Community Q&A

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[00:00:04] **Dr. GG deFiebre:** Thank you so much, Dr. Sotirchos, for joining us again today for another kind of Q&A session after the MOGcast yesterday. So, just to start, can you just describe MOG antibody disease just for those who may not be familiar with the disorder?

[00:00:22] **Dr. Elias Sotirchos:** Yeah, definitely. So, MOG antibiotic disease: It's an autoimmune condition that affects the central nervous system. And when we say central nervous system, that means the brain, spinal cord, and we're also referring to the optic nerves, which are the wires that carry information from the eyeball to the brain to tell the brain what the eyes are seeing.

[00:00:42] And so, MOG antibody disease is a condition that's characterized by the presence of antibodies in the blood directed against a component of the insulation around the nerves in the central nervous system called myelin. Specifically, MOG means myelin oligodendrocyte glycoprotein. And that's an ingredient of that myelin sheath. And so, the thought is that the presence of these antibodies, it's essentially the immune system is attacking that myelin sheath. It shouldn't be doing that.

[00:01:13] Our immune system is there normally to fight up infections, but it becomes misguided in the immune response and attacks part of the own body. And generally, the way that MOG antibody disease manifests is with kind of discrete attacks we would call them or sometimes relapse is the term that may be used, especially for the second or third attack if somebody has more than one, with kind of a development of symptoms over a period of a few days to weeks involving depending on the part of the central nervous system as well.

[00:01:47] So, if it's the optic nerve that will lead to vision problems, the spinal cord can cause weakness, numbness. If it's the brain, it can cause confusion, sleepiness, so there are a variety of symptoms. And typically, these episodes will last weeks to months and with each episode where somebody may recover afterwards, but the degree of recovery is variable from person to person. Some people may recover very rapidly with acute treatment of steroids in some people there might be some degree of permanent damage that can leave disability.

[00:02:18] **Dr. GG deFiebre:** Great. Thank you. And then I just wanted to ask a question about, we talked yesterday in the MOGcast about different treatments. And so, we talked about IVIG and subcutaneous IG. Is there a possibility of getting those approved for use, at least in the US?

[00:02:37] **Dr. Elias Sotirchos:** So, I think that all treatments have the potential for approval. What they would be required though in order for formal approval by the Food and Drug Administration, the FDA, would be at least one randomized clinical trial, which kind of means that people are coming into the study. We essentially flip a coin and randomly assign people to a treatment, or a placebo-controlled trial would be necessary because

there's nothing approved right now for MOG antibiotic disease in order to kind of conclusively demonstrate that these medications actually work because yes, we have the experience of just putting people on treatment and seeing that attacks stop.

[00:03:20] But there are a lot of things that have been proposed to work for a variety of conditions, but when they actually get put to the formal test of doing a clinical trial, like a formal experiment, they don't actually work. And so, that would be what is required, and that's kind of the threshold, the bar of evidence that the FDA has in order for approval.

[00:03:42] And that's why currently there are two phase three trials going on with treatments that are randomized control; they couldn't just put people on them and see what happens. The placebo is really necessary because yeah, and some people with MOG might do well even without treatment, sometimes it can be a single attack and not have another one where people can go several years without an attack.

[00:04:01] So, you have to be able to kind of account for that when you're examining whether a treatment works or not and also get an idea for just how well it works. And then the other issue that also the FDA examines is safety and kind of tolerability. I have to say, with IVIG subcutaneous IG, that's relatively well described because those are medications that have been used for years and many years for other indications as well, but especially with kind of newer treatments, that's something that needs to be characterized fully.

[00:04:32] **Dr. GG deFiebre:** Great. Thank you. And then I see a question here from Julie. What does extreme emotional or personal negative stressors play in either the development of MOGAD or the increased risk of relapse? So, many talk about an illness that led up to a relapse or onset of disease, yet others point to a divorce or death of the loved one preceding the onset.

[00:04:55] **Dr. Elias Sotirchos:** That's a great question. It's really difficult, I'd say, to pinpoint what causes MOG and how it can influence relapse risk in general. I mean, I have to say we don't really know why some people develop MOG and some people do not. The same is true of many other kinds of similar conditions. So, for multiple sclerosis, for neuromyelitis optica, it's very difficult to kind of put our finger on specific triggers.

[00:05:25] A lot of things have been proposed, but it's very difficult sometimes to ascertain what is because there are so many things that are happening in our lives. We're exposed to so many things: viruses, infections, stress, vaccines, things like that. And it's difficult to kind of pinpoint one thing versus another causing it. And to be frank, it's likely not with just a single thing. It's likely kind of a perfect storm, I would say.

[00:05:50] Maybe a combination of getting an infection at a specific time, some sort of other environmental factors that we might be exposed to, possibly some sort of genetic predisposition, I think, likely exist, and we do think that these exist with a lot of these autoimmune conditions, but they don't fully explain developing the disease. And so, I mean, we know that clearly in MOG infections play a role since many people will develop their first attack following or preceding infection.

[00:06:22] And I mean, that kind of makes sense. It's an autoimmune disease; maybe the infection somehow revs up the immune system. You can imagine it in a way that the immune system then starts attacking parts of your own body, but stressors and emotional stressors and things like that can definitely also can be caused, have a lot of kind of impact on our bodies as well.

[00:06:46] Clearly mood, significant life events, and things like that can have effects on our body that can impact; also, other things like our diet, our sleep quality and things like that, and that can impose a stress on the body. So, it is conceivable in my mind that that could influence the development of the disease, but it's

something that's really difficult I would say to study just because they think they're also relatively common in the background.

