questions there. One's about telemedicine. During COVID, the federal government and Medicare, suspended rules about state licenses. They didn't suspend it, but they weren't prosecuting it. So, what does that mean? It means that there's a Medicare law that says a doctor has to be licensed in the state where the patient is currently sitting. So, Krissy, where are you located right now? Where are you sitting?

Krissy Dilger: [00:29:59] I'm in Cleveland, Ohio.

Dr. Michael Levy: [00:30:01] You are in Ohio, so in order for me to give you medical advice, I have to have an Ohio medical state license. And so, I don't have that, so I can't give you advice. To get licensed in every state in the union costs $50,000 a year and hours, and hours, and hours of medical education that's required to keep it all up. And nobody does that except like ten people in the country. So, that's been very difficult. Through COVID though, they suspended some of those rules and they were like, well, if it's your patient and you already know them, then fine, they don't have to come to your facility and get exposed to COVID. You can communicate with them by video.

[00:30:41] And so, we were doing that, and it was great and new patients were signing up, and I loved it and I was sitting here, and many of you might recognize the background. But, now that COVID is, well, not gone, but going away, they've restored those rules, so you can't do that anymore. Now the patients have to be, the doctors have to be licensed in the patient's state again.

[00:31:04] Second question is about the IgA deficiency. It's important for patients who are, of course, starting IVIG. You want to get a baseline IgG level and that includes an IgA level. There are few people in the world who don't make IgA. It's a different kind of antibody. It's protective. It's protective against COVID for example. And, for people who get IVIG, there's a little bit of IgA contaminant in it, so if you're going to get IVIG and you don't have any IgA, you're going to mount an immune reaction against the IgA in that bottle, in that medication. And so, that can be very harmful if it causes an acute allergic reaction. So, that's why we measure IgA levels. It's not a genetic test. It's very easy to send for. Most of the time we just check it as IgG, IgM, and IgA levels. Good question.

Krissy Dilger: [00:32:00] Got it. Thank you. Our next question is, how frequently should an MRI be done in a stable patient of MOG antibody disease? And another question, I guess, I can kind of combine, is how often should antibody testing be done?

Dr. Michael Levy: [00:32:18] So, for MRI monitoring, for MS, the only reason we get MRIs on a yearly basis is because a lot of their relapses are not detectable. They're not noticeable to them. So, I can't have my MS patients tell me about every single attack they're having because some of them are just not noticeable, and that's why we get MRIs. If my NMO patients, they can tell me about every single attack. Same with MOG, same with transverse myelitis, hopefully they're not having anymore. And in all of these conditions that involve the optic nerve and spinal cord, almost every attack is detectable, and I don't need an MRI to tell me something my patients don't feel.

[00:32:58] So, we don't routinely monitor by MRI unless the patients tell us that there's something wrong, there's something new, there's something different. Then we'll get an MRI to investigate. As far as antibody testing, we don't retest aquaporin-4 antibody. Once positive, always positive. But it has to be reliable positive. For MOG antibody, we do retest on a fairly regular basis because there are a lot of people where the MOG antibody will go away, and that's associated with immunity to MOG going away all together. You can stop medication in some of these people and they won't have any more attacks. Now, it's possible that with the right immunological stimulus they will relapse, and they'll start making MOG antibody again. It's not that they're not vulnerable anymore, but they may be able to come off of medication for a period of time.

Krissy Dilger: [00:33:54] Thank you. We are getting a lot of questions about preventing relapses in MOG antibody disease, and I know we already talked about the most common treatment options, but I guess are there any non-treatment strategies, or complementary strategies, to prevent new attacks? Is there anything that can be done?

Dr. Michael Levy: [00:34:19] Like, non-medical?

Krissy Dilger: [00:34:21] Well, besides the therapies you already mentioned, I guess.

Dr. Michael Levy: [00:34:25] Yeah. We don't know what triggers attacks. If we knew what triggered an attack, we could avoid that trigger. We think vaccines and infections, or any immunological stimulus can do it. It's not a specific bug or germ, it's almost anything that activates the immune system and then there's that rogue element that attacks your MOG.

[00:34:48] And so, I don't really have any specific strategies beyond keeping the immune system calm with medications. And so, IVIG works, CellCept, Imuran. These are medications that calm the immune system down in this regard. Maybe IVIG also gets rid of the MOG antibody. Other strategies, vitamin D we recommend as holistic good for immune system type supplementation, but not based on any evidence. It's just not

harmful, so we suggest it. Other strategies? I don't have any other specific strategies, it's really medication focused at this point.

Krissy Dilger: [00:35:34] Thank you. We had a question from someone who has optic neuritis, and they are just wondering if there is any hope for recovering some of the vision that they lost?

Dr. Michael Levy: [00:35:47] Depends how far out you are. We do think that there is recovery, that most of the biological healing, that is making new myelin, re-establishing connections between nerves, we think most of that occurs in the first 6 months. And so, if you're just out of the hospital and you're worried that you're not making a good recovery, you don't have to worry yet, okay? These things do take time and the recovery is kind of a like a stock market. It goes up and down, up and down, every day may be different. But overall, when you look back week over week, you should be a little bit better.

[00:36:24] And once you start to flatten out, the expectation is that there's not going to be much more healing that occurs after that, after it's 6, or 12, or 24 months. Now, if you're young, you have a little bit more healing capacity than if you're older. And there's nothing really that you can do to optimize the healing process after optic neuritis. There's no optic rehab or anything like that to really get those nerves healed, so it's really just a matter of time.

Krissy Dilger: [00:36:58] Thank you. Someone asked what research is being done for double negative NMOSD or any kind of statistics for the progression of the disease?

Dr. Michael Levy: [00:37:12] That is a good question. This double-seronegative, so no MOG antibodies, no aquaporin-4 antibodies, it's not a small group of people. So, the last time that I looked at my patient list at Mass. General, in the past 2 years, I had an equal number of aquaporin-4, an equal number of MOG, and an equal number of double-seronegative. So, it's this whole group.

[00:37:37] But it is a heterogeneous group. It's not all the same. You have some with optic neuritis, some with transverse myelitis, some with brain lesions, some heal well, some don't. There really seems to be a hodgepodge of patients, and what we really need to do is sort them all out. We need better testing, we need new testing to figure out if their conditions, we need to know if basically the immune system is targeting a different protein. Not aquaporin-4, not MOG, but something different. And if it is, then we need to be able to characterize that, develop a good blood test for that, and then we can move along the pathway we've been doing for aquaporin-4 and MOG.

[00:38:22] That is something that we've been doing a little bit in the lab. It's something that we're partnering with Quest Diagnostics on to try to find these new biomarkers, but it does take time, and unfortunately there's no appetite for companies to invest, to develop drugs for people that don't have a blood testable disease, and that's really driven by the FDA.

[00:38:49] There were companies that tried to do it, that wanted to do it, that came to the FDA with the drug and says, "We want to target seronegative whatever." Seronegative encephalitis, for example, is the last thing that we tried. And the FDA was like, "No. There's too much in there, too many different diseases that you're mixing up and so we don't like that. We want a blood test. We want you to sort out who has what, and then develop a drug just for that." So, that's been a major challenge with double-seronegative NMO.

Krissy Dilger: [00:39:22] Okay. Thank you. Someone asked about, just in general, they're worried about their symptoms, possibly indicating that they are progressing into MS and they have transverse myelitis. Are there

any indicators that transverse myelitis diagnosis might actually be becoming an MS diagnosis? What are things that they should look out for or talk to their doctor about?

Dr. Michael Levy: [00:39:53] MS can cause transverse myelitis. It's actually pretty common. The reason that you might be in the SRNA, as opposed to MS support group, right now, is that we mostly expect that by the time an MS patient has a transverse myelitis, they'll have a brain MRI that's already consistent with MS. So, we'll look at your transverse myelitis. We'll look at your brain MRI. We'll often get spinal fluid to confirm a diagnosis of MS and you'll be on that path already.

