MOG Antibody Disease (MOGAD)

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Dr. Michael Levy: [00:00:05] Hello everyone. My name is Michael Levy. I'm an associate professor at Harvard Medical School and a neurologist at Massachusetts General Hospital. And today I'm going to talk to you about MOG antibody disease. This is a primer. This is a general explanation of what the diseases and some features that we now understand about it. And then a little bit about the treatment of MOG.

[00:00:30] So, how did MOG come about? Stands for myelin oligodendrocyte glycoprotein. This is a protein that's found only in the central nervous system. Only in the brain and the spinal cord and the optic nerves. And it was recognized back in the 1940s to be really special protein. So, even before we knew about this disease, we knew that the protein was special, and it was special because it was useful in a mouse model. If you take MOG protein from a related species, like from a rat to a mouse or mouse to a rat and you injected under the skin, the immune system is going to react to that MOG protein. And then when it surveils its own central nervous system and sees that MOG protein, it's going to say, I just saw this foreign stuff under the skin. It looks a lot like my own MOG. I'm going to just destroy all the MOG because I know it's all foreign and it causes a demyelinating disease that looked like MS.

[00:01:33] So, back in the 50s and 60s all the way through today, we still use this MOG rodent model to see what happens in demyelination. And so, MOG is a very common name in the lab that we've been using to identify this mouse model. It's only more recently since 2015 in the UK and 2017 in the US that we have an antibody test for MOG antibody disease in people. And because the antibody binds MOG we just kind of call it MOG antibody disease. It doesn't have a name coined by someone a long time ago like Dr David who coined Neuromyelitis optica in 1895. We don't have a beautiful name like that. We just have a MOG antibody disease. But that's where it came from.

[00:02:23] Now, over the past 20 years people have been trying to understand where MOG fits because when the antibody was first discovered way back in the late 1990s and early 2000s, the group that discovered it first thought that it identified MS patients because let's face it MOG patients have demyelinating disease that kind of looks like MS And so, the first thought was well maybe it's a marker of MS But only about 5% of people tested positive for it and all the studies around the world. And yet the antibody test itself wasn't that good and a lot of healthy people were testing positive, and it caused a big commotion, and everybody was like all right we're done with this antibody test. Most of the world gave up on it. But the discoverers in Austria

who first picked up on it was like we really feel like it labels a distinct class of people, and they looked around okay if it's not MS and who are these people testing positive for MOG?

[00:03:27] And the next group of people they came upon were children with acute disseminated encephalomyelitis or ADEM. And they noticed that a lot of those kids were testing positive, they didn't really know what to make of it. The kids had a generally good outcome. And so, we weren't sure what it does. It really isn't meaningful that these kids were testing positive. And then the next group of people were the ones who had neuromyelitis optical who fit the criteria with optic neuritis and transverse myelitis. But they did not have the aquaporin-4 for antibody. And so, those people that one out of every two or three people with that disease phenotype but without the aquaporin anybody, those patients were testing positive for MOG.

[00:04:12] And then in 2015 as the antibody test got improved to be much more specific, then we started seeing the breadth of MOG antibody disease. So, it's not just an MMO thing, it's not just an ADEM thing and it's definitely not an MS thing. It's actually broader than that. It actually covers quite a bit of demyelinating disease across the spectrum that probably overlaps with MS and ADEM and NMO. And I'll show you a little bit more about what we know about this disease.

[00:04:46] We now have two antibody tests for people with optic neuritis and transverse myelitis. And even for cases with lesions in the brain, we still test for MOG. We only had aquaporin-4 since 2005 and MOG since 2017. And these are the two tests that we test for in demyelinating disease currently. If you look at people with the MOG antibody and you say, okay well if we don't confine them to NMO or ADEM and who are these people who are testing positive for the MOG antibody? They're pretty uniform. More than half. In fact, probably closer to two thirds of people who have the MOG antibody will have an optic neuritis.