[00:07:11] And it's tough to tease out what really caused some… just because something happened after something else doesn't necessarily mean you can say 100% that it was caused by it. So, I think that we need more research to better understand that.

[00:07:27] **Dr. GG deFiebre:** Thank you. And I'd also just encourage the participant here, too. You can unmute and ask questions too. So, feel free to do that. Let's see, we got a question here about the clinical differences between NMO and MOG. They have different antibodies, but the symptoms seem similar, and I know some folks may have been misdiagnosed as having NMO, and then when the antibody test came out being diagnosed with MOG. Do you mind just talking a little bit about the differences between the two?

[00:08:01] **Dr. Elias Sotirchos:** Yeah, definitely. So, I mean, I think that there are a few differences overall, just starting kind of from the age and the characteristics of the people who get one versus the other. MOG antibody disease is relatively common at least in patients who have central nervous system autoimmune diseases in children, actually. So, whereas aquaporin-4 antibody positive NMO is rather rare, it can happen in children, but it's not common at all.

[00:08:31] So, that's kind of a difference, kind of off the bat, that MOG is generally more common quite a bit common in young adults and children compared to NMO, which has kind of a median age of onset around 40. But again, both of these conditions can really occur at any age. Another, I think, important difference is the difference in the sex of people who have the disease.

[00:08:57] So, based on kind of sex assigned at birth, in NMO, about 90% of people with NMO are women. So, there's kind of a very exaggerated ratio between females and males in terms of who's more predisposed to the disease. In MOG, there does seem to maybe be a slightly increased risk amongst females. But the risk is that the ratio is much lower. It's maybe 1.5 with females to one male with the disease.

[00:09:27] So, that's another I think characteristic that's quite a bit different. In terms of the clinical difference in what people are experiencing. So, they both can cause attacks. And so, it's similar in that aspect, both can cause optic neuritis, transverse myelitis. There are some distinctions in the way that they look on imaging that can help us distinguish.

[00:09:46] Generally NMO attacks and MOG attacks can both be severe with NMO attacks can often be more severe than MOG. But definitely there's a lot of overlap. But the main difference that we've observed quite a bit is in the recovery from an attack. So, in MOG especially with kind of a single attack, recovery can often be good. Now again, this is just—we're talking on average because there's variability in all these things and these are all heterogeneous diseases.

[00:10:13] So, there are a lot of people with MOG who can develop significant disability even with a single attack. But kind of on average we're discussing here, people with MOG generally will recover better after an attack. Whereas in NMO the attacks can be somewhat more severe, and the recovery can sometimes not be as good. Another difference is that in MOG, often people will have ADEM. Well, at least in kids, it can often manifest with something called ADEM acute disseminated encephalomyelitis, which involves the brain, the spinal cord as well.

[00:10:46] Whereas in NMO generally, brain involvement is relatively rare. So, it's more common in MOG. Another difference is that in MOG, optic neuritis seems to be much more common, especially in adults with

the disease. And whereas NMO can affect the spinal cord somewhat more frequently than in MOG, but overall, there's a lot of overlap.

[00:11:09] **Dr. GG deFiebre:** And are people ever—do they ever test positive for both aquaporin-4 and MOG?

[00:11:17] **Dr. Elias Sotirchos:** That's a great question. It's somewhat controversial. So, there have been reports of people testing positive. However, by both, however, we have to understand that the MOG assay especially is not a perfect test. So, the MOG test can sometimes be positive in people who don't actually have MOG antibody disease. So, at low levels, we sometimes can find that in people who are healthy controls or in people who have something that is clearly not MOG antibody disease.

[00:11:47] And so, whereas the NMO test actually with the newer cell-based assays is very specific, and it's very rare to see false positives. And so, there is some controversy about these cases that have been reported to be double positive about if these patients actually had just NMO and the MOG was a false positive. And that has been my experience.

[00:12:11] The only cases that I've seen where I've been positive for both the clinical kind of picture and all the characteristics have been clearly consistent with NMO, for example, I felt that the MOG was a false positive. I've also seen the reverse happen where somebody was tested for NMO by an older test called an ELISA.

[00:12:30] Which, that can sometimes have false positives, was very clear that this child had a MOG antibody disease, but they were misdiagnosed with NMO. So, my personal interpretation of the data is that I don't think that there are people who are really positive for both. I think that most cases that have been reported are likely false positives or kind of a spurious positive you can think of.

[00:12:58] **Dr. GG deFiebre:** Great, thank you. Julie, do you want to ask—I see you got some questions here in the chat?

[00:13:03] Audience Member: Yeah, I'm a little shy today. I probably asked them this question because I've been sick for almost a week now or at least half a week. And somebody has been, well, and this is obviously me talking about myself. So, somebody's been well under control with their preventative, yet kind of carrying a good titer, like, say one to 100. You know, viruses and infections and things like that have not really caused relapses so far.

[00:13:35] In other words, the preventative seems to be really great. Is it still possible for any really bad infection, viral or whatever, to cause a relapse? So, what I'm saying is in other words, can a MOGAD patient ever really like to be confident and rest easy that they're preventative is if it's working is going to continue?

[00:14:00] **Dr. Elias Sotirchos:** That's a good question. I've got to say, it's really difficult. It's a tough question to answer. I mean, one thing, I'd say that in many cases, we do see that the first attack is following an infection for example. I have to say, like with relapses, it's not necessarily clear to me that the pattern is as well time locked to infections. It seems to me more random and sometimes just occurs out of the blue in my experience.

[00:14:29] But definitely an infection can potentially be associated with a relapse. Although, I would say that again, infections are so common, right? Like people are going to have at least a few colds a year, especially if they're in, people have children at home or people who are working kind of in an environment with a lot of other people. So, I'd say it's difficult to say, I think one other complicating factor is that sometimes people might feel worse in the concept of an infection.

[00:14:53] Something that may be termed a pseudo-relapse, where when people are sick or under stress for some other reason, kind of old symptoms may reemerge or become worse due to the fact that you're tired, you're not sleeping as well, you're having a fever. And we know that overheating or fever can cause old symptoms to reemerge because we think that what happens is that nerves that are lacking myelin actually, when they're overheated, the signals, electrical signals actually slow down.

[00:15:24] So, it's not really a new attack. It's not a new attack of the immune system on that part of the body. We think that it's kind of the old symptoms re-emerging. I mean, I would say that if somebody has been stable for years on a maintenance therapy and we haven't changed the dose, I find that very reassuring in general, but that doesn't mean that it's impossible to have an attack.

[00:15:48] I think that we always have to kind of take new symptoms and these kinds of things seriously and consider whether an attack could be occurring, but you also can't avoid infections completely. I mean, again, we tried that with COVID and in general it didn't work. I mean, it worked temporarily, but you can't do that indefinitely.

[00:16:09] So, people are going to be exposed to infections. I think the best thing that we can do is try to mitigate that risk with appropriate vaccinations as indicated and common-sense measures like hand washing, like not exposing ourselves to people who are sick, things like that. But there's only so much that we can do overall.

[00:16:33] **Dr. GG deFiebre:** And then does the timing of an MRI make a difference in investigating a relapse of MOGAD? So, can an MRI that's either too late or too early make a confirmation of a relapse difficult?

[00:16:49] **Dr. Elias Sotirchos:** Yeah, I mean, definitely the timing does seem to matter, I would say, in my experience. I'd say there's not that many studies, I would say, out there on exactly this topic. And one of the tricky things is that sometimes we've seen people who clearly have an attack, but the MRI doesn't really show it. I mean, usually in those situations, what I've seen is that either of the MRI is delayed, especially if it's done after somebody has started steroids, kind of empirically.

[00:17:16] Not talking like one or two days, but I'm saying like a week or two after somebody has gotten steroids, that might kind of calm down the lesion and then you might not see it, or you might not see contrast enhancement, which we often look for to tell us that something is active. Or sometimes it's just kind of, especially in the spinal cord, it can be tricky sometimes to see a lesion because the spinal cord is small.

[00:17:38] It's moving with our taking a deep breath. Also, if somebody is moving a little bit in the scanner, there can be motion artifact, and that might make our ability to detect the small lesion compromise it. So, I mean, the most important thing really is clinically to kind of define whether we think there's a relapse going on by the neurologic exam.

[00:18:00] There's a clear objective finding that we can have. And then I think the MRI is useful for confirmation, but generally, you have to interpret it with a grain of salt, especially if it's been delayed and done a week or two after steroids. Cause one of the characteristic things of MOG also is that at least long term in studies that have been done, we have seen that sometimes MOG lesions may disappear on the follow up MRI.

[00:18:27] Which is something that we don't really see. I have to say with MS in general or with neuromyelitis optica, usually you're going to see something stay there, some sort of scar that remains visible. But with MOG antibody disease, sometimes we've seen lesions just disappear on MRI and you might not see them if you scan somebody too late.

[00:18:47] **Dr. GG deFiebre:** Thank you. Julie, do you want to ask your question? Cause it's kind of related to confirming a relapse with MRI?

[00:18:57] Audience Member: Yeah, it has to do with some people that have contacted us at the MOG project about trying to get into a clinical trial and the trouble that they've had and just, I'll give you a specific example that seems to be repeated a couple of times. Somebody who's on a medication that's not quite working for them, like Rituximab, for example.

[00:19:21] Sometimes it seems to work pretty well, but yet they're having some increased symptoms, and their insurance isn't such that—maybe they're on Medicare, they really can't get IVIG or subcutaneous IG to try that. So, their options are limited. So, they wanted to go towards a clinical trial and with these increased symptoms, there's no MRI findings.

[00:19:50] And so, they're not being confirmed as having a relapse, despite the fact that they're feeling worse, and they're getting worse in some cases. And so, I guess my question is, if a person has these worsening symptoms that are measurable in exam despite no MRI findings, is there a way to get them confirmed, their eligibility confirmed for one of these clinical trials or do you know the answer to that?

[00:20:25] **Dr. Elias Sotirchos:** Yeah, I mean, I'd have to go back to look at the protocols. If I recall correctly, I mean, the trials don't require MRI confirmation that a relapse has occurred, but it has to be something that's clearly kind of a relapse at least. So, let's say that somebody is having worsening symptoms. They also would have to have been evaluated by a neurologist with kind of clear objective worsening on neurological exam compared to their baseline.

[00:20:51] So, that the neurologist could then say, "Yes, this clinically I can define this as being a relapse." Cause again just to provide more background the two clinical trials that are recruiting only people who have relapsing MOG antibody disease, which means that they have had two or more attacks total in their lifetime with at least one within the past year or two within the past two years, if I'm not mistaken.

[00:21:19] So, in general, people have to have at least one attack, but I don't believe that it was requiring MRI for those historical attacks. It's just that you have to have some sort of documentation from a neurologist at the time. That kind of clearly can say, "Okay, this is an attack." So, one of the things that we sometimes see is that symptoms can reemerge and again it's sometimes it's not. And again, I'm not saying they're not a relapse, but sometimes it can be subtle, or it can be mild, and the neurological exam might not see that change.

[00:21:49] And so you can't really say 100%---it could be a pseudo-relapse or something else going on. And so, for trials especially, we want to make sure that we're kind of rigorous and as accurate as possible. So, you don't want to enroll people in a trial who might not meet the criteria because then you might dilute the effect of the drug and the ability of the trial to actually demonstrate an effect of the trial medication.

[00:22:18] Audience Member: Yeah, that's interesting, and just a follow up comment. I mean, I think one of the biggest complaints from patients that we hear, because they're sort of venting to us, is that maybe their neurologist isn't as versed in understanding these relapses. And something that they have come on—that months later, it's like, "My arm is numb now forever," and it came on slowly.

[00:22:48] They were controlled under one of these medicines like Rituximab, just using that as an example. They now have this what seems to be just something that will be there forever. And they're like, "Well, I couldn't really get this relapse confirmed or treated," and I think that's a difficulty that patients face.

[00:23:11] **Dr. Elias Sotirchos:** Yeah, I mean, that's challenging, and I mean, it's difficult to say without kind of being involved in specific cases or examining. But I mean sometimes, yes, in my experience, especially kind of mild changes can sometimes potentially be missed. But also, sometimes there are things like pseudo-relapses or other things at play, and sometimes it's not even MOG. Like, I've had a MOG patient develop new back pain kind of. And I was concerned they have neuromyelitis.

[00:23:40] I bring them into the office and their exam to me is more consistent with a herniated disc. And we did an MRI, and they had a herniated disc pushing on a nerve. So, just because somebody has MOG doesn't that, they're immune to getting other more common things that can also cause these sorts of symptoms that might look like MOG for all intents and purposes. So, that's one of the challenges too to make sure that it's actually due to MOG and not something else that's going on.

[00:24:07] Audience Member: Thanks.

[00:24:10] **Dr. GG deFiebre:** Yeah, and so we have a question, too, from someone that says that they were newly diagnosed with MOG. Should they expect to have a relapse, or maybe if you could talk a little bit about what predictors of relapse we know about, if there are any?

[00:24:26] **Dr. Elias Sotirchos:** Yeah, no, that's a really challenging question. I mean, ideally, and I think that's kind of one of the very important avenues that we have to investigate in our research. Because what we know currently is that the risk of a relapse varies quite a bit. About 50% of people may have a monophasic course, which means a single attack. And it's kind of—at least during the follow up that we have in the studies that exist—that might be the only attack that they experience in their life.

[00:25:00] But a proportion of patients may go on to have a second attack. And there are many people who may go on to have not just a second attack, but several attacks. Even every few months we've seen people who are highly active. And so, there is a spectrum kind of in terms of the way that the clinical course of MOG can manifest from person to person.

[00:25:21] Now, in terms of predictors, there is no foolproof way, I think is the first problem, to predict whether somebody is going to have an attack or not. But there are some features that may be associated with a higher versus lower risk of attack. But none of these things are kind of absolute, they kind of shift the probability a bit, but they're not necessarily 100% accurate. So, a few things that we like that are kind of the most well recognized.

[00:25:47] One is pediatric onset, especially in pediatric cases with ADEM, acute disseminated encephalomyelitis. So, in those cases, I would say there's quite a higher than 50% probability based on my experience in existing studies that those patients will have a one-time attack. And that if we actually look back at the literature on ADEM, before MOG was even discovered, it was kind of described as this monophasic disorder of childhood initially.

[00:26:17] And then we recognize that, oh, by the way, 60 to 70% or even more of these kids actually have MOG antibodies if you test them at the time of the attack. So, that's I think the first category. So, pediatric onset and ADEM are features that seem to portray a higher chance of a monophasic course. But that doesn't mean that somebody with ADEM can't go on, like we've seen children have ADEM.

[00:26:42] And again, we don't start treatment because we don't know if they're going to have another attack. We don't want to expose them to medications and the inconvenience of medications as well. And then, for

example, we've seen kids two years later then have an optic neuritis. And so, they then demonstrate kind of a relapsing MOGAD, of course, so that can occur.

[00:26:59] Or sometimes patients can have a second episode of ADEM. So, that could definitely occur, but more likely monophasic. Other features that may be associated with a monophasic course are some studies have suggested that maybe lower titers of MOG antibody at the time of the first attack might be associated with monophasic course and then potentially becoming negative on follow up testing.

[00:27:23] So, if you test at the time of the first via attack, and then you retest a year later is kind of in most studies, what have been shown is that if that becomes negative at a year, that might be associated with a lower risk of attack. However, that's not foolproof. So, we've seen people who remain positive and don't have another attack, at least for the years that we've been following them.

[00:27:44] We've also seen people who become negative but then become positive again and then have a further another attack, so it's not 100%. Other features that might be associated are the type of the attack in adults. So, there's a couple of studies that show that perhaps spinal cord involvement. So, TM, transverse myelitis, might be associated with a lower risk of relapse compared to optic neuritis in adults.

[00:28:10] And those are really the main features otherwise, I mean, there are some things that are being investigated, like there was a recent publication from a group in Australia that kind of investigated, like, what part of the MOG protein does the antibody bind to and show that potentially if the antibody binds to a specific part of the MOG protein that, that might be associated with a higher risk of attack.

[00:28:36] But this is kind of like just the first study. And so, these are findings that it's not a commercially available test or anything that needs to be validated and investigated further, but it's definitely very promising and interesting kind of finding that could allow us to better prognosticate for people with that first attack, whether they're going to have a second attack.

[00:28:58] **Dr. GG deFiebre:** And so, if someone is currently kind of testing negative, whether they had an attack of optic neuritis or transverse myelitis, if they currently test negative, how often should they retest, or is there kind of like a protocol for that?

[00:29:15] **Dr. Elias Sotirchos:** Yeah, that's a great question. I mean, I would say there is no protocol and it's very controversial. I mean, some would say that it's not really going to change, maybe, what you do to retest frequently, and so might not need to retest. Others may want to have that piece of information and help it guide them. So, they might do annual testing sometimes.

[00:29:38] I mean, I do generally check annually but I have to say it doesn't have a huge impact on my clinical decision making. I do it often for potentially more for research purposes in order to kind of monitor things over time. Although sometimes it can be useful. The main, I think use case in my opinion is kind of that one-year mark after the first attack. If somebody becomes negative, would that kind of help to counsel them that, you know, maybe your risk of a future attack is somewhat lower.

[00:30:07] But then I think there are other features to take a drug count is that a lot of the treatments we use can make the MOG antibodies titers go down or become negative. So, just because it became negative, doesn't mean that the person is cured of MOG. It could be that the treatment did it, and then you could stop the treatment, and then it could come back. But it's not entirely kind of clear how to best use MOG titers, I would say at this time.

[00:30:35] **Dr. GG deFiebre:** How does MOG affect a child's behavior, or is that related to ADEM potentially?

[00:30:49] **Dr. Elias Sotirchos:** I mean, that's a great question. I think that there's still work to be done there. What we do think is that, I mean, first of all steroids in and of themselves, of course, can affect the behavior of children, like they can cause irritability, they can cause psychosis, they can disturb sleep. There's a lot of things just from a treatment itself and the steroids especially are a culprit very frequently.

[00:31:10] I mean, ADEM does affect the brain. And so, that can potentially kind of—even though a lot of these children improve quite a bit and very rapidly—that can potentially kind of affect behavior and even maybe cognition to some extent. And so, I think there's a need for more studies for this. We've been referring more—again, I'm not a pediatric neurologist, but I do have colleagues here and I work with pediatric neurologists, and I do see children.

[00:31:42] And we've been working with a child neuropsychologist to refer these children to and have them undergo formal neuropsychological evaluation to try and identify behavioral changes or maybe cognitive domains that might have been affected by their ADEM. But I have to say, it's very interesting that often it's rather mild and we've had children who were very confused, kind of had very severe ADEM were in the ICU.

[00:32:15] And then a few months later after steroids, they're back in school and performing as they were before the event. But sometimes we're able to pick up some subtle deficits on the neuropsychological testing. So, it varies quite a bit from person to person, but the brain involvement definitely is something that's been documented.

[00:32:35] And I think, but I definitely think there's need for more work to better understand that with detailed neuropsychological assessments. MRI that's a good quality research grade MRI to look at kind of brain volumes and development of the brain over time and maybe specific structures that could be involved in order to characterize the effects of ADEM on children's brains.

[00:32:59] **Dr. GG deFiebre:** Thank you. Julie, do you have a question?

[00:33:02] Audience Member: So, this is maybe a loaded question. I'm not sure if you can answer it or not, or maybe generally. So, we're sort of under the impression that the way that statistically that phenotypes occur in patients is if you've had optic neuritis, you could get TM, you could stick with the NMOSD symptoms or if you have ADEM, maybe you could get ON later.

[00:33:28] And so, there's sort of at least for us there's a known pattern to like, if you start with this, you get this, if you're a child, you're more likely to get ADEM or autoimmune encephalitis, and you might go later to ON. So, is it unusual for an adult who had had a severe, and this comes from one of our community members, she had a severe attack of optic neuritis and a little TM in her life.

[00:33:55] She's completely blind, and under Tocilizumab last year she had a massive autoimmune encephalitis attack that was very damaging. Is that something that patients, I don't want to say have to worry about, but is it very uncommon, is it something that you've seen before where something like that could happen? Even an ADEM attack or something in the brain can occur from somebody who's had just maybe bilateral optic neuritis?

[00:34:28] **Dr. Elias Sotirchos:** I mean, that's a good question. I mean, I think that it can definitely happen, but I would say that it's rather uncommon. So, the majority of people who have had optic neuritis in my

experience, really their recurrences have often also been optic neuritis. So, I would say that in general, brain involvement, especially in adults, is relatively uncommon.

[00:34:54] Then if somebody who had optic neuritis and had a recurrent optic neuritis as their initial presentation to then go on to have brain involvement, it's very uncommon in my experience. Now, I have to say one caveat is let's say somebody's had three episodes of optic neuritis, we typically will have them on a treatment.

[00:35:17] And so, I don't know if they had not been on treatment, if they would have gone on to have had a brain involvement. But sometimes we've seen people who have had optic neuritis recurrent for a decade and they've just been treated with steroids again and again and again. And I have many patients like this and never really got put on a maintenance until later in the course of the disease and never had brain involvement really that we can tell even though their eyes had been severely affected by the multiple recurrent attacks.

[00:35:43] So, I would say, I mean, you definitely have to be—people with MOG need to be aware of the potential symptoms, need to kind of be vigilant about them and report them to their neurologist. But I think that in general, that is an unusual, relatively uncommon. It can happen with MOG, anything can happen, but it's uncommon, I would say.

[00:36:08] Audience Member: Okay, so diligence in all of the symptoms and report anything is the right thing to do. And the MOGAD community is small, and we all talk to each other, at least a lot of us. And something like that gets out, which it will, and everybody is in a fearful mode. So, I think that's very helpful, thank you.

[00:36:34] **Dr. GG deFiebre:** And so, the next question I have is actually from, I'm translating it with Google Translate from Italian. So, hopefully it is accurate. But so, this is—and I'm going to kind of direct this to both Julie and Dr. Sotirchos, where the parents of a two-year-old child who following an ADEM attack discovered the presence of anti MOG antibodies.

[00:36:56] "We are entering this world. Everything seems very big to us. We wanted to start…" I guess they kind of want the right awareness of "what the future of our little guy could be, and above all, how we can give ourselves and give him the best support possible." This will start with Julie.

[00:13:03] Audience Member: Well, I mean, my advice as a patient is to get to one of the best doctors you can. And one of the doctors on our medical advisory board is Elias [inaudible]. And I hope this translates well, I really do. I unfortunately don't speak Italian, but also connecting to us, that is one way that can be very helpful. We're able to use tools like Google Translate and also use some of our advisors for pieces of advice around the area to try to find some support.

[00:37:54] But we have a lot of resources, and learning the best that you can, it gives you the best chance to do well with this disease. And so, we're lucky that we have all these experts like Dr. Sotirchos who offer us these services where he comes in and talks about it. You really can't get that from your local doctor. And so, connecting to an organization like the SRNA, the MOG project. I mean, we work really well together to try to make sure that everybody has what they need as far as information goes.

[00:38:29] **Dr. GG deFiebre:** Yeah, thank you Julie. Dr. Sotirchos anything kind of from the provider perspective?

[00:38:35] **Dr. Elias Sotirchos:** I mean, I think that in general I would echo Julie's thoughts about kind of establishing care with an expert neurologist to get kind of the best treatment that you can. And then kind of preparing for the course ahead. I mean, there's a lot of unknowns, as I mentioned previously. I mean, on the one hand, this could be just a one-time thing and often pediatric ADEM it doesn't happen again.

[00:29:03] But you do have to be vigilant and be aware of the symptoms and be on the lookout because there are always—there is a potential risk of relapse. So, you do want to make sure to be vigilant about that to ensure that your child receives treatment as early as possible. And the best way to do this is to be linked with a neurologist who has expertise in these diseases so that they can guide you through and make sure that the work up has been done appropriately to begin with and make sure that the diagnosis is accurate.

[00:39:31] Because again, one of the things that we have to be aware of is that the diagnosis is, it's not like all the test is done and it's positive and we're done, you have to make sure that everything is kind of compatible and the diagnosis is correct. But the first thing, I make sure whenever I'm first seeing a patient referred for a diagnosis of MOG antibody disease.

[00:39:49] And then when you're, if you're linked up with a neurologist with expertise in that in the disease, they could help guide in the situation. Again, hopefully that situation never occurs, but if a relapse does occur, they can help you be prepared in order to seek treatment immediately because we do think that early treatment in the case of a relapse can help ensure better outcomes.

[00:40:12] **Dr. GG deFiebre:** And then we often get asked this, if there's any kind of natural method or alternative complementary therapy to prevent relapse in MOGAD?

[00:40:27] **Dr. Elias Sotirchos:** That's a great question. I think that it's very important that we investigate lifestyle factors and other things like that and see how they can complement or do some treatments. I'd say that we don't really know. I mean, what is I think the short answer, I think that we can potentially try and extrapolate from some other autoimmune conditions such as MS and see what we know about lifestyle factors, dietary factors, vitamin deficiency and try and apply that to MOG antibody disease while we're trying to accumulate more data.

[00:41:04] In my opinion, the most important things are: one, is a healthy lifestyle overall. So, diet, exercise. And when I say diet, I mean, there are a lot of things that have been proposed in general. I personally am a proponent of a Mediterranean style diet, which does have relatively good evidence for just general health, cardiovascular health, but also for neurological diseases for things like dementia.

[00:41:32] There are studies, for example, in multiple sclerosis that support that a Mediterranean style diet may be associated with a better sense of wellbeing and less disability. Exercise is very important. Again, any sort of exercise is adequate. It's whatever somebody will actually do and likes and enjoys doing.

[00:41:53] Whether that be some sort of a sport, whether it be anaerobic, like weights, whether it be jogging or running or biking, whatever, just staying active or walking, just walking. I mean, any sort of exercise that somebody can do and stay active, I think is very important, and we know that it has impacts both on the immune system and on the nervous system as well.

[00:42:15] So, impacting kind of both of those things in a positive way in people with autoimmune disease. Now, one other thing that has been implicated quite a bit in multiple sclerosis, but trials have been negative, is vitamin D deficiency. Now, vitamin D is a vitamin that is mainly produced actually in the skin by exposure to sunlight rather than through dietary intake.

[00:42:40] There have been a number of observational studies that have shown that people with lower vitamin D levels may have had a higher risk of developing MS and also that lower vitamin D was associated with more relapses in the multiple sclerosis and with eventually higher disability. There are a lot of studies in mice looking at experimental models of MS and MOG that have supported that vitamin D can potentially be beneficial.

[00:43:06] However, clinical trials that were done in MS using high dose vitamin D did not demonstrate an effect on relapse rate. So, my interpretation kind of that data has been, it's a little bit difficult to kind of come up with a concrete recommendation but at least avoiding insufficiency. So, very low vitamin D levels, I think, is probably beneficial. Also, people with MOG antibody disease may often be exposed to steroids which can negatively impact bone health.

[00:43:37] And so, making sure that somebody has a vitamin D within the normal range they think is appropriate. And so, those are really the main ones, like otherwise, there are a ton of things that you can find people claiming on the internet or elsewhere that might have a benefit. I have to say a lot of these have not been studied or another thing with a lot of supplements and things like that is that they're not well regulated.

[00:44:03] So, you might not actually be buying what the label says it is, at least in the United States where there's a lot of unregulated products out there. So, I would advise—what my recommendation is in general for my patients is kind of a Mediterranean style diet, exercise, vitamin D with a goal of being within kind of a normal range. But other than that, I would say that we don't have great evidence to support other sorts of supplements and things like that.

[00:44:34] **Dr. GG deFiebre:** Thank you. Julie, did you have a follow up question?

[00:44:38] Audience Member: I think it was just about some of those supplements, and I hope the Mediterranean diet includes the baklava. So, but I'm guessing that's limited. It's the actual good part of the Mediterranean diet. But a lot of people in chat rooms and things like that, they come and they say they've used Lion's mane and things like that. And we don't know what to think of that.

[00:45:08] People say they've gone on anti-inflammatory diets and felt like they've had success, but at the same time, MOG and the relapses just naturally can be far apart anyway. So, you never know what's working. And so, even if you did a study on that type of thing, how would you, with the really unpredictable way that MOGAD relapsing happens, how would you even get reasonable data on that?

[00:45:43] **Dr. Elias Sotirchos:** That's a great question. I mean, you nailed the issue on its head because that's one of the reasons why a lot of literature and data and kind of diet and impact on diseases is somewhat, I mean, I wouldn't say limited. There are a lot of studies out there but you always, like if you follow the news, you'll see studies like, "Coffee is good for you. Oh, coffee is bad for you," and every week it changes, right?

[00:46:11] And a lot of this has to do with the fact that there are so many things going on and these are not being examined in the context of a clinical trial. As I was saying previously, which is the gold standard to show that something really works where you take people, you assign them randomly to be on a diet or not be on a diet or be on a drug or be versus a placebo and follow them for years and see what happens.

[00:46:35] Dietary research, I mean, there are a lot of things that you have to account for when you're kind of doing these sorts of analysis because, for example, people who are more financially well off, for example, will often have better access to food. I mean, we know in the United States, especially, that is the case with food deserts where people may not have access to fresh vegetables and fruit if they're not financially well off and live in kind of underserved areas of the United States.

[00:47:06] And all of those things are, it's not necessarily that the diet is what's impacting, it might be their access to health care. It might be a lot of other things that are kind of impacting their outcomes and their relapse rate rather than actually the food that they eat. You have to account for all of these other factors when you're doing this analysis and that can be challenging.

[00:47:25] The other thing is that doing trials of diets, I personally haven't done them, but I have colleagues who have done them, they can be quite challenging because people, I mean, food is something that is kind of ingrained in our lives. It's a cultural thing. It's not just the medication that you take every day. People eat for not just for nourishment, but it's kind of a social tradition to some extent.

[00:47:49] And the other thing is that people won't necessarily take the food that you assign them to. I mean, people will eat whatever they want to. And we've seen that in a lot of trials that people don't necessarily adhere to the diet that they're assigned. So, it's difficult. I mean, I would say that a trial would be the best way to examine this kind of prospectively rather than just handing out a questionnaire asking people what they eat and then trying to say, “Oh, people who ate this did better than those.”

[00:48:16] And so, the best way to do this would be to take people with MOG, assign a diet and kind of see what happens over time, try and follow blood work, MOG antibody levels, things like that, MRI features. And I know that there are people who have tried to look into this and design studies like that, but it's just very complex, I would say, and difficult to examine that in kind of just, especially with a rare disease. I mean, this is something that and I'm going to end with this. It's like even in heart disease, as I was saying, like this whole “coffee is good for you or bad for you.”

[00:48:51] These are studies that are looking at stroke or heart attacks or things like that. And we don't like you see kind of conflicting studies all the time in a rare condition where you have much less people to really examine and collect data on. It's even more challenging sometimes. But I do think that well designed prospective studies might be able to answer some of these questions and provide more evidence for various diets versus others.

[00:49:18] **Dr. GG deFiebre:** Thank you. And we got a question about just an update on research, which is I know is quite broad and we talked a little bit about some research yesterday during the MOGcast, but I didn't know if you had any particular research that you're very excited about or think that it would be important to mention for those with MOG?

[00:49:38] **Dr. Elias Sotirchos:** Yeah, I think that's a great question. So, I mean, there's a lot of research going on. Again, I think we made a very big stride just within the past 16, 17 years since the initial report of the MOG antibodies being detected in humans with CNS diseases. I'd say that, I mean, a few things just to discuss from recent, I think. One was what I mentioned previously about this proposed kind of test that could help stratify risk of relapse.

[00:50:14] Again, this needs to be validated. It's not something that's available. But I think that that was very intriguing finding that perhaps what part of the MOG protein the antibody targets could be associated with the risk of relapse. I think another very interesting thing is, over the past two years, there's been a lot more literature on the issue of spinal fluid MOG testing.

[00:50:37] And actually just within the past week, there have been a couple of other studies come out, and I'd say that overall, these have kind of pointed to the fact that about 10% on average across the studies of people with MOG antibody disease may test negative in the blood but positive in the spinal fluid. And so, that, I think, is a very interesting finding, and the availability and this will lead to more availability of CSF testing.

[00:51:08] And optimizing the test for detecting MOG antibodies in the spinal fluid will allow for the diagnosis of people with MOG antibody disease who don't—we can't find it in their blood. Because again, we sometimes see people who kind of, for all intents and purposes, clinically based on their MRI based on their clinical course, they look like MOG antibody disease, but they're negative in the blood.

[00:51:32] And again, about a tenth of patients, it seems for these studies may be like that. And so, I think that that's a very important binding that will allow us to improve our ability to diagnose MOG antibody disease. More work needs to be done, though, to understand whether those patients are different than those who are positive in the blood.

[00:51:55] Some studies have hinted that maybe there are some differences such as people who are positive in the spinal fluid, either only or also positive in the spinal fluid on the blood may have a higher risk of relapse. So, that remains to be determined. Also, it seems like people who have just optic neuritis, but don't have other parts of the nervous system involved may be less likely to be positive in the spinal fluid.

[00:52:18] So, it seems that those people who are positive in the spinal fluid only are more likely to have a brain involvement or spinal cord involvement. So, I think that that's a very interesting avenue of research. In terms of, I mean, others, I mean, there's a lot of studies going on, as I mentioned, kind of observational studies that are collecting data in order to gauge people's risk of relapse. The two phase three clinical trials, which we kind of alluded to a little bit and we discussed yesterday.

[00:52:51] So, these are two international phase three clinical trials that are ongoing of satralizumab, is one of the drugs, and rozanolixizumab is the second drug. And these are, as we said, randomized control trials, half the people in the trial are getting a placebo, half of the people are getting the active drug, and these are trials that are ongoing.

[00:53:13] Both of them are currently recruiting and so we have to finish recruitment and then these patients have to be followed for a period of time. So, we anticipate results within the next few years. But if one or both of these are positive, that could lead to regulatory approval by the Food and Drug Administration or regulatory authorities in other countries or treatments for MOG antibody disease. Everything currently is off label.

[00:53:40] **Dr. GG deFiebre:** Great, thank you. Julie, you have a question?

[00:53:45] Audience Member: It's more of just asking Dr. Sotirchos to elaborate a little bit on just—and this is based on some work that we did together with patients on the quality of life for MOGAD, and this includes anxiety, depression, just social stigma that comes up and also any kind of other mental issues. It's seen as a big concern in the community because people seem to have that. Could you talk a little bit about that before we end?

[00:54:24] **Dr. Elias Sotirchos:** Yeah, definitely. And so, I think that this was a really nice collaboration that we had with the MOG project to administer a survey to examine quality of life in people with MOG antibody disease. And we had a lot of people participate and report their experience. Over 200 people participated in this survey using the standardized instrument called the Neurological Quality of Life.

[00:54:54] And this examined a lot of it examines a lot of domains, it examines depression, anxiety, self-reported kind of cognitive function. Again, not an objective assessment of it, but if people felt that they were experiencing cognitive dysfunction, kind of if they felt that they had social stigma and symptoms like that. And I do think that it was quite illuminating overall.

[00:55:20] We did find a relatively large percentage of people with MOG antibody disease reporting anxiety, reporting social stigma and impairment of social function and some people reporting kind of issues with kind of like brain fog cognitive symptoms as well. We didn't find kind of a clear relationship, I would say, between specific features being associated with that except for—the main one was really that people who were relapsing MOG antibody disease, which kind of makes sense.

[00:55:52] People who had more than one attack had higher levels in general of anxiety and some of these other kind of symptoms, which makes sense because if you've had more than one attack, I mean, people might have had more damage potentially, but also more anxiety that, "I'm going to have another attack because of the fact that I've had two or more attacks already."

[00:56:13] And so, that is something that we've presented at a conference and we're currently in the process of publishing. But I think that that will be kind of an important, it's an important kind of initial study to generate a hypothesis and kind of gauge the prevalence of these symptoms in people with MOG antibody disease. And moving forward, I think that we would like to try to do these in a more rigorous manner where we're actually administering the surveys ourselves directly to people who, we have their medical records, for example, and can kind of abstract from that all the treatments they've been on all of these things in a more granular fashion.

[00:56:53] But there are only so many questions you can fit into a survey before somebody gets tired of it and doesn't do it. So, we had to make the survey relatively short just so that we can maximize people's participation. But if we were to follow this up, kind of looking at people across sites where we actually followed at our institution, I think we'd be able to get a little bit into more details of that and see what kind of factors are associated with these symptoms and ways potentially that we can treat them better as well.

[00:57:25] I think there's another important finding of this study that it kind of raises the issue that neurologists and patients should be aware of these symptoms, should be on the lookout for them, should screen their patients for them and refer to psychology, psychiatry as appropriate so that these sorts of symptoms are managed in our patients.

[00:57:45] Not looking just at MOG antibody disease and whether somebody's going to have a relapse, but looking at the symptoms, some of them non-physical as we're examining here, that may be associated with the disease and making sure that we're addressing those as well.

[00:58:02] **Dr. GG deFiebre:** Great, thank you. Well, thank you so much for taking the time today and yesterday, Dr. Sotirchos. We appreciate it very much. This will be a great resource for folks who weren't able to join live. So, yeah, thank you so much. We really appreciate it.

[00:58:19] **Dr. Elias Sotirchos:** Thank you so much for having me. It was my pleasure.

[00:58:22] **Dr. GG deFiebre:** All right, bye everyone.