Live Q&A Session

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[00:00:04] **Krissy Dilger:** Hello, thanks to everyone who's joined us so far for this MOGAD Together event. We are so excited to be able to have this Q and A session with Dr. Anastasia Vishnevetsky and Dr. Elena Grebenciucova. Dr. Anastasia is a fellow at Mass General Brigham, starting as faculty soon here. And then Dr. Grebenciucova is from Northwestern, correct?

[00:00:39] **Dr. Elena Grebenciucova:** Yes.

[00:00:41] **Krissy Dilger:** Awesome. Thank you both so much for your time today and I'm excited.

[00:00:46] **Dr. Anastasia Vishnevetsky:** Happy to be here.

[00:00:50] **Krissy Dilger:** Awesome. So, our first question, just what is MOGAD and how is it similar to other rare neuroimmune disorders? Can you start us off, Dr. Anastasia?

[00:01:03] **Dr. Anastasia Vishnevetsky:** Yeah, absolutely. So MOGAD is a relatively recently identified or discovered disorder stands for myelin oligodendrocyte glycoprotein antibody associated disease or disorder. And it really, I think is helpful to think about it in the paradigm of how is it similar to multiple sclerosis and how is it different and how is it similar or different from a neuromyelitis optica spectrum disorders, NMOSD. All three of these are predominantly relapsing neuroinflammatory disorders that affect the central nervous system. So, central nervous system meaning brain, the optic nerves, and the spinal cord and not so much the peripheral nerves or the muscles.

[00:01:47] And all three of these disorders, there's a predilection for the optic nerves and the spinal cord. In MOGAD and in NMOSD, there's more of a predilection for the optic nerves and spinal cord compared to the brain, which is more significantly affected in multiple sclerosis although all three of these disorders can cause abnormalities in the brain as well. MOGAD is also a little bit unique in that it can be both relapsing and monophasic. So, a one and done type of attack. Some patients up to maybe 50% or so, 40%, 50% will have a one-time clinical event, an inflammatory attack associated with MOGAD and then they'll never have another one. Whereas the other half might go on to have a one, two, maybe many relapses.

[00:02:40] And that's more similar to NMOSD and multiple sclerosis that are almost always essentially relapsing diseases or by definition are really relapsing diseases. Some other things that are unique about MOGAD are its pathophysiology and the underlying cause of it. We know that there's a specific antibody associated with MOGAD just as there is for NMOSD, for NMOSD, it's aquaporin-4 and for MOGAD, it's myelin oligodendrocyte glycoprotein or antibody against that, so anti MOG antibody. And in MOGAD, it's the covering of the nerves, the myelin sheath that is the target. Whereas in NMOSD, it's the astrocytes, which are other supportive cells that help support neurons.

[00:03:31] And some other key distinguishing features of MOGAD are just the length and severity of the optic nerve attacks and the spinal cord attacks, often the attacks are quite severe, but there's actually very often a significant recovery, almost a dramatic recovery associated with MOGAD more so than with some of those other disorders that we talk about. So overall, MOGAD it's either a monophasic or a relapsing neuroinflammatory disorder. It has approximately a 1-1 male to female ratio and can affect both the children and adults.

[00:04:15] **Krissy Dilger:** Thank you. That was a great overview. Anything to add, Dr. G?

[00:04:21] **Dr. Elena Grebenciucova:** No, that was a great overview. I'm ready for the next question.

[00:04:24] **Krissy Dilger:** Awesome. Well, our next one is for you. How does testing work for MOGAD? If someone had ADEM or TM, should they be tested for MOGAD?

[00:04:35] **Dr. Elena Grebenciucova:** Yeah, absolutely. So, patients should be tested for MOG antibody. And the way we typically test is by sending it in the blood and we utilize tests of higher sensitivity which are the most likely to pick up MOG positivity they are called cell-based assays. And generally, we send them out to Mayo, but some other labs do that as well. And when MOG antibody comes back positive, one has to be very careful with interpretation of that. Very low numbers of that antibody can happen in some other autoimmune conditions. So, for example, a MOG antibody titer of 10 or 20 really a lot of times may be an innocent bystander, but the person may have something else.

[00:05:26] So an example of that would be a person with optic neuritis, inflammation of the optic nerve who actually has multiple lesions that are a mass multiple sclerosis defining and somebody sent MOG antibody and it came back at this very low titer, most of the time it's an innocent bystander. However, MOG titers higher than 1-40, say 100 or 1000 have higher specificity. So, for example, when you're at a low titer of 40, honestly, 50% of patients will end up having a different diagnosis than MOGAD. So, physicians have to be very careful with diagnosing MOGAD when antibody titer is at 40 or lower, very careful.

[00:06:11] However, when the titers are 100 or 1,000, those titers are more specific for the diagnosis of MOGAD. So that's the first step, testing the serum, the blood and testing it with a high sensitivity assay, and also interpreting the result with caution. How high is the number of MOG? Do I really have MOGAD? Or is it something else? So here we have to carefully review the imaging characteristics on the MRIs and the types of symptoms and cerebrospinal fluid profile. And of course, cerebrospinal fluid profile does play a role in the diagnosis of MOGAD as well. We want to make sure that there are no atypical findings in the cerebrospinal fluid. And in some patients, we also do send MOG in the cerebrospinal fluid where it rarely but can be positive as well. But the serum, the blood test is the standard of care in the MOGAD diagnosis.

[00:07:15] One has to exercise caution when diagnosing MOGAD. For example, if a patient comes to me and they had optic neuritis or transverse myelitis a month ago and they were managed elsewhere, and they had received intravenous steroids plasma exchange. Now a month ago - now that it has been a month and they have received immunosuppression, they have received plasma exchange, I will still check MOG antibody, but it could be negative or really low titer simply because the person already received a lot of immunosuppression and plasma exchange. In those instances, if the result is negative, I would strongly consider repeating it in three to six months to make sure that it has not become positive. That's why another caveat in the diagnosis.

[00:08:17] And a couple of things to say also about - as my colleague already mentioned, some of the MOGAD presentations can be monophasic meaning that a person has optic neuritis or maybe transverse myelitis or another manifestation and their MOG antibody is positive, but then somebody retracts it, and it goes away

and it's now negative. So, it doesn't always mean that that person is not at risk of a relapse. So, we definitely have seen patients in whom MOG antibody becomes negative in subsequent result. But then that patient still has another attack subsequently. So, it's not a guarantee that it will be monophasic or a one-time deal. And so that's a little bit about the diagnosis and some of the caveats. And I don't know if Anastasia has anything to add.

[00:09:15] **Dr. Anastasia Vishnevetsky:** Yeah, there was one thing that you mentioned just about the proportion of patients that might have a MOG antibody that isn't indicative of MOGAD disease. And I think a key concept is that that proportion is going to vary and change depending on how often you send a MOG antibody and in what situation you decide to send it. So, if I decided to send a MOG antibody in every single patient with multiple sclerosis that I saw or every patient with a neurologic disorder that I saw that proportion of false positives would be really, really high because my pretest probability, my chances of having MOG antibody disorder at the beginning is really low.

[00:09:59] If we are sending MOG in situations where it's more appropriate and where it is of higher suspicion, then the chance is that that's a true underlying cause of disease is a lot higher. And so, you'll probably hear different estimates from different doctors about what proportion of MOG antibodies are false positives or false because it depends really on the population in which you're testing and looking at it and MOG antibody is an antibody. It's a test that is more sensitive than it is specific in some ways. And so, it's important to choose the right population to test in.

[00:10:45] And to the specific answer of ADEM or transverse myelitis, ADEM is definitely a presentation where in most cases would send a MOG antibody, especially in kids. We now know that a very significant portion over 60% of kids with ADEM end up having a MOG antibody. With transverse myelitis, there's a lot of other imaging features and also cerebrospinal fluid features that can influence whether I think a MOG is likely to be at play, but often we'll send it. I think with optic neuritis that is otherwise not typical for MOG, it may be short, it's not as severe, those are cases where it's a little bit more case by case.

[00:11:33] **Krissy Dilger:** Great. Thank you both so much. That was definitely very informative and thorough. So, I appreciate it. Our next question has to do with vaccination. So, someone was wondering, could the MOGAD have been caused by vaccination? And do you advise MOGAD patients to stay current on boosters for protection against COVID-19, Dr. Anastasia?

[00:12:00] **Dr. Anastasia Vishnevetsky:** Sure. So overall, I would say we do recommend that our MOGAD patients stay current on boosters for protection against COVID-19, but I will say that with the caveat that, we haven't done extremely large scale studies, epidemiologic studies that could assess the association between COVID vaccination and MOGAD specifically, there have been just several case reports across all of the patients who are vaccinated, which is I think a large majority of the folks that we see, at least in the Boston area, almost all of our patients have been vaccinated and there hasn't been an uptick to our knowledge in MOGAD cases.

[00:12:49] MOGAD does more so than some other autoimmune conditions often follow some trigger. And so, we do have patients where we think that a particular attack may have been triggered by an infection or by vaccine. There have been reports preceding the COVID-19 vaccines of, just case reports here or there of a patient having an attack 2-3 weeks after a vaccine. In our clinical experience, we certainly have seen cases that we've attributed to being triggered by COVID infection. Quite a few that are just very short, temporal association. That being said, during the pandemic, most of us did get infected at some point or another. And if somebody had, MOGAD baseline and we're going to have an event, it's always hard to disassociate causation and correlation or correlation and causation.

[00:13:50] So often, one thing we will do is in the acute phase that somebody is being treated for a relapse or that we know that their immune system is over inflamed and they're in the midst of their optic neuritis attack or they're in the midst of their transverse myelitis attack. If they had a scheduled vaccination, at that time, we often do say, just out of an abundance of caution, defer that until you're out of that hyper acute event. I will admit that that's not a particularly evidence-based recommendation. And there's variation in our own practice between different doctors. And the final piece I'll say is that there was a little bit more of a signal with some of the adenoviral vaccines, AstraZeneca vaccines in terms of triggering central nervous system, autoimmunity, transverse myelitis, and a couple of cases of MOGAD that are a little bit more convincing than with the DNA based vaccines.

[00:14:57] But overall, advise patients to continue to get vaccinated. One other piece to just expect and be upfront about is that, the vaccine often makes people feel unwell for a few days and often some people feel warm or feel a little bit -- like they have low grade fevers just amongst even the healthy population. And for patients who've had a neurologic attack in the past, that can manifest differently and that can feel more severe. So, we've seen these transient worsening where patients who had optic neuritis before in the setting of their getting a vaccine, they feel like their previous symptoms are flaring up or worsening a little bit. When we've specifically cautioned patients about that because we know that fevers and illness can trigger some of these old neurologic symptoms to come back, that's not indicative of new inflammatory damage, but rather old symptoms resurfacing.

[00:16:02] **Krissy Dilger:** Thank you. And Dr. G, do you have anything you'd like to add?

[00:16:06] **Dr. Elena Grebenciucova:** Yeah, I would say that from the practical approach, I would like patients to think about vaccines with MOGAD this way. When it comes to any autoimmune disorder, there isn't one specific trigger. It takes usually a genetically predisposed individual interacting with their environment viruses. Vitamin D deficiency, for example, in MS and other things to culminate in the development of autoimmune disease, whether it be multiple sclerosis, MOGAD, neuromyelitis optica. And across virtually all autoimmune disorders, what we know is that people often present with their first attack of autoimmune disease shortly after an infection or shortly after a vaccine. Historically, that's true for any kind of infection we get or for any kind of vaccine we get.

[00:17:05] So to us in neuroimmunology, it's not surprising when we see a patient present shortly with their first multiple sclerosis attack or MOGAD attack shortly after a recent flu or shortly after a recent cold infection, shortly after COVID, shortly after absolutely any vaccine. And from the perspective of saying, hey, people can have presentations with their first autoimmune attack after any infection or after any vaccine should let you know that the fear of getting vaccinated in terms of it triggering an attack, it's really not scientifically founded. Because if you are afraid of getting a vaccine because it's going to trigger something, well, an infection could do the same thing. And as human beings, it's impossible to avoid infections for a lifetime, we are exposed to infections, we get infections. And so when my patients are afraid of say getting COVID vaccines, we talk about the fact that if you are worried about the COVID vaccine stimulating your immune system, guess what, COVID itself is going to stimulate your immune system even more powerfully, except COVID itself, of course, in a patient who has high risk of severe illness could create many more serious issues as we know.

[00:18:33] So I agree with my colleague, I do recommend vaccinations to my patients. And I genuinely also agree that in the acute setting. So if you're somebody who just had optic neuritis or transverse myelitis or ADEM, absolutely within the 30 days of the onset of those symptoms, within that acute stage, you probably should be avoiding any vaccines, because you are in the stage of inflammation where inflammation is trying to calm down, things are trying to recuperate, recover, start regenerating a little bit and you generally do not want to stimulate your immune system at that time with the vaccine. And so, I generally ask my patients to

delay any vaccinations by at least 30 days and even then, discuss with me what's being done. Is the timing appropriate? Is this vaccine really an emergency in that setting? Just clinically depending on case-by-case basis on what is happening with the patient. How are they doing? So those were just a few of my comments.

[00:19:46] **Krissy Dilger:** Well, thank you both so much. I think that provides really good context for people who have questions and concerns about vaccinations. Our next question has to do with fatigue. So why does MOGAD cause fatigue if that's even known? They want to - this person wants to learn more about terminology around fatigue, how to describe how they're feeling different kinds of fatigue and then how to respond to it. Oh, sorry. Dr. G, how about you start us of?

[00:20:23] **Dr. Elena Grebenciucova:** Yeah, absolutely. So, I think that fatigue is a unifying symptom for so many autoimmune conditions. Virtually, every autoimmune condition we know of whether it's multiple sclerosis, neuromyelitis optica, MOGAD or systemic autoimmune conditions like lupus, rheumatoid arthritis. Virtually, all of these conditions do involve fatigue and fatigue can have different etiologies or causes. So often people can feel extraordinarily tired because they actually have developed some level of depression. And one of the symptoms of depression is really what we call like a leaden paralysis where everything feels so heavy, and you really can't do anything. It feels like you can't even get up and do things and you spend 15, 20 minutes doing an activity and then you just run out of that energy.

[00:21:22] So sometimes undiagnosed and/or undertreated depression can come up as fatigue as one of the symptoms. And it's important that - I feel it's important that I talk about it first before addressing any other types of fatigues because people who live with neurological disease, people who live with chronic disease go through an extraordinary amount of stress and depressive feelings quite often. Not only because of the neurological disability that they developed, not only because of the troubles with pain, spasticity, or bladder issues, not only because of sometimes trouble sleeping, but also because of the fear of the future of unknown, of what could happen. Sometimes fear of medications and their side effects, sometimes not get right communication with their physicians or treating team. So, a lot of angles through which people who live with autoimmune chronic conditions can become prone to developing anxiety, depression. And sometimes it's tough to even recognize the fact that maybe part of what I'm feeling is depression based on what I'm struggling with and what's been happening in my life.

[00:22:49] So one of the first things that I would say is please, if you are suffering from fatigue, think about two things. Get screened for depression, Number 1, Number 2, think about your sleep. I often have patients with MOGAD or neuromyelitis optica or multiple sclerosis come to me, and they say, “My fatigue is so severe Dr. G, what do I do?” And the first thing that I ask them is, “How is your sleep?” And probably seven out of 10 times, people will say, “My sleep is terrible.” Well, if your sleep is terrible, this is the quickest and the fastest explanation of why you are feeling so exhausted and so tired all the time. Our brain needs rest and when our brain doesn't get adequate rest, everything will feel like it's getting worse, including your mood and emotional liability sometimes and including your ability to sustain activity, sustain prolonged attention focus. So you may feel extraordinary tired.

[00:23:53] So if you're somebody who struggles with falling asleep, for example, because you are anxious, you're thinking about things or maybe because you're in pain, maybe you have neuropathic nerve related pain that needs to be managed better or maybe it's the bladder issues that are keeping you up because you have to use the bathroom all the time. Or maybe you don't have an explanation, you just can't fall asleep, talk to your doctor, whether it's primary care doctor, your neurologist, or even sleep medicine doctor, sleep neurology doctor about starting to manage that sleep issue. And of course, if it's bladder issues, then we need to see urology or talk to our neurologist about managing those bladder symptoms. If it's chronic pain, that is preventing you from sleep again to your neurologist or a pain management doctor, if it is some anxiety

or worrying too much, talking to your neurologist, primary care doctors, psychiatrist, of course, as well. So those are some of the first things that I think about when I discuss fatigue with my symptoms.

[00:25:03] Also, some people have obstructive sleep apnea in which they're snoring. So, people as they get older, particularly if they are somewhat overweight or sometimes obese, have an increased risk of developing obstructive sleep apnea. In obstructive sleep apnea, people often feel un-refreshed in the morning. Sometimes they get bad headaches, they often gain weight and have trouble losing weight. And they really feel very, very fatigued and their sleep is unrefreshing. Diagnosing obstructive sleep apnea is done via a sleep study. And a sleep medicine doctor can do that, a neurologist can order that. That is an additional cause of fatigue in some of the people.

[00:25:44] Another cause of fatigue is the lack of exercise. Now, I understand of course that some patients who have transverse myelitis and limited ability cannot exercise with ease. But for people who have the ability to exercise, working on a plan of regular exercise, working with a physical therapist perhaps is critically important because exercise tends to improve fatigue across most autoimmune conditions, and in general, healthy population, not only by improving the blood supply to the organs, but also by secreting certain chemicals into your blood stream is that boost the sensation of energy and help in you feeling more energetic throughout the day.

[00:26:32] In terms of the fatigue that is more inherent to autoimmune conditions themselves, we feel that it is likely modulated by inflammatory cytokines or hormones that our immune system can secrete. So, for example, interleukin 6 to tumor necrosis factor alpha, often the same immune hormone or cytokines that make you tired when you get an infection. So, remember how you get flu, and you get all achy and tired and you just want to lay down, you have no energy, very similar hormones or we call them cytokines like interleukin 6 to tumor necrosis factor alpha, they're secreted by the immune system that is now inflamed. So, we see these cytokines or immune hormones during an infection or during inflammation in the body or inflammatory attacks.

[00:27:26] And so those are some etiologies or causative factors of fatigue associated with many autoimmune conditions. And the truth is, of course, it is also not entirely well understood. So, it is very multifactorial but when it comes to the management of MOGAD related fatigue, it's really important to know is it thyroid dysfunction? Thyroid autoimmune disease is commonly coexistent in people with other autoimmune conditions. So, get your thyroid checked. Is it your vitamin D deficiency? Because it is so common and vitamin D deficiency is associated with increased levels of fatigue. Is it B-12 deficiency in which people can experience a lot of fatigue, cognitive slowing down, even depressive symptoms and tingling and even worsening balance of vitamin B-12 is very low? Is it your sleep? Is it obstructive sleep apnea? Is it untreated depression? Is it untreated neuropathic pain?

[00:28:29] Even though MOGAD doesn't cause headaches, but people who live with chronic conditions are more prone due to stress to development of headaches. And frequently patients suffer from frequent headaches and headaches can be exhausting to somebody who lives with chronic headaches or chronic migraines. So, addressing some of these pains, headaches that are maybe coexistent with MOGAD is really important because those will exhaust you, make you feel absolutely awful and add to that fatigue. And sleep, sleep, sleep, sleep hygiene, making sure that sleep is as improved, getting like 8-9 hours of sleep ideally a night as possible.

[00:29:13] When it comes to the treatment beyond, exercise, physical therapy, healthy diet, which diets certainly play a crucial role in combating fatigue. There is no such a thing as the one true anti-inflammatory

diet. And if you've read about anti-inflammatory diets, that claim to be anti-inflammatory, often contradict each other as well. And what they claim to be anti-inflammatory and what is pro-inflammatory in reality, you are what you eat in a sense, so the state of your health is directly related to what you put inside your body. So, what we generally recommend is a lower salt diet. It's not well studied in MOGAD specifically, but in many of our inflammatory conditions, we know that high salt diets can cost you a little bit more at least in multiple sclerosis, some data about higher salt intake and inflammatory activity in some studies. So, we generally recommend lower salt diets.

[00:30:20] It also protects you from high blood pressure, which we know that outcomes of most neurological conditions are related to other coexistent issues. So, for example, high blood pressure, high blood glucose, diabetes, because all of those take a toll on your blood vessels and blood vessels supply your brain. And so, if you have issues in the blood vessels of the brain and spinal cord could have higher burden of issues long term. And so basically when it comes to the diet, we generally recommend Mediterranean style diet is probably the easiest one to follow and the one that's filled with anti-inflammatory compounds really. So, thinking about fruits, vegetables, nuts and seeds, olive oil, healthy low-fat protein to include both chicken and salmon and different types of fish, nuts and seeds and tofu. Tofu, of course, is not the Mediterranean diet, but just healthy proteins really provide best evidence across all neurodegenerative and autoimmune conditions to improve both their health status on average and across many disorders, the fatigue associated with it.

[00:31:33] And then in terms of medications that sometimes are used off label, off label medications that are used for the treatment of fatigue across multiple sclerosis, neuromyelitis optica, MOGAD are the same things that we use to treat narcolepsy such as modafinil, known as Provigil, Nuvigil. And these are essentially mild stimulants. They're not cures, but they have some effectiveness for some patients that struggle with fatigue after ruling out sleep issues, chronic pain issues and other things.

[00:32:08] **Krissy Dilger:** Well, thank you so much. I think that's such great information for people. This is definitely an issue I think a lot of people struggle with. Dr. Anastasia, did you have anything to add?

[00:32:20] **Dr. Anastasia Vishnevetsky:** I just wanted to really take a moment to validate just the patient experience and probably frustration related to the treatment of fatigue. As a clinician I have a similar approach to Dr. G in terms of trying to find other reasons that fatigue is secondary to. Is it secondary to depression or sleep or any of the other things that she discussed? And I think I just want to acknowledge that that's in large part because we don't have a treatment for that part, is directed at the fatigue that's directly caused by - it's very well studied and documented in multiple sclerosis. There's some ongoing work about fatigue in MOGAD. But in MS we know that patients with even good sleep and no depression and no other triggering cause still experience fatigue at drastically higher rates. And it's a fatigue that I think to speak a little bit to the question, where you say terminology, how do you get away from that word fatigue that I use? Or anyone uses to mean, I'm just a little tired today and I'm a little overworked today and just acknowledge that this is a very different fatigue. This is a fatigue that debilitates people that makes it hard to work, makes it hard to spend time with family.

[00:33:43] And it's a frustrating word because we don't really truly distinguish those two. It's not the same as - for some people it might just feel like normal tiredness. But I know for a lot of patients it's really not. So, I think there was a big study in MS looking at three different commonly prescribed medications for fatigue and none of them showed a significant improvement over placebo, but that being said, certain patients really do experience a significant improvement or difference on one drug versus another. And it's a little bit of a personalized trial and error process. And that's something that I engage with, even though I know the

data that on an aggregate, there isn't one silver bullet. Different people respond differently to medications, and this can be a really debilitating aspect of the disease. So just a word to keep advocating if this is a really debilitating part of your experience and disease, there are different strategies for it.

[00:34:45] And I would say, lack of exercise can make anybody tired but we do know specifically in MS studies have not been done in Mayo, but extrapolating from MS, we know specifically that exercises does improve energy levels and does improve symptoms of fatigue and so strategizing about how to do that. Sometimes people say that heat makes exercising really difficult. So, strategizing on using cooling vests or swimming or finding ways to exercise, despite the fact that that can be a real challenge. So just find somebody that you feel like you can work with and try to get those around you to understand what it is that you're going through. It's real and it's a really challenging and difficult thing to experience.

[00:35:38] **Krissy Dilger:** Thank you so much. That's such a great point. I can speak to the fact that if you do suffer from fatigue, it can be frustrating when someone tries to - they're in with the best intentions relate to you by saying, oh yeah, I'm tired too. It's different. So, our next question is going back to the diet, topic of conversation, but this person wants to know the best way to handle GI issues related to MOGAD. They say they can barely eat anything without having severe inflammation or GI distress and they have been on an anti-inflammatory diet for eight months and it doesn't seem to be clearing the issues up. Dr. Anastasia?

[00:36:33] **Dr. Anastasia Vishnevetsky:** Yeah, absolutely. So, I think one key point here is I would certainly want follow up. I have a lot of follow up questions about what are the specific types of GI issues. There are things that I think of related to MOGAD as being related to the disease, particularly things like constipation or even fecal incontinence after an episode of myelitis, which is an attack on the spinal cord, there can be nausea or vomiting related to attacks in the brain stem or in the cerebellum. So, there's a variety of different root causes of GI issues that can be related to MOGAD. But that being said, some of the classic food activities or irritable bowel syndrome type of symptoms, alternating diarrhea and constipation and abdominal pain if not related to a specific relapse or specific spinal cord attack that caused constipation and abdominal pain or something like that.

[00:37:44] That's not actually a core part of MOGAD and it's not something that I would consider to be part of the disease. So it would be really important to talk to a GI doctor or get a referral to see a GI doctor, have a proper GI work up done, talk to nutritionists as well to look for alternative causes because while there's a lot of things that can be related to MOGAD and again, patients can have GI issues related to specific attack, just generally general GI distress is not something that's a part of MOGAD to our knowledge. Again, everything that I think we say is a little bit with the caveat that this is a newly discovered disorder, and it hasn't been around for that long and we've been proven wrong about things that we thought we knew with other disorders in the past as we've learned more. But this would be pretty - just general GI distress is pretty far outside of our current understanding of MOGAD.

[00:38:49] Another interesting thing just to point out or to discuss is with NMOSD, aquaporin-4 related NMOSD, we see a very strong association with other autoimmune diseases with other rheumatologic conditions. With MS, we certainly see autoimmune disorders running in families and that predisposing patients to having MS. With MOGAD there's that association, doesn't seem to be as robust. A lot of our patients don't have any other autoimmune disorders or most of our patients don't have any other autoimmune disorders. But I would say many more that compared to MS or NMOSD don't have any even autoimmune disorder history in their family. So just another reason to go look for another cause if you can barely eat anything without having severe inflammation or GI distress looking for inflammatory bowel disorder, bowel disease or IBS or other things like that.

[00:39:50] And then to the diet point, in the group that I worked with they did conduct a survey on diet looking at different diets, not a robust clinical trial by any means. And those results aren't published, but we didn't see a huge signal for one diet over another. But I will say that on a person-to-person basis, many patients will say, I did XYZ in my diet, and I feel so much better, or I really tried this diet, and I feel like it's been transformative to me. Often, it's very different diets, person to person, but I think there's no question that people have an individual response if you have a diet that is really working for you, I validate that and encourage you to continue with that. And if you have a diet that you've been told to do try by somebody and it's not working for you, I will say there's not strong data to just any particular diet over another in MOGAD, certainly. Even in MS, the best data we have is for a Mediterranean diet. But the signal that really makes a substantive difference in any of the underlying kind of pathophysiology and anything other than just generally feeling better and energizing because you're eating healthier, I think that the signal that it's really doing something on that substantive level is pretty low.

[00:41:24] **Krissy Dilger:** Great. Thank you. And Dr. G, did you have anything to add on this one?

[00:41:29] **Dr. Elena Grebenciucova:** Yeah, I think Anastasia, I agree with everything said. I'd like to add a couple of things. So, GI disturbances in somebody with MOGAD, I would say that if that person has been on steroids recently or is currently on chronic steroids, it would be really important to know whether they develop gastritis or stomach inflammation with some reflux disease, secondary to steroids, recent steroids or chronic use of steroids. And that's something that certainly we treat with a PPI like omeprazole and others. But that's something to discuss with your primary care doctor or a GI doctor even better. So that's Number 1. That's one consideration. Number 2 consideration is that sometimes there can be medications that you're taking otherwise like some of the SSRIs that could cause some GI symptoms or genuinely new medications that you might be on you want to make sure you discuss with your physician. Never assume that a new medication is the cause of your symptoms, but always discuss with the physician if there is a possibility of that.

[00:42:35] And three, I would also say that people who were recently diagnosed with a serious neurological disorder or are struggling from resultant disability or significant pain, a lot of times are under a lot of obvious stress and chronic stress can certainly predispose you to more of the issues with reflux disease and even gastritis. In some patients, they can have an infection called H-pylori that is treatable with antibiotics is the cause for their stomach issues. There are people just like Dr. Anastasia mentioned who can have another autoimmune condition that's affecting their intestines, for example, and causes something similar to irritable bowel disease, but actually inflammatory disease and those are usually diagnosed via colonoscopies. So, there are some case reports of interstitial colitis or inflammation of the intestines in association with, for example, B cell depleting treatments that we utilize in the treatment of some of these conditions. So, for example, rituximab or Ocrevus rare cases, but nevertheless worth mentioning. Sometimes medications like CellCept, mycophenolate mofetil or even azathioprine, Imuran can also have GI side effects. So, I think of course we don't know the details from your personal history of the GI struggles. But those are some of the thoughts and some of the things to think about just generally when encountering GI problems. But then of course, stress, anxiety and the quality of your diet also play into how you're feeling. So, if you're somebody who is eating a lot of spicy things or a lot of fried things that can contribute to some level of gastritis in some patients as well.

[00:44:32] **Dr. Anastasia Vishnevetsky:** Medications is a key one.

[00:44:37] **Krissy Dilger:** Thank you both for your thorough answers. Our next question is about treatment options. If someone has a new attack or if they're having a relapse, what treatment options are available and how do you identify if someone needs IVIG, steroid treatment, or anything else? Let me start with Dr. G.

[00:45:04] **Dr. Elena Grebenciucova:** Yeah, absolutely. So, the core of treating acute attacks of MOGAD are intravenous steroids with a subsequent prednisone taper orally, so medication by mouth, depending on how the patient is doing, how severe the attack is and how the patient is doing with steroids and after steroids. In some instances, a plasma exchange may be given as well. Once the patient is hopefully doing better, recovering things are getting better, the question is always, does this patient have a relapsing disease or will this be monophasic, a one-time deal? The truth is we don't know, but what we know is about 40% of patients will have a relapsing disease. But from the get-go from the beginning, we don't know who will be who.

[00:45:59] So there are two schools of thought on that topic. One school of thought says, well, if there's a 40% chance, so to say that this patient may have a non-monophasic disease, they may develop another attack or be prone to more attacks in the future, discussing a preventive medication for them should be an option with an understanding that we don't know. Will that another attack ever happen again? So, there we discuss certain preventive medications and I'll get back to it in a moment. The other school of thought says, well, wait a minute. So, if there's only 40% of people who develop more attacks and say 50% or 60% of them will not, how do we know whom to treat? Maybe we should just wait and see if that person does have another attack and they do prove that they have that relapsing type of disease, then we put them on the treatment. So, there are two types of schools of thought on that topic still.

[00:47:03] And why is there such a thing as two schools of thought? Well, Number 1, we don't know who will have a relapse and who will not. That's Number 1. Number 2 is, all of these medications, they're serious medications. And you are not going to be taking them for just a year or two years. You're taking them chronically and certainly many of them are associated with side effects. And so, it's a matter of discussion and a mutual decision making with a patient, whether this is the time to start medication and which one for those people who are just presenting with their first event. Obviously, those people who have relapsing the disease where it's been proven that they had two attacks or more, they should be on preventive medications. And there's a number of medications that we utilize in the treatment of MOGAD, and the data on the effectiveness of those is mainly retrospective and thus is not always the highest quality of evidence, meaning - and some perspective but mostly retrospective data when we look back, look at say 100 patients and we see how many of them were in CellCept, how many on azathioprine, how many on rituximab, and what was their incidence of relapses, etc., etc.

[00:48:16] So some of the medications that are utilized are oral medications such as CellCept, mycophenolate mofetil, azathioprine which is Imuran, and also infusions such as rituximab. There's also a clinical trial looking at anti interleukin 6, so satralizumab, in the treatment of relapsing MOGAD right now. And certainly IVIG, intravenous immunoglobulin with a newer data showing some excellent response in people with MOG mainly retrospective data showing that people can do really well on IVIG. The data that we have are limited. Number 1, it's a new condition, only recently so to say discovered. And Number 2, our diagnostic criteria have really evolved because what was often back then diagnosed as MOGAD was just a low titer of 1:20 or 40. A lot of times those people may have evolved into manifesting themselves into something else. So, some of the old data is a little bit murky.

[00:49:26] But I think that, we generally discuss all four methods of treatment with patients, whether it's oral azathioprine or mycophenolate mofetil or rituximab, or intravenous immunoglobulins. I think that three of them mycophenolate mofetil, azathioprine and rituximab, are major immunosuppressive medications that do increase the risk of infections. Intravenous immunoglobulin and non-immunosuppressive, they do not increase risk of infections, but they have their own rare unique side effects, increasing risk of blood clots for example, or very rarely ischemic stroke is extremely rare complications mainly in people who are already at risk for those. And that happens because intravenous immunoglobulin is basically when you get an infusion,

it makes your blood more viscus for higher densities. So, you have to hydrate extremely well. There are other rare side effects to intravenous immunoglobulin as well, but generally, they're very well tolerated and they can be of high risk to people with severe renal dysfunction in which they are generally - if they're ever used, they're used with great caution and not in severe renal dysfunction, but with MOG kidney monitoring.

[00:50:46] And so, currently, from my perspective and I know Anastasia is going to weigh in on it with some data in just a moment most likely. But I think that I personally have to be yet convinced that some of these medications are definitively better. So, some data with IVIG certainly has shown that people on IVIG were less likely to relapse than in comparison to other medications. But the data are mixed, most of it is retrospective. And so, I think from my perspective, I would still need years and years of perspective data to really make a huge statement to say definitively, this should be used as a first line, versus definitively, this should be used as a second line. So that's my point of view on the treatments. Anastasia, any comments?

[00:51:40] **Dr. Anastasia Vishnevetsky:** Yeah, I think it's really great to have multiple, like not just different clinicians but different clinicians from different hospitals and practices to weigh in. And I think there truly is debate amongst the people who are the most experienced with MOGAD in terms of what are the best options moving forward. So, I think first, the question asked about acute treatment options and whether someone needs IVIG or steroid treatment. And here at Mass General with - I worked very closely with Dr. Michael Levy and patients who already have a diagnosis of MOGAD really like actually treating acute events with IVIG. IV steroids followed by a longer oral steroid taper are certainly a mainstay of therapy I would say worldwide.

[00:52:30] But one thing that we've observed is unlike, for example, multiple sclerosis where you treat someone with 3-5 days of IV steroids, you take them off of the steroids and then they go on their way, with MOG antibody disease associated disorder, patients may actually struggle to get off of that initial steroid dose and you have to go very, very slowly over time, decreasing their oral steroid taper. Sometimes patients are on these steroids for months. And a lot of patients really experience a lot of side effects. And when you think about the fact that many of the patients who are diagnosed are relatively young, those side effects can add up. And we see patients worsening as we start to decrease their steroids. And so as much as we can, and this is again, something that I think our practice does differ from a lot of places and a lot of very reasonable places and reasonable clinicians. But one thing that we've recently more pushed to do is try to avoid starting patients on the steroids at all and treating acute attacks with IVIG. And part of the reason is that it's a nice then transition to a chronic therapy if that's the route that they decide to go.

[00:53:42] In terms of the, do you treat an acute attack, a first attack with immunosuppression? Agree that that is a very hotly contested issue and it's very difficult slash impossible to predict who's going to have another relapse from the get-go. I usually am pretty upfront with patients about that fact and that different people might go different ways because different patients have really different preferences with that. And I think that that plays an important role. There are some patients who are like, do I really have to be on a therapy? I really don't want to have to take a therapy every day, maybe I'm going to just be fine. And I say to them, no, you don't have to, you definitely don't have to. And I'm not even going to say I definitely recommend it and just be real - we discuss the first signs of a relapse and to have a really low threshold to call and what to do.

[00:54:39] And then other patients say, what do you mean I'm going to have a 40% chance of this happening to me again right after this really traumatizing scary event that's life altering and there's nothing I can do about it. I want to do anything I can, and I say, well, then in that case, we do have things that we can do about it. We can start a medication; we can talk through those different options and make an individualized decision. That's acknowledging the fact that we don't have better data to guide that. And sometimes with folks who want to start a treatment up front, we do a time limited trial. So, we won't keep them on the medication

forever. We will keep them on it for a certain period of time. Often two years, we're recently starting to think about a more - and again, this is not data driven. So I want to just give that disclaimer, but we're thinking about a more almost induction approach where we treat patients upfront, the six month type of period of treatment with the thought, at least rationale for us being that in studies, looking at patients who relapse, a lot of the relapses do cluster in the first six months to a year after the initial attack.

[00:55:55] And so our thought is can we get them through that more high risk period, hopefully get over that initial trauma of the event that occurred, get them on the road to recovery. And then with time - because we don't want to keep somebody on a medication forever when they may not need it, the toxicities tend to build over time. So, at that point, we'll, taper off. But I think it's a very individualized approach but steroids, IVIG and then PLEX are the acute options and then there's that whole range of further options. And just one last point, with MOGAD we really do treat predominantly discrete attacks. So many patients with MOGAD will say things like, I just don't feel well, or I have a headache or I'm having more pain related to an old attack. Those typically are not something that we treat with an acute treatment like IVIG, or steroid treatments is really predominantly when there is a new neurologic event with signs and new neurologic symptoms. And usually, but not always, we can capture that on an imaging study as well. And that's when we pull the trigger because IVIG and steroids are both not fully benign treatments.

[00:57:24] **Krissy Dilger:** Awesome. Thank you both so much. And I love that point you made about really catering to what the patient wants and working with them to make sure they're an equal part in the decision making. We only have about two minutes left. So really quick, it's tied into the point I think you were just talking about. But this person wants to know that given that these are rare diseases with unusual presentations, do you find that evidence and progression of the disease is missed on MRI reports occasionally? Dr. Anastasia?

[00:58:09] **Dr. Anastasia Vishnevetsky:** Yeah. So, I think that often on MRI reports, especially initial MRI reports, what is seen might be just called evidence of demyelinating disease. That's really, I would say where the general radiologist job ends. If they say that, then I think it's up to the neurologist and the treating physician to judge for the rest. So, I would say that almost never is MOG specifically called out. With a few exceptions, sometimes with very typical longitudinally extensive optic neuritis, they'll specifically call out or perineuritis, they'll call out MOG. But in most cases, they'll just say that there's a demyelinating event. It could be MS, it could be MOG, it could be some other cause of it. So, I think in that sense, it's important to have a neuroimmunologist. Most neuroimmunologists today are very well aware of MOGAD, and it's been all over conferences and things like that for years. So as long as you're seeing a neuroimmunologist, they should be able to guide you through the process of MS versus MOGAD versus NMOSD.

[00:59:17] And in terms of the question of evidence or progression of the disease missed on MRIs, beyond that after the initial diagnosis is made, MOGAD is - typically there is not progress, we don't think of there being progression outside of discrete relapses, which is a big distinction from multiple sclerosis. That's something that we're still investigating. So, I will give that ever present asterisk that we might still learn more about that. But there doesn't seem to at least be significant evidence of atrophy or neurodegeneration that's occurring outside of these discrete inflammatory attacks. So, we don't even actually routinely check MRIs every year for MOG patients. We only wait if they have an attack or a symptom and they're not sure if it's related to a discrete MOGAD attack, then we'll get an MRI. But we don't just routinely look because we don't normally, when we have, we haven't seen new lesions accumulate.

[01:00:24] MOGAD is interesting and a little bit different from MS and aquaporin-4 in that there's more - or aquaporin-4 plus NMOSD and that there's more radiographic events that can then resolve. So sometimes in Mayo you'll image in the acute period, and you'll see a very aggressive large lesion. And if you were to image 6 months later, it might be gone or almost gone or much, much smaller. We see lesions shrinking or

becoming less, they're being less swelling in other conditions. But in MS and NMOSD almost always you'll see a scar where there was a lesion. And in MOGAD that's not always the case.

[01:01:07] So we've had patients who we believe very strongly had an optic neuritis or had a spinal cord attack, everything fits, they have the antibodies but when we image them in the future, their imaging looks normal or you have to really look over and say is there a tiny bit of atrophy, it has it gotten a little bit smaller in that area or not. So, in that sense, I would say, whereas a completely normal MRI report to me rules out multiple sclerosis entirely, for MOG antibiosis early in the course, you sometimes have to be vigilant for those falsely negative MRI reports.

[01:01:53] **Krissy Dilger:** Great. Thank you so much. That is the end of our time, unfortunately, but I appreciate you both joining us and I'm sure our community does as well. I think this went so well. You all answered all the questions very thoroughly and we really appreciate that. And then hopefully this conversation can continue throughout the month because it is MOGAD awareness month but also into the future.

[01:02:24] **Dr. Elena Grebenciucova:** Thank you so much for having me.

[01:02:26] **Dr. Anastasia Vishnevetsky:** Thank you for having me. Bye.

[01:02:27] **Krissy Dilger:** Bye.