[00:05:31] Optic neuritis, inflammation in the nerve behind the eye starts with pain with eye movements and then it leads to blurry vision. You can even lose your vision. In many cases up to almost 1/4 the inflammation is in both optic nerves; we call that bilateral optic neuritis. And that's a kind of unique feature of MOG. You could see some percentage of people with MOG antibody have ADEM, that's kids. Some people have a combination of optic transverse myelitis at the same time and then some people just have transverse myelitis. Now there's some kids with brain lesions who don't have ADEM, and they might just have a seizure disorder. And that's not reflected on here.

[00:06:15] Now, the criteria for MOG are still being worked out. There's a general consensus that people who have inflammation mostly in optic nerve but also spinal cord and also brain who test positive with this good test that we have, now that's been improved for the MOG antibody. And then the challenging part is ruling out other things. There are some cases of MS that might test positive for MOG. Got to rule that out. People who have aquaporin-4 for NMO. About 10, maybe more people who test positive for aquaporin-4 and MOG. So, what's that about? Well, we still clearly have a lot to work out, sort this out, but if you don't have anything else, but you do have the MOG antibody in the context of the inflammation in the central nervous system, that's generally what we call MOG antibody disease.

[00:07:06] Now, the demographics of people with MOG antibody disease is sort of bimodal, meaning there's one group of children who have ADEM and optic neuritis. And then there are the grown-ups. And it seems to be two different bumps, like we have a bump in the younger age and a bump of patients in the middle age. And we do have some older folks. My oldest MOG patient is in her 70s. And it's especially prevalent in the young and children who have optic neuritis and ADEM. I put predominantly Caucasian. That's because our country is still predominantly Caucasian. And so, that reflects basically our country's demographic. If you really break it down, it's not a predominantly Caucasian disease. It seems to be equally prevalent in all races and does not have a predilection. And so, you'll find MOG antibody disease in Asia and many other

countries. The sex distribution is probably not quite male equals female but it's pretty close. Whereas with other diseases that are autoimmune females generally outnumber males. That's still a little bit true in MOG but not as much as in other diseases there are a lot more men. So, if a man has optic neuritis, it's much more likely to be MOG than it is to be NMO.

[00:08:35] On MRI, this is an MRI section. Looking right at the optic nerves here. These two bright areas here are the optic nerves. They are the nerves that connect the eye to the brain and this white stuff here is the harmless die at the end of the MRI. That's injected and leaked out into areas that are actively inflamed. So, you can see that they're white here because they're inflamed where the arrows are pointing both optic nerves. This happens to be a child tested positive for MOG. This is classic MOG antibody disease.

[00:09:11] In the spinal cord, the attacks tend to be lower down. You can see where this red arrow is. This is a section of the spinal cord where you're cutting a person down this way and opening them up and looking at them on the inside like a refrigerator. You can see all these square bones here are the vertebrae that hold up the spinal column and the spinal cord here is in gray. You can see that nice dark contrast, but that white area here is the lesion. I used a red arrow to point to it. That happens in MOG. It often attacks the lowest part of the spinal cord that innovates the legs, the bladder, and the sexual organs.

[00:09:49] So, here's how we've been understanding MOG. We often compared to aquaporin-4 NMO. We also compare it a lot to MS. When you compare to NMO, the age group is younger because the kids drag down the number. Like I said, we still have numbers in the elderly but not quite the same as aquaporin-4. If a person has transverse myelitis in their 70s, they're still more likely to have aquaporin-4 than MOG. But if they have optic neuritis in their teenagers, they're more likely to be MOG than aquaporin-4. The gender skew we talked about, one of the things that's interesting about MOG is it does not have a lot of overlap with other autoimmune diseases. With aquaporin-4 NMO. For example, you'll hear about lupus and the family. The patient themselves might have lupus or Sjogren's or psoriasis. Many, many autoimmune diseases that run in that family. MOG is not like that. It does not seem to overlap with these rheumatology diseases as much as aquaporin-4 and NMO does.

[00:10:53] Now when a patient first comes in, they may be completely blind from their optic neuritis. Whether it's MOG or aquaporin-4 NMO, they kind of have that same initial presentation that tends to be very severe. It's scary. You might be blind; you might be paralyzed. That's not unusual at all for either condition. But if the antibody comes back MOG the outcome tends to be much better. So, I do feel comfortable telling people, "Look, you might not be able to see anything out of your eye right now, but you tested positive for MOG and that portends a much better recovery than if you tested positive for aquaporin-4 NMO."

[00:11:29] In brain MRIs we often see lesions that kind of look like ADEM even in people who are doing fine. I once had a teenager telling me about school and she's doing great, but she had a big lesion on her MRI just looked exactly like ADEM, but she didn't have a bad neurological consequence from it. It was bad radiologically and concerned me a lot and it doesn't take a lot for a bad MRI to turn into something bad clinically. So, we do treat that of course.

[00:12:01] Alright so now we're going to go into treatment in the second half of this presentation. And I divide the treatments into two, acute and preventive. Acute is like putting out a fire, there's inflammation going on right now in your central nervous system that should never be inflammation in your central nervous system unless you have an infection there. So, if you have inflammation for MOG you got to put it out like putting out a fire. Then there's preventive treatment. This is designed to prevent the next attack. Preventive therapies don't do anything for the prior attacks. They don't make you feel any better. They don't do anything for you except prevent the next attack. You got to think about them in two different separate parallel tracks.

[00:12:39] Let's start with treatment of acute attacks. There's a fire in your optic nerve. You got to just put it out. So, how do you put it out? You smother it with steroids. Steroids almost always work for MOG. It works in almost all cases, especially at high doses. The trouble with MOG is getting people off of steroids. Once you start steroids, you got to wean them off slowly because if you withdraw it after that five days like we do for multiple sclerosis will often do high doses of IV steroids just to put out the fire and then in MS you can just stop the IV Steroids, no need for much longer. There's no rebound in MS but in MOG, there is a horrible rebound. In order to avoid the rebound you have to take them down lower and lower doses over time over a longer period of time to get them off.

[00:13:35] There's some cases that don't respond to steroids or not perfectly well and you really want to suppress that fire. You can use plasma exchange, or you can use intravenous immunoglobulin IVIG. And to be honest, more recently I've been turning to IVIG as the treatment without steroids because I hate getting people stuck on steroids. It's hard to get them off. So, many more side effects with steroids. I've started using IVAG and a high dose in the acute setting and we've seen some good outcomes will be publishing that soon.

[00:14:08] Here's a study that demonstrated the potency of that steroid withdrawal effect. The bars here indicate the number of attacks that occurred in this patient population with MOG when the steroids dose was being changed. So, at high doses you don't see a lot of relapses then you bring the dose down and you see the relapse is going up and up and up. Every time you bring a dose down you have a risk of relapse. And then when you stop the steroids that's the biggest risk. And then over time that risk goes back down. So, steroid withdrawal is a very, very potent trigger for MOG attack.

[00:14:48] Now there haven't been a lot of studies looking at what works best to prevent MOG attacks. In aquaporin-4 NMO you might recall that we have dozens and dozens of observational studies. This is where a site will put together 20 patients and say I treated all of them like this and this is the outcome. And so, we learn a lot from that just by experience. Now, we don't have a lot of that information for MOG yet because remember the antibody test itself is only available for about five years in the US. So, you have to put these data together and see if the treatment actually works. When the UK, they had a jump start on us two extra years to collect their patients. And my colleague at UCL University College London, Dr. Hacohen, she is a pediatric MOG doctor and she put together a whole, all of her experience with preventive treatment and her kids. She looked at MS therapies. And the number I put at the bottom here is the number of kids who failed that treatment. So, if you use the injectables with MS 10 out of 10 will fail. No point in doing that.

[00:16:01] What about azathioprine? About 10 out of 20 failed. Mycophenolate? Also, about half. Both of these are immune suppression drugs that just generally keep the immune system calm. We use them for a lot of other diseases, autoimmune diseases where we're trying to just calm the immune system down. rituximab, very popular choice in the aquaporin-4 NMO patient population. Six out of nine failed. And we put a study together in grown-ups where about two thirds will fail rituximab. So, rituximab great for NMO, not so great for my MOG.

[00:16:41] IVIG seems to be the best. This is intravenous immunoglobulin. We still had a failure rate in four cases here and some of that relates to the dose. We did a study in grown-ups with Mayo Clinic, Dr. John Chen led that study. They showed that if used the regular dose of IVIG you have a failure rate of about 40% but if you use the higher dose, your failure rate drops to only 20%. So, we're getting better at it. IVIG seems to be the best of the options that we have so far.

[00:17:14] Here's that study in grown-ups, I was telling you about with rituximab where each horizontal line here represents a patient. There were, I can't remember how many patients in the study. We could see a lot of patients and all of these dots represent relapses. So, here's a patient that had relapse, relapse, relapse,

relapse then a remission and relapse, relapse. And then at this time point here marked by the vertical line rituximab was started and then any dot after that was a relapse. So, you can see all of these here are relapses. Everything on this side of the vertical line is a relapse were basically about two out of every three patients relapsed despite the rituximab. And that's not what we see with aquaporin-4 NMO. aquaporin-4 NMO we see an 80% response rate where this whole area under the curve you would have very few dots. So, MOG not as responsive to rituximab as we were hoping.

[00:18:12] Now, there are some approaches that seem to be useful. I showed you data with steroids. We don't like to use steroids on a long-term basis. Lots of side effects. I don't have to go into those. I'm sure people who have used steroids know them better than I do having experienced them. IVIG and subcutaneous IG which is another formulation that a little bit safer is a very useful approach, both in adults and kids. Same with immune suppression. You get about a 50-50 shot there. Then there are new approaches using a cytokine blocker like tocilizumab blocks IL-6. In clinical trials, I'm just going to name two of these here. One is called cosMOG. This is a trial of Rossano Ixekizumab which mimics the effect of IVIG in a different formulation and hopefully doesn't cause as many side effects.

[00:19:07] Wherever IVIG is useful in other autoimmune diseases, this drug is being developed in those diseases and is proving itself useful. Now for MOG this is a placebo-controlled study, but people are only allowed one relapse. To make it ethical we don't want people to relapse over and over and over again. If you relapse once you're in the open label phase, no more placebo. Then you get drug for certain from then on. It's a one-to-one randomization and we need to accumulate about 50 relapses or so in order to make a good statistical conclusion about whether this drug works. We've just enrolled our first three patients; I think it's expected to report out in 2025.

[00:19:57] In order to get the number of patients we need for all of these relapses we're going to open sites all around the world. You can see on this map here where we're going to go. And the criteria require that people with MOG have recurring disease. So, it's not just the monophasic type. You can't just have one attack. You have to have more than one. You have to have a recent attack. You have to test positive for MOG and then you can't be on another therapy. You have to come off. The primary endpoint is can we prevent attacks. That's basically what we're trying to do here.

[00:20:36] Now, the second study is very similar in the design to Rossano Ixekizumab but it's testing satralizumab. Satralizumab is an interleukin six blocker. Interleukin six is pro inflammatory. We want to try to suppress inflammation associated with MOG. It's proven in aquaporin-4 NMO and there's good data using the older version of satralizumab in MOG. We think that that is a hopeful approach. And you can see this is using the old version of satralizumab called tocilizumab. You can see all these relapses occurring before the vertical line here. All these diamonds are relapses. Not many diamonds after that vertical line. So, after you start, the older version of satralizumab you don't see a lot of relapses. That suggests this approach by blocking IL-6, it's going to be useful. The criteria are primarily the same. This is going to be a phase three randomized. It's going to be placebo controlled. But if you're on azathioprine or mycophenolate you don't have to come off of those. Otherwise, the criteria mostly the same. We're trying to prevent relapses. And this is being evaluated worldwide. Hopefully, we'll have two FDA approved drugs by 2025 or shortly thereafter in MOG antibody disease. Thank you so much.