MOG Antibody Disease (MOGAD)

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[00:00:00] **Lydia Dubose:** We're pleased to be joined today by Dr. Michael Levy. He is Associate Professor at Harvard Medical School, Director of the Neuromyelitis Optica Clinic and Research Laboratory, and the Research Director for the Division of Neuroimmunology and Neuroinfectious Disease at Massachusetts General Hospital. Thank you for joining us, Dr. Levy.

[00:00:28] **Dr. Michael Levy:** Thank you, Lydia, and thanks to everyone for joining today. Is everybody who's going to be here here, Lydia, or should I just jump in? Okay, I'm going to assume that's a yes. All right, so the topic for this session is MOG antibody disease and, for lack of better title, this is basically a broad overview, everything you need to know about MOG. Here's a quick outline. We're going to talk about the history. We're going to talk about the IgG test that we use to diagnosis MOG, typical case presentation, some of the immunology and the treatment. So, how did we get this disease, MOG antibody disease? Well, it really came out most recently from this pie that makes up the neuromyelitis optica spectrum disorders. If you were diagnosed back in the first decade of this century, you'll remember that most of these cases were previously diagnosed as multiple sclerosis.

[00:01:35] Most of the pie is still multiple sclerosis, but now we have a little wedge in there that's not multiple sclerosis of demyelinating disease like optic neuritis and transverse myelitis. We recognize that it's not all MS, and a part of that pie is neuromyelitis optica spectrum disorder. It has the aquaporin-4 antibody, and then among those who don't have the aquaporin-4 antibody, we recognize a lot of them had the MOG antibody. And now that we have improved on the MOG antibody test, we recognize that the spectrum of MOG is not just NMO but looks a lot like MS and has various different forms and manifestations, and I'll show you some of those in a minute. First, the name, okay, MOG was not coined by someone like Dr. Devic. Dr. Devic coined neuromyelitis optica. It's a beautiful name in French. We don't have that benefit in MOG. MOG comes from the name of the protein to which patients mount an immunity.

[00:02:39] That protein is myelin oligodendrocyte glycoprotein, which very simply describes where the protein is and what it looks like. It's a protein on the outer surface of the myelin sheath. It's made by a cell called an oligodendrocyte, and it is a glycoprotein, meaning it has a sugar component and a protein component together. So, it really just bluntly describes the protein, and patients with MOG antibody disease then mount an immune response to it and produce antibodies as part of that immune response to MOG. Now, we've

been using MOG in animal models for a long time. It turns out if you take MOG from a rat and stick it under the skin of a mouse, along with some harmful bacteria like pertussis and tuberculosis, the immune system will get all revved up from the infectious bugs, and because MOG is in that mix, it's going to think that MOG is part of the problem and mount an immune response to it and they'll get transverse myelitis and optic neuritis, just like MOG patients do.

[00:03:48] And so this mouse model is actually, rat and mouse model, has been around for a long, long time, and people have been using it to develop drugs in MS and multiple sclerosis, and a lot of those drugs work in the mouse and the rat and did not work in MS people, and that's because, of course, this model is a much better model for MOG disease rather than multiple sclerosis. So that's where the name comes from. In the world of demyelinating disease, we have two antibody tests now. We have aquaporin-4 and MOG. There's no blood test for multiple sclerosis that's reliable. And then for people who test negative for both of these two antibodies, we don't have any really good biomarkers that are currently in clinical use. There are many in development, but not currently being used. The blood test for MOG has been improved over time.

[00:04:43] The only purpose of this slide is to show you what aquaporin-4 test used to look like on the left. It was a pattern recognition and has now been improved into a cell-based assay, which is probably about 85 percent sensitive for aquaporin-4, meaning if you have aquaporin-4 antibodies, the test is 85 percent likely to detect it. And the specificity for MOG, meaning if you test positive, what's the likelihood that you actually have NMO? For aquaporin-4 it's about 100 percent. MOG, the numbers are still emerging. The test for MOG is on the right and it's been improved since 2015 in the UK and 2017 in the US. There are a lot of papers using tests that were not as good, and all those papers published prior to 2017 are not super reliable, so we don't have good sensitivity and specificity numbers for you. The test is available at most testing centers. If you're out west, you're getting tested at ARUP. If you're at an academic center, perhaps, you're getting tested at the Mayo Clinic. If you get tested by your private doctor, it's going to Quest or LabCorp.

[00:05:57] LabCorp and ARUP still use the ELISA test, which is, actually, I take that back. LabCorp and ARUP are using the ELISA test for aquaporin-4. For MOG, LabCorp should be sending it to Mayo Clinic, but they are trying to improve on their ELISA assay for MOG and see if they can get even better than the Mayo's cell-based assay. Currently, though, for MOG, the academic community loves the Mayo assay the best. Over time, there are a bunch of studies that have looked at the MOG antibody. Back in 2003 or so, there was a huge "New England Journal of Medicine" paper and it said that MOG was a great marker for MS. So, everyone in the world started looking at MOG antibodies back in 2003, 2004, and 2005. And they couldn't find any patients with MS, less than 5 percent of patients with MS were testing positive. Healthy people were still testing negative, so it seemed like, well, they weren't really sure what this test was detecting.

[00:07:05] And then when they looked at ADEM people, they found that about 40 percent of kids were testing positive, and among aquaporin-4 positive, not a lot, but aquaporin-4 negative, also about 25, 30, 40 percent of people were testing positive for the MOG antibody. And so, this really defined a new spectrum for MOG that wasn't MS. It wasn't NMO. It was its own thing. It had a lot of overlap with ADEM. And so, on the localization spectrum, this is kind of where we put it. If you think of transverse myelitis as being confined to the spinal cord by definition, and multiple sclerosis is involving the entire neuraxis, brain, optic nerve, spinal cord, neuromyelitis optica is optic nerve, spinal cord, and MOG is kind of optic nerve, spinal cord also, but a lot more optic nerve, and also some more brain compared to NMO. There's a lot of overlap with MS.

[00:08:03] When we use the MOG antibody to distinguish people with MOG from MS, this is what we see people presenting at onset. On the right side in those blue pie pieces, you'll see all of those are optic neuritis, either unilateral, one eye, or bilateral, both eyes. So more than half of people will start with optic neuritis and in fact will continue having recurrent optic neuritis attacks. It's mostly kids who have ADEM, acute

disseminated encephalomyelitis associated with MOG. Many of those kids will have ADEM first and then their optic neuritis later. And transverse myelitis is a part of the MOG process. We've seen long lesions, about 14% will have them. And we've seen short lesions that look like MS lesions, to be honest. Now, we don't have formal clinical criteria. If you say, "I want to know if I check all the boxes for MOG, if I meet the criteria for MOG antibody disease."

[00:09:05] We don't have consensus criteria. About four or five different groups have proposed criteria, they should have this or they should have that, but we haven't agreed on anything yet. The basic outline is fundamentally the same. We all want to know that you have some sort of inflammatory attack of the optic nerve, the spinal cord, or the brain. We wanted to know that it's associated with the MOG antibody or immunity to MOG. We want to make sure you don't have anything else. And that's hard to do. But we rule out aquaporin-4, we try to rule out MS as best as we can, and if all that's left is the MOG antibody and MOG antibody disease, then that's the general gist of the MOG criteria that's under development. And if you use that framework, the demographics of MOG are emerging.

[00:09:53] There is a group of kids and teenagers who have MOG and then there's a group of grown-ups. Not a lot of older folks, but some, and so this bi-modal age group is what's emerging with MOG and that's different from aquaporin-4 and NMO. And the race seems to be confined mostly to Caucasians. I have a handful of non-Caucasians. There are certainly a lot of Asian studies coming out of Japan and other places where they are describing MOG antibody disease, but at least in the US, especially compared to our experience our experience with the aquaporin-4 NMO group, MOG is much more Caucasian, and MOG has a lot more men than the aquaporin-4 group. I don't know if it's exactly equal, male equals female, but it's pretty close, and a lot of young men with recurrent disease end up having MOG as opposed to Black women with recurring disease, long lesions of the spinal cord, those are usually aquaporin-4 NMO.

[00:10:56] Here's an example of a person, a 27-year-old, no past medical history, working, parenting, doing everything that they would normally do. Woke up with pain behind the left eye one day and that evolved over the course of a week into light sensitivity problems and then vision blurring. This is what the MRI looks like. This is a person who's laying down in the scanner looking up. Here's their nose and the two eyes, and their legs are kind of sticking up at you, and so this is the right optic nerve, the nerve that goes from the eye to the brain, and the left one is here. You can see how bright white these are. They're not supposed to be like this. They're not supposed to be white. They're supposed to be grey and dark like this. And so, the reason that they're white is that that harmless metal dye that's injected at the end of the MRI is leaking in. It's following the immune system.

[00:11:52] Wherever the immune system has breached the barrier between the blood and the optic nerve, that dye follows, and so we can see where the inflammation is. And in this case, it's both optic nerves. Just like I showed you a lot of people with MOG have bilateral or optic neuritis in both eyes, this is a classic case like that. Now, the examination showed that the patient had 20/200 vision. That's legally blind in the United States. 20/200 or worse is legally blind, and that's what happens with MOG people. The initial attack can be blinding, and it can be in both eyes. But look at what's really interesting about MOG is that when we treat with steroids with a long taper and they come back to clinic in 6 months, look at that vision recovery, back to 20/20. That's something that you don't see with a lot of autoimmune diseases. This ability to recover so well, that is a unique phenomenon with MOG.

[00:12:52] In fact, when we see that recovery process, my first thought is MOG. I even think it should be part of the clinical criteria, given how reliable it is with MOG. Now, there are still problems. There's light sensitivity, there's problems with low contrast vision, seeing subtle grays on white. There are long-lasting problems from the damage that was done. But compared to aquaporin-4 people, MOG is a very different recovery phase.

And of course, this person tested positive. We can talk at some point about the meaning of the titer. With a titer this high, meaning 1 microliter diluted 999 times into saline or some sort of dilutant, the antibody is still detectable. That's a very, very high level of MOG antibody and very reliable for making the diagnosis.

[00:13:47] There are data that are emerging that help to differentiate between MOG and aquaporin-4 that we looked back and were like, "Those patients that we thought had NMO, which is now associated with the aquaporin-4 antibody, but they were really different. They didn't have the aquaporin-4 antibody. They were Whiter. They were maler. They had fewer autoimmune overlap diseases, and they had better outcomes." Now, we look back and we're like, "Okay, those were MOG people and they're different from aquaporin-4 NMO." The immunology of MOG is fascinating. I won't go too deep into it today. We just don't have the time. But MOG is found on the outer surface of a myelin sheath. If you think about, I don't know how well you can see this.

[00:14:33] This is the wire powering my laptop. If you think about myelin being the insulating sheath of this wire, MOG is on the outside. And it interacts with the immune system, and we don't really know what else it does. It doesn't really have a lot of known functions. In the mouse, if you remove it genetically, if you knock out the MOG protein, then it's fine. There are no deficits. We don't know of any people who are born without MOG, but we don't really know what its function is. People do seem to mount immune reactions to it, though. In fact, most animals can. If you look all across the animal kingdom, rats and mice and lemurs and monkeys and many other different animals can all mount immune reactions fairly readily to MOG when they can't to aquaporin-4 and other proteins. My body knows that aquaporin-4 itself and will not make an immune reaction to it, and NMO is unique in that regard in that they are attacking their aquaporin-4 protein.

[00:15:41] But MOG, MOG is a little bit different. In almost every mammal, you can trigger a reaction to MOG in that animal model. There's something special about it that allows the immune system to attack it and then often in many cases stop attacking it. It's sort of like a little bit freer in its ability to cause immunity, but also in its ability to restore tolerance. So, the immunology of MOG is really fascinating and I don't have any time to go into the pathology of MOG, but suffice it to say, it looks mostly like MS. So, if you're a MOG patient and you get a biopsy and you're told this looks like MS, it could still be MOG. Pathology doesn't provide us any unique insights into distinguishing MOG antibody disease from MS. This is just a comparison between MS and MOG.

[00:16:37] What we think goes on with MOG disease is there's a blood-based immunological problem. We think it lives in the blood and then it invades the central nervous system, the optic nerve, and the spinal cord mostly, on a regular basis to cause damage, and then retreats back into the blood. And there are many different immune cells that might be responsible. We know B cells are playing a role. They make the MOG antibody. We know T cells have to be involved in that process, because B cells can't make that antibody without T cell help. And we think that there are a lot of other immune cells that are involved as well, especially during the breach into the optic nerve where these immune cells can cause damage and demyelination. And exactly how that happens and in what order we don't know yet.

[00:17:28] Now, I have a few more minutes. I'm going to go into the treatment. The way we think about the treatment is acute and preventive. Acute treatment is like a fire. It is an inflammatory burn going on in the spinal cord and we need to put it out, so it doesn't cause any more damage. And then there's preventive therapy to prevent the next fire. In treating the acute relapse, the inflammation, the fire, we use a standard of care that's been established for demyelinating disease for decades, and that is high dose steroids. And I have to say, with MOG antibody disease, it's pretty rare that steroids don't work. There are certainly conditions where it doesn't. I have a few cases like that myself. But in most cases, it does.

[00:18:19] In following the course of steroids, you need to bring the steroid dose down slowly, because one of the most potent triggers for another MOG attack is to stop the steroids suddenly. So, if you get 5 days of high dose steroids and then go home, a week later you'll be back with a relapse, almost certainly. It's one of the best triggers for an attack. So that's why, after you get your steroids, you have to come down on the dose slowly over the next few weeks to months to make sure that you don't trigger another relapse. Plasma exchange is also wonderful for MOG, as is what we're discovering is maybe IVIG can be used in the acute stage and then you don't need any steroids and you don't need any taper. And so, then there won't be any steroid dependency if you use something like IVIG.

[00:19:12] On the preventive side, there's not a lot of data. Let me show you a couple data slides with steroids and other treatments, but suffice it to say, these numbers are small. The cases represent just a handful. Here's steroids. I can tell you, steroids work. In each of these patients, the hash marks on the left represent an attack prior to treatment, and then at time 0 everybody is lined up to start the treatment, and you see, in this case, for example, there are many attacks after steroids. And that's because there's probably a set level above which no relapses occur, and below which relapses can occur as usual. There seems to be a threshold effect, and for most people, it's somewhere between 15 and 25 milligrams a day, and if you're above that, you're fine, and if you're below that, you keep relapsing. But that kind of dosing is not a sustainable treatment because long-term consequences of chronic steroids, you don't want them, the weight gain, the blood pressure, the blood sugar, the diabetes, the bone thinning. You just name them on and on and on.

[00:20:24] All these metabolic consequences make treatment with steroids nearly impossible. Here's that phenomenon I told you about called steroid withdrawal effect. So, most of the relapses that occur while on steroids occur when the dose is low, so it's coming off of the steroids and then the most potent time for relapse, look at how many of the relapses occurred right after the steroids were done, in that very first few months after the steroids are completed. That's the most potent time for triggering a relapse of MOG. IVIG has not been tested in a lot of people. This is grown-ups, showing a whole bunch of relapses before and then at time 0, these two patients seem to fail. In kids, though, I'll show you better data that IVIG seems to work. It seems to depend on the dose.

[00:21:19] You have to use the higher dose and that seems to work better than the usual dose. This is the largest study we have, and you can see the numbers aren't great. This is in kids who used MS treatment where 10 out of 10 failed. Okay, all of the injectables used for MS, doesn't work in kids with MOG. 10 out of 20 failed Imuran and about half failed CellCept. 50 percent efficacy ain't bad in a new disease where you don't have any FDA-approved treatments. So, for these two general immune suppression approaches, we do recommend them, in the sense that they can be taken by mouth on a regular basis without too much hassle and they're cheap, much cheaper than rituximab, for example, and they seem to work about half the time. Rituximab and MOG ain't great. Shouldn't use the word "ain't."

[00:22:16] But in NMO aquaporin-4, rituximab is wonderful. But in MOG, it's not that effective, really different diseases. Six out of nine failed. IVIG seems to have the best effect, where only four out of 12 failed. And again, I think a lot of those cases that failed have to do with the dose of IVIG. This is data showing that rituximab just is not that good. Here are all the relapses. In many cases, we all contributed to, all the relapses that occurred before starting rituximab, and then this is after starting rituximab to the right of that line. You can see there are just as many dashes. I think the statistical outcome is about a 37 percent reduction in risk, which isn't great. It's really not a drug that we think we want to develop for MOG. So, there are new trials coming out, and I'm proud to announce that one of them just launched last Friday using a drug called rozanolixizumab, Rozimab is the easy name, easy way to pronounce it. It involves a patch that you put on your body once per

week and we think it works in the same way that IVIG does. The trial has just launched. We'll be recruiting and enrolling patients starting around December, so definitely ping me if you're interested in that. And with that, I think we have about 5 minutes for questions.

[00:23:43] **Lydia Dubose:** Yes, thank you so much, Dr. Levy. We have a few questions that have come through the Q&A section and in the chat. So, first off, somebody had asked if you had noticed an increase in MOG patients since the COVID pandemic began because of the virus.

[00:24:03] **Dr. Michael Levy:** No. No, I haven't. I think it's the usual number, but I don't think there's anything specific about MOG. I've seen cases that emerged after COVID infection. I've seen cases that emerge after the COVID vaccine. But not more than any other infection or any other vaccine.

[00:24:24] **Lydia Dubose:** Okay, great. Somebody else was asking about the new trial drug you were describing. If you could spell it out or just let them know what it is a little bit.

[00:24:36] **Dr. Michael Levy:** Rozimab, the easy, that's the short name. R-O-Z-I-M-A-B. Maybe I can just type it in here. Actually, I'll put the whole name: rozanolixizumab. And what you can do is copy and paste that into clinicaltrials.gov and read all about it. This drug is being developed for other indications, like myasthenia gravis. So, look for that one associated with MOG and you'll see the trial details.

[00:25:04] **Lydia Dubose:** Okay, great. We had another question about if you'd give rituximab to somebody with the CLL and MOGAD despite its lower efficacy.

[00:25:16] **Dr. Michael Levy:** So, chronic lymphocytic leukemia is a blood disorder. Sometimes it needs to be treated, sometimes it doesn't. It depends on how aggressive it is and what the underlying proliferative disease is. If it's B cells, while it wouldn't, then rituximab might be the way to go, in which case you're always looking for a twofer, right? If you can treat two diseases with one drug, that would be ideal. Now, I will admit, I do have some MOG patients who respond well to rituximab. Are they part of that 37 percent group? Do they have MS-MOG overlap and really we're treating the MS part of that?

[00:26:01] I don't know, but some people do seem to respond well, and so if you're on rituximab with MOG and you're doing well, by all means, consider continuing treatment. I don't want to take you off of it. But if you have two conditions and one is very responsive to rituximab and then you have MOG also, it might be reasonable to just try rituximab first to try to treat both conditions.

[00:26:28] **Lydia Dubose:** Thank you. Yeah, that's great. And that answered another question that came in here, as well. Laura asks if injection steroids for, say, a knee issue is, I'm sorry, I don't know how to pronounce that.

[00:26:46] **Dr. Michael Levy:** Contraindicated.

[00:26:46] **Lydia Dubose:** Yes.

[00:26:47] **Dr. Michael Levy:** It's worrisome, to say the least. Steroids for any reason in the MOG patient, I say worry about it. Don't necessarily accept steroids for anything. Hip injections, back injections, always look for an alternative first, because otherwise, it's a potent trigger after the steroids wear off, and otherwise you'd have to do a taper. So, yes, do be wary.

[00:27:13] **Lydia Dubose:** Okay. If anybody has any other questions, feel free to drop it in the Q&A or in the chat. We have just a couple minutes before our next stage session. So, all right, that looks like that's it. The

next session, you'll hear from Dr. Flanagan about acute treatments at onset and relapse, so head to the stage in just a couple minutes and we'll see you there.