[00:40:25] But there are some people who get transverse myelitis early in the course of MS, so that the diagnosis of MS is not obvious at that time, at the beginning. So, it does happen, yeah. You might have a transverse myelitis and, if we're thinking it's kind of a small lesion, it's not typical for NMO or MOG, you might have two lesions on your spinal cord and one on your brain, or something that's looking like early MS. And in those cases, we'll recommend yearly MRIs, specifically to look for MS. And so, what we expect is if you do have MS, new lesions will show up. Usually in the brain, but often in the spinal cord as well. And, once you've demonstrated that you have new lesions, it usually becomes a little bit more obvious which pattern you're developing, a pattern of MS or a pattern of something else.

Krissy Dilger: [00:41:22] Thank you so much. Someone did ask about any updates you could provide on your tolerization research?

Dr. Michael Levy: [00:41:32] Tolerization research is just beginning to get the attention of industry. So, what is tolerization research? Tolerization is when you reeducate the immune system to become tolerant to the protein you keep attacking in autoimmunity. With MOG, the immunity is to MOG. With NMO, the immunity is to aquaporin-4. So, we know in those two conditions exactly what the immune system is targeting, and so they are more amenable to tolerization therapy, which is when we tell the immune system don't attack those two proteins.

[00:42:09] When you get a vaccine for COVID for example, we teach your immune system to attack those proteins, but we also have technologies to teach your immune system not to attack those two proteins. And so, that's what we're developing. The company that made the COVID vaccine with Pfizer, BioNTech, they've also been dabbling in autoimmunity and MOG specifically. And, they demonstrated in a mouse model, that they can make a new lipid particle with MOG inside of it and send it to the mouse spleen where it gets processed into a tolerization signal so that these mice with a MOG-like disease stop attacking their own MOG.

[00:42:58] And, we're in discussions with them to try to collaborate on a human study, but there are other companies as well interested in MOG and interested in aquaporin-4 NMO to develop this type of strategy, and you can see the benefit right away. You're not suppressing the immune system and the potential for a cure is even there, whereby you can permanently re-instruct the immune system not to attack. And so, that's why we're particularly excited about tolerization.

Krissy Dilger: [00:43:30] Got it. We are almost at the end of our time, but I think we might have time for one more. Someone asked about getting the COVID vaccine and I know we have a talk on that on the last day, but I guess, what are your thoughts on the community, especially if you have MOG antibody disease or neuromyelitis optica, and the COVID vaccine.

Dr. Michael Levy: [00:44:00] I think this is definitely an individualized decision. My experience with these with my patients is that, as long as someone is on immune therapy to keep the immune system calm, I haven't seen any bad outcomes from the vaccine, specifically for COVID. There are people who are undertreated

or not treated correctly or people who are not on any treatment and didn't even know they had a disease, where their disease was triggered by the vaccine. I can probably count on one hand the number of cases I've seen like that. So, it's rare, okay?

[00:44:41] The vast majority of people who've had bad outcomes have had it from the virus itself. So, the COVID virus can trigger relapses just like the vaccine can, but I think the virus is even more potent than the vaccine. So, when you're weighing the decision about whether to vaccinate or not, in most cases I would say the evidence weighs in favor of the vaccine rather than getting the infection itself. The one exception to that, I would say, are people who are in a recent healing period. For example, if you've had a recent attack and you're just in the recovery phase, you don't want a vaccine right then and there, that could potentially flare what you just had. I would say, I tell all my patients, wait at least 90 days after an attack before you get any vaccine, and that includes COVID. We will talk about this more, I think, on Sunday. Right, Krissy?

Krissy Dilger: [00:45:47] Correct. Yes. Unfortunately, that is the end of our time. Thank you so much for joining us, Dr. Levy, and answering so many questions. If everyone can head over to the stage area, that is where our next talk will be. Thanks so much.

Dr. Michael Levy: [00:46:02] Thanks, Krissy.