MOGAD and NMOSD

Is MOGAD Part of NMOSD or a Distinct Diagnosis?

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Intro: [00:00:00] ABCs of NMOSD is an education podcast series to share knowledge about neuromyelitis optica spectrum disorder, or NMOSD, a rare relapsing autoimmune disorder that preferentially causes inflammation in the optic nerves and spinal cord.

[00:00:22] ABCs of NMOSD podcast series is hosted by SRNA, the Siegel Rare Neuroimmune Association and in collaboration with the Sumaira Foundation for NMO, The Connor B. Judge Foundation and Guthy Jackson Charitable Foundation. This education series is made possible through a patient education grant from Horizon Therapeutics.

GG deFiebre: [00:00:51] Hello, everyone, and welcome to the ABCs of NMOSD podcast series. Today's podcast is entitled "MOGAD and NMOSD: Is MOGAD Part of NMOSD or a Distinct Diagnosis?" ABCs of NMOSD is an education podcast series to share knowledge about neuromyelitis optica spectrum disorder.

[00:01:12] My name is GG deFiebre, and I'm from the Siegel Rare Neuroimmune Association, and I will be moderating this podcast. This podcast series is hosted by the Siegel Rare Neuroimmune Association in collaboration with The Sumaira Foundation for NMO, the Connor B. Judge Foundation and The Guthy Jackson Charitable Foundation.

[00:01:30] This podcast is being recorded and will be made available on the SRNA website and for download via iTunes. ABCs of NMOSD is made possible through a patient education grant from Horizon Therapeutics. Horizon is focused on the discovery, development, and commercialization of medicines that address critical needs for people impacted by rare, autoimmune, and severe inflammatory diseases. They apply scientific expertise encouraged to bring clinically meaningful therapies to patients. Horizon believes science and compassion must work together to transform lives.

[00:02:05] For today's podcast, we are pleased to be joined by Dr. Eoin Flanagan. Dr. Flanagan is an Associate Professor of Neurology and Consultant in the departments of Neurology and Laboratory Medicine and Pathology at the Mayo Clinic in Rochester, Minnesota. He completed his medical school training at University College Dublin in Ireland in 2005. He completed medical residency in Ireland and became a member of the Royal College of Physicians of Ireland in 2008. He then pursued neurology residency at Mayo Clinic and is board certified in neurology in the USA.

[00:02:39] He completed fellowships in autoimmune neurology, multiple sclerosis, and behavioral neurology at Mayo Clinic. He received a master's degree in clinical and translational science at Mayo Clinic. He works in the autoimmune and multiple sclerosis neurology clinics and the neuroimmunology laboratory at the Mayo Clinic.

[00:02:57] His clinical expertise and research is focused on the diagnosis and management of autoimmune neurological disorders with an emphasis on inflammatory autoimmune spinal cord disorders and their mimics, including their MRI patterns. He also has an interest in the epidemiology of inflammatory demyelinating diseases of the central nervous system and autoimmune neurologic disorders.

[00:03:19] Welcome, Dr. Flanagan, and thank you so much for joining us today.

Dr. Eoin Flanagan: [00:03:23] It's a great pleasure to be able to reach out to everyone and thanks to the SRNA and to you for inviting me to talk on this exciting topic and these really interesting diseases. It's great to be able to reach out to patients in this way.

GG deFiebre: [00:03:38] Yeah, great. Thank you so much. So, to start, can you just kind of explain the similarities and differences between NMOSD and MOGAD and maybe describe kind of what each of these diagnoses are as well?

Dr. Eoin Flanagan: [00:03:53] Yeah, so when we think about these diseases, they kind of come under an umbrella of diseases that we term demyelinating diseases of the central nervous system. And that means that these are diseases where there is inflammation autoimmunity where the body's immune system is attacking itself and it removes that insulation that surrounds the nerves and that causes patients to have symptoms. And there are a few of these that we recognize and in neurology and patients will be aware of the most common being multiple sclerosis but, in recent years, in the last two decades, we've discovered two new diseases.

[00:04:29] One I consider is called aquaporin-4 antibody positive neuromyelitis optica spectrum disorder, or NMOSD, and the other is MOG antibody associated disease. And these were really discovered by, we now have a blood test for these disorders that we can diagnose them. So, we can test for the MOG or the aquaporin-4 antibodies in the blood. And that has shown us that these are different diseases, and they differ in many ways. So, the NMOSD it tends to affect more females and tends to affect a little bit of an older age group. So, the median age would probably be 30 to 50 for that disease. While with the MOG antibodies, it tends to affect more children.

[00:05:14] And it tends to be an equal male to female ratio, while, with the NMOSD, females predominate by a large proportion, up to 10 to one, in terms of a ratio. The diseases cause similar symptoms, so patients can have inflammation in the optic nerve that we term optic neuritis. They can also have inflammation in the spinal cord that we term transverse myelitis.

[00:05:39] And when you have those in combination, the term neuromyelitis optica is sometimes used, which means neurologic, for neuro, so that's a neurologic disease, myelitis, meaning inflammation in the spinal cord, and optica, meaning the optic nerve is affected. So, we know that those diseases affect those areas, but they can also affect some other parts of the brain.

[00:06:00] And there's a disease called acute disseminated encephalomyelitis, or ADEM, which is a common manifestation of the MOG antibody disease, much less so with the aquaporin-4 antibody NMOSD.

[00:06:13] The MRI features, when patients undergo an MRI, do overlap, so we can see abnormalities on the brain MRI. We can see abnormalities on the spinal cord MRI and abnormalities in the optic nerve showing inflammation, but there are some subtle differences that we can sometimes pick up that can give us a clue towards each of these disorders. And also, because multiple sclerosis is a good bit more common, at least

in the United States, than these disorders, we also try and use those tools to distinguish these disorders radiologically. So, when we're seeing a patient who has optic neuritis or transverse myelitis, when we order these MRIs, we use that to try and distinguish, could it be the MOG antibody, could it be the aquaporin-4 antibody positive NMOSD, or could it be multiple sclerosis?

[00:06:58] So that's a lot of what we do on those MRIs and sometimes there are features that can help us distinguish, but other times, you know, we use the antibody tests to distinguish between them.

GG deFiebre: [00:07:10] Got it, thank you for that overview. And so, I know you talked a bit about some of the diagnostic tests like, for example, the blood test and looking at MRI but, overall, what are the diagnostic tests and tools that are used by physicians to kind of distinguish between someone who might have an NMOSD diagnosis from someone with a MOGAD diagnosis?

Dr. Eoin Flanagan: [00:07:32] Yeah, so I think we look at the demographics. So, we look, you know, in children, the MOG antibodies are going to be more common. So, that would be a clue towards, you know, thinking about the MOG antibody disease. If the patient has one of these clinical syndromes, we, as I mentioned earlier, we can sometimes use the MRI to look at differences. And the spinal fluid can sometimes be useful because we know that, with MS, we often have a marker in the spinal fluid called oligoclonal bands, and that's very common in MS, up to 90% of patients, while we only see that in about 10% of patients with MOG antibody and maybe 20% with the aquaporin-4 antibody NMOSD, so that can also be a useful discriminator.

[00:08:11] And then really the main discriminator is going to be this blood test. So, it's actually quite easy to order and we can test for the aquaporin-4 antibody and the MOG antibody in the blood. They're best tested in the blood. And there are many laboratories available. We test it here, at Mayo Clinic, but there are also many other laboratories available.

[00:08:31] So this is a readily available test and very useful test to be able to diagnose these conditions because with multiple sclerosis, unfortunately, we don't really have a blood test, so we have to weigh up all of the MRI features and the spinal fluid features and make sure that we kind of compile those together to figure out the diagnosis.

[00:08:51] I will mention that sometimes with the MOG antibody, it's kind of a little bit of a sticky antibody and sometimes we find some other diseases that can have a low level of MOC antibodies. So, we need to be a little bit careful. We don't see that as much with the aquaporin-4 antibody, but sometimes, with the MOG antibody, we can see it positive in a low percentage of MS patients or patients with other diseases, maybe one or 2%. So, patients need to be aware that it's not just the antibody, but we have to be sure that the rest of the features match the disease because the MOG antibody, for some reason, is a little bit sticky and sometimes we can see a low level of positivity with other conditions.

GG deFiebre: [00:09:32] Got it. And so then how does someone go about getting tested for these antibodies? Is it kind of one blood test for both? Is it two separate blood tests? You know, does their physician just have to order a particular kind of set of tests? How does that work?

Dr. Eoin Flanagan: [00:09:45] Yes, so different laboratories do it in different ways.

[00:09:48] You know? At Mayo Clinic we offer a panel where you can do both or you can order each one separately and other laboratories do similar things. It's available. You know, most neurologists would know how to order this. Many times, it would be a send-out test for community neurologist or a big center.

[00:10:04] Sometimes they'll do it in their own lab, or they will send it out to a laboratory. So, it's quite readily available. And, as I said, it's best tested in blood, so the spinal fluid is not quite as useful. So, in general we recommend the blood testing for both of these antibodies.

GG deFiebre: [00:10:21] Got it. I have two questions here. If someone is negative for both of these antibodies, but has optic neuritis and transverse myelitis, how is the diagnosis determined? And then also can someone be positive for both of these antibodies at once?

Dr. Eoin Flanagan: [00:10:37] That's an excellent question. So, firstly, if you have optic neuritis and transverse myelitis and you have neither of these antibodies, the first thing on my mind is do you have multiple sclerosis?

[00:10:50] Because we know that multiple sclerosis is quite common, in the United States, at least. And it's probably 50 times more common in the region where I am, in Minnesota. So, we really want to think about does the features of this look like multiple sclerosis? But some patients won't have features that are consistent with multiple sclerosis.

[00:11:08] And then sometimes they are termed as having seronegative neuromyelitis optica spectrum disorder. And that's an area where we're trying to discover more and maybe we'll discover new antibodies. But, in the meantime, we try and treat them with similar treatments that we use with the aquaporin-4 positive NMOSD on the MOG antibody associated disease.

[00:11:29] I will say these antibodies very rarely coexist, probably, you know, less than 0.1% maybe of the time. So, you know, one in 500, one in a thousand. Usually if they co-exist, like I said, that MOG antibody is a little bit sticky. So, usually, if they co-exist, the clinical syndrome, and it probably should be treated more like the aquaporin-4 because the MOG antibody is a little bit sticky and sometimes we see it with other conditions.

[00:11:56] So usually if we see them both together, the aquaporin-4 antibody is very high and the MOG antibody is usually at a low level that we think may not be significant. So, usually we treat those as if they're the aquaporin-4 positive NMOSD.

GG deFiebre: [00:12:11] Got it. And then we did have a question come in that this person can't have an MRI because they have a device for their bladder. And so, in terms of diagnosis, obviously there's the blood test, but, if they can't get an MRI, what else can kind of be done to make sure that a diagnosis is correctly given?

Dr. Eoin Flanagan: [00:12:29] Yes, so, you know, we take a history when we see the patients, we do a neurological examination, we can look in the back of the eye and, if the patient had symptoms of optic nerve inflammation a few weeks ago, or they're in the middle of an attack of that, we can sometimes see findings on examination, swelling in the optic nerve that we see commonly with with MOG antibody associated disease. We might see some pale color in the optic nerve that can tell us.

[00:12:53] We also have other tests. There's a test called an optical coherence tomography, or OCT, that many patients who have these disorders will have gone through, which takes a picture of the back of the eye. And sometimes we can see at the optic nerve is thinned a little bit that suggests old damage from an optic nerve episode. So, we can use that. A CT scan is not really as useful - a cat scan - of the brain, but we could potentially use that with contrast to look for active inflammation. So, that would be one possibility. And then the spinal fluid we could still do and look for inflammation. So, that's a possibility, too.

GG deFiebre: [00:13:31] Got it. Thank you. And so then, you know, moving on from diagnosis to then treatment. So, someone's been diagnosed with either NMOSD or MOGAD. What are the treatments used for NMOSD,

kind of the most commonly used ones? And then also, what are the treatments for MOG? Are they the same? Are they different?

Dr. Eoin Flanagan: [00:13:50] Yes, excellent question. So, we've had a real great success in the last two or three years with treatments that are available for the NMOSD that's positive for the aquaporin-4 antibodies. And we now have, in the United States, three FDA approved medications for this disease.

[00:14:06] One is called eculizumab. The other is inebilizumab and satralizumab. There are three medications that are very effective in this disease and, really, they're probably the first choices, once insurance covers those medications. They are quite expensive, which can sometimes be a barrier.

[00:14:22] Another medication that is commonly used with the aquaporin-4 positive NMOSD is rituximab. That one is not yet FDA approved, but there is some good evidence with randomized control trials to show that it works just like the other three medications I mentioned. So, these are all the four really effective medications that are used in that disease.

[00:14:44] There are some older generation medications that we used, and one is called azathioprine and the other is mycophenolate. There again, they were used for many decades, but really these newer medications are replacing those old medications and seem to be most effective.

[00:15:00] For MOGAD, we don't really know quite as well how to treat MOGAD, so we use a variety of treatments, but we're not really sure yet what works and we're hoping to be able to get some clinical trials where we can enroll patients and really prove that medications work. So, just like we did with the aquaporin-4 positive NMO, we've now proven that there are four medications that work very effectively. We need to do the same with MOG antibody disease, but we don't have those available yet. So, for now, we use those kinds of medications that we had experience with with the NMOSD. So, we sometimes will use azathioprine, mycophenolate, we might use IVIG on a regular basis to prevent attacks. We can also use rituximab. Tocilizumab is another medication. So, there's a few different options.

[00:15:50] These medications I mentioned are kind of used to prevent attacks. So, we have two types of treatment with these diseases. One is the acute treatment when a patient has an attack and then the others are the attack prevention treatment, which I just mentioned. The acute treatments with these diseases tend to be when patients present with their episode, we'll often give them high dose steroids. Many patients will know that they'll get an infusion of steroids or a very high dose oral steroids sometimes.

[00:16:16] And then, with the MOG antibody, they tend to respond very, very well to the steroids. And a lot of times that is all they need. And sometimes we slowly taper the steroids over, you know, many weeks or months while with the patients with the aquaporin-4 positive NMOSD, we often use a treatment called plasma exchange, which is a treatment where we put a line into the neck and we remove all of the patient's antibodies. Because we think that this aquaporin-4 antibody is causing a problem. So, one way of treating that is to remove all the antibodies. So, that's one way we use for acute treatment. So, there's differences. There's acute treatment and then there's treatment to prevent attacks. So, hopefully that made sense.

GG deFiebre: [00:16:56] Yes for sure. Thank you. And so, you know, B cell depleting drugs, like for example, rituximab or ocrelizumab, you know, potentially work on aquaporin-4 positive patients. But do they not work as well with MOGAD?

Dr. Eoin Flanagan: [00:17:12] Yeah, the reports suggest that they don't quite work as well. We don't know exactly why that is. The rituximab is a medication that depletes the B cells, as we said, and the B cells make

your antibodies. So, the idea is if you prevent them from being produced, that might be helpful. But for some reason, with the MOG antibody disease, patients can still have disease breakthrough.

[00:17:33] It tends to be more effective with the aquaporin-4 positive NMOSD. So, we really need to look and find treatments that we can prove work with the MOGAD. And I think that's the goal for all of the physicians in the field, if we can get a treatment that can help our patients and prevent these attacks.

GG deFiebre: [00:17:51] Got it. And then we did get a question whether or not, you know, people who have seronegative and MOG or MOGAD, whether using satrilizumab or inebilizumab are used for NMOSD or MOGAD?

Dr. Eoin Flanagan: [00:18:06] Well, so I think right now the medications are only FDA approved for the aquaporin-4 positives. So, for the negatives, they're not yet approved so, therefore, we'd have to use them off label and some of them are quite expensive, so it might be difficult to get an insurance company to cover that. So, sometimes we'll have to use other medications that are less expensive or that the insurance company's willing to allow us to use.

[00:18:30] But I think those kinds of medications are going to be trialed, I suspect, in the MOGAD. So, over the next many, you know, five to 10 years, I'm hoping that we'll have a proven medication. The medications like satralizumab, inebilizumab, eculizumab, they may be studied further in the MOG antibody disease, but we don't know yet if they work in that disease.

GG deFiebre: [00:18:53] Got it. And then we did get another question that someone received IVIG but is now being investigated for MOG or encephalitis. Is, you know, is there a time period after receiving IVIG that one should wait before sending in serum or cerebral spinal fluid specimens for results to be valid in terms of making a diagnosis.

[00:19:14] I doubt the IVIG would cause a positive. Sometimes we can see that because what you're doing is you're pooling immunoglobulins or antibodies from the general population and you put it in. And if one of those people who donated their blood had MOG antibodies that could, you know, theoretically go into you and then you test it and you find a positive.

[00:19:35] I think it's probably reasonable just to test those patients anyway, because it's unlikely to be a false positive. The big issue we get is if they have plasma exchange where we remove all of their antibodies, if we test them after that, we often have a negative result because we've just removes all of their antibodies. So, MOG antibodies, every single antibody has been removed and, therefore, the test will usually be negative. So, usually we'll recommend waiting three months or so to test after that.

[00:20:04] Got it. And then in terms of aquaporin-4 antibody levels or MOG antibody levels, can this be affected by, you know, either acute treatments for, so for example, steroids or plasma exchange or IVIG, or any of these more long-term treatments that are used?

Dr. Eoin Flanagan: [00:20:20] Yeah. So, like I mentioned with the plasma exchange, definitely if you test the patient after they've completed their plasma exchange, they will be negative for both antibodies. But, in general, with the aquaporin-4 antibody, it tends to stay. And even with treatments, it tends to persist in the vast majority of patients over time. With the MOG antibody, it's a little bit different in that some patients, the antibody will go away, and as patients may be aware, some patients with the MOG antibody will just have a one-off event and never go on to have another event.

[00:20:52] And sometimes their antibodies will go away. So, they have an episode of optic neuritis or of ADEM, like we mentioned, their antibody is high and then a few months later it goes away. So, and sometimes it can go away with time. Other times, if you test them, it's best to test patients or to have patients be tested during the midst of an attack when the inflammation is greatest, and we see that the MOG antibodies tend to be higher at that time. But I'm not sure about the other treatments, how much influence they would have. I think the main one is the plasma exchange.

GG deFiebre: [00:21:24] Got it. And then, why is it that some people with MOG antibodies don't stay on treatment forever or maybe kind of have this more monophasic disease course versus those with aquaporin-4 positive?

Dr. Eoin Flanagan: [00:21:40] We don't know exactly why, but what we do know is that with the aquaporin-4 positive, in patients that we've taken off of treatment and monitored them, some of those patients have had very bad relapses, which could leave them, you know, losing vision or with permanent paralysis. So, we really like to treat those patients very, you know, in the long-term and keep them on treatment, because without treatment, these patients can have really devastating relapses.

[00:22:06] And what we've recognized, in fact, is that with this aquaporin-4 positive NMOSD, since we've started all of these treatments, the outcome is far, far better for patients. Back in the 1980s, 1990s, these patients had a really poor outcome when they weren't treated. They would have severe devastating attacks and, you know, they would develop a lot of disability and even patients would die at a younger age.

[00:22:29] So, I think these medications, it's really important to stay on the medication for the aquaporin-4. With the MOG antibody, what we know is that some patients can have a one-off event. We don't know why that is, but what we don't want to do is put them on a medication that lowers their immune system for many, many years if they're destined never to have another attack, then that would put the patient at too much risk.

[00:22:51] So, we usually treat mostly patients who have relapsing disease, which means we treat them after they've had two episodes. And we generally just treat the first episode and then observe over time in most cases. But we do make exceptions for very, very severe episodes. But, in most patients, we treat the relapsing disease. So, those that have more than two episodes.

GG deFiebre: [00:23:13] Got it. And then, can individuals with MOG relapse if they have negative titers, and if so, why does this happen? And the same kind of question for those with aquaporin-4 positive NMOSD.

Dr. Eoin Flanagan: [00:23:28] Yeah, so, I think, with the aquaporin-4 positive NMOSD, we, we rarely see them convert to negative, and those patients, once positive, kind of always positive and always at risk of a relapse, we think. With the MOG antibody, most patients who go to negative will not have another relapse, but some patients do. We don't know exactly why that is. Or sometimes the antibody might go negative and then return to be positive.

[00:23:52] But I think we're trying to study patients, and this is something I have a grant from the NIH to do, which is to study patients over time and see, get repeated blood tests from them and see what happens to our antibody and see what we can learn about that. Because, sometimes that can help tell, you know, what's going on and can we predict if that's going to predict that they're more likely to relapse and that kind of thing.

[00:24:14] Because sometimes if the antibody stays positive over time, even if you've had one episode, you're probably more likely to go on and have another episode. So, we like to observe those patients a bit

more closely, while if it goes negative after your first episode, then those patients we don't tend to need to observe as closely.

GG deFiebre: [00:24:32] Got it. And then, I guess, relatedly, when would you make a definite decision to not take a MOG patient off of treatment?

Dr. Eoin Flanagan: [00:24:40] I think patients who've had quite severe relapses. If they have vision loss already. You know, if they have vision loss in one eye and then we get concerned about the other eye, because that could leave them blind. So, if they're relying on their one eye, we sometimes will keep patients on treatment for those reasons. So, we don't yet know, you know, how long we should treat. And of course we don't know how effective the treatments are yet either.

[00:25:03] So, I think there's a lot to learn with the MOG antibody disease, but the great news is we've just done it all with the aquaporin-4 antibody disease. So, it should make it much easier to help us figure out what treatments work for MOG, how long to treat, and those kinds of questions. So, over the next many years, I suspect we're not going to have the answers to a lot of those questions for patients.

GG deFiebre: [00:25:25] Got it. And then, if someone tests positive with MOG once, and then six months later, tests negative, does that mean that they will likely not have a recurrence?

Dr. Eoin Flanagan: [00:25:34] I think it means they're less likely, but it's not a hundred percent. So, if they did develop new symptoms, we'd still want to see them back. But a lot of those patients, in general, we would not treat them after the first relapse, then we kind of observe. And then, you know, it makes it less likely that they would go on to relapse. Yeah.

GG deFiebre: [00:25:52] Got it. Okay. And then, moving on to sort of questions about prognosis or ongoing care. Can reoccurring MOG or NMOSD attacks lead to severe disability or blindness, for example? And if so, after how many attacks? Can it just happen after one, is it usually after kind of a cumulative number of attacks?

Dr. Eoin Flanagan: [00:26:15] So, this is this is an excellent question, and it's different for the aquaporin-4 versus the MOG. So, the aquaporin-4 positive NMOSD, I would, we need to really treat these attacks aggressively because patients do develop a good bit of disability with each attack, and that can mean that with one attack, they might, you know, drag one leg. After a second attack, they might require a cane. After a third attack, they might require a walker.

[00:26:40] So, we really want to be careful to treat those attacks aggressively, and that means steroids and that plasma exchange. So, in the majority of patients, we should be using steroids and this plasma exchange or PLEX treatment that patients will recognize. So, it's really important to treat that acute attack, because that might prevent or lower the amount of disability they get from each attack.

[00:27:04] And then, that just highlights the importance of preventing attacks with the maintenance medications that I mentioned earlier, the rituximab, eculizumab, inebilizumab, and satralizumab. It's really important to stay on those medications to prevent that disability, because it does tend to creep up very quickly with each attack.

[00:27:22] And, you know, a single attack can leave the patient, you know, paralyzed or blind in one eye. So, it's really important to treat those aggressively. With the MOG antibody, we tend to see better recovery. So, patients can still be very severely affected when they have an attack. They might require a wheelchair, not be able to walk, or be blind in their eyes, but they tend to recover quite well with the steroids.

[00:27:42] So, what we see is that patients don't develop as much disability from each attack. So, but in the long-term, after each attack, they do tend to develop a little bit more disability. And then the long-term, you know, over the course of 15 years or so, we did a study on this, and we found that less than 10% were blind in one eye.

[00:28:01] So, most patients do very well. It does tend to be centric to the eye, the MOG antibody disease. So, we always worry about the vision. But less than 10% required, you know, a cane to walk, and less than 10% were blind in one eye after a median of 15 years of disease. So, that is overall a much better outcome.

[00:28:21] With the aquaporin-4 positive NMOSD, what we see, particularly in those who are not treated aggressively with their attacks or not on maintenance treatment, we can see that disability rise very quickly, and a much higher proportion of those patients may require, you know, you know, may be blind in one eye or may require a cane to walk. So, it, it needs to be really aggressively treated, the aquaporin-4 positive NMOSD.

GG deFiebre: [00:28:47] Got it. So, I mean, is there anything else that you kind of want to add about the prognosis for someone with NMOSD in comparison to someone who's maybe been diagnosed with MOGAD?

Dr. Eoin Flanagan: [00:28:56] Yeah, I think, you know, with the treatments and, you know, treating the attacks aggressively, patients are doing much better. What we're seeing in our clinics is patients are doing much, much better. So, I think the outlook is much improved for patients. So, I would take a positive note here and say that the future looks bright for patients who, you know, get this, you know, difficult diagnosis, devastating diagnosis, but we can really treat it and prevent it very well.

[00:29:22] So that is the good news with the aquaporin-4. But, without treatment and without treating the attacks aggressively, it can creep up very quickly. So, we have to be very careful. With the MOG antibody disease, patients can have a lot of episodes where they get inflammation in their optic nerves or inflammation in their spinal cord or brain, but they do tend to recover very well, which is good.

[00:29:42] And it's probably a bit better, but we don't really know what treatments work yet. So, we've more to learn with the MOG antibody disease. But overall in the longterm, the outcome is, is good. And the other thing to mention differing from MS, we don't see that progressive course that we see with MS. So, many MS patients after 20 or 30 years of disease have slow gradual deterioration over time that results in them developing disabilities, sometimes requiring a cane or walker to walk and that kind of thing. And we don't see that progressive course with the MOG antibody disease or the aquaporin-4 positive NMOSD, which is really great. We don't see that in the long-term.

GG deFiebre: [00:30:23] Got it. And then, are people with NMOSD more likely to relapse than people with MOGAD?

Dr. Eoin Flanagan: [00:30:29] I think it's probably similar. It's quite variable. You know, now that we have the treatments available with the aquaporin-4 positive NMOSD I, I see that patients tend to be very stable over time and not relapse as much, while with the MOGAD, because we don't exactly know what treatments are effective and we don't have proven treatments, we tend to see more relapses. But again, they tend to recover from those pretty well once they're treated with steroids.

GG deFiebre: [00:30:56] Got it. And then, are those who test positive for MOG antibodies more likely to have ADEM or get kind of like an ADEM-like presentation than those with aquaporin-4 antibodies?

Dr. Eoin Flanagan: [00:31:08] Yeah, exactly that. And that just highlights the difference. You know, we see that in patients who have a first episode of ADEM, for example, 30 to 50% of those will be MOG antibody positive, while probably less than 5% will be aquaporin-4 antibody positive. So, definitely there's a difference. And the patients with the MOGAD are more likely to go on to develop ADEM.

[00:31:29] So ADEM is much more common with the MOG antibodies. Exactly right, yep. I see a question in the chat. Maybe I should just answer that while we're on the topic of ADEM.

GG deFiebre: [00:31:37] Yeah, that would be great, thank you.

Dr. Eoin Flanagan: [00:31:40] It's "What is ADEM?" And that's an excellent question. I think I mentioned that earlier. ADEM stands for acute disseminated encephalomyelitis, which is a bit of a mouthful. But basically what it means is that there's inflammation in the brain and the spinal cord.

[00:31:54] So, 'encephalo' means brain and 'myelitis' means spinal cord, and 'acute' means it comes on acutely. So, and 'disseminated' means it's involving multiple areas. So, the words can kind of be complicated, but really what it means is that there's inflammation in the brain and the spinal cord at the same time.

[00:32:12] And a lot of those patients will have some confusion with that where they're, you know, not able to communicate, they might have seizures or other problems. So, the, the problems that those patients have tend to be a little bit different than with the transverse myelitis or the optic neuritis where they won't be confused. So, there's a bit of a difference there with the ADEM, but thank you for that question, and it's important to clarify that for you.

GG deFiebre: [00:32:36] That was great. That was going to be my next question. And so, another question that we got was that this person had a history of transverse myelitis and evidence on OCT of past optic nerve damage. They've also had additional spinal lesions and a history of brainstem lesions. They were never tested for NMOSD because their eye involvement was mild. Are there mild cases of NMOSD?

Dr. Eoin Flanagan: [00:33:02] There can be, yeah. It might be unreasonable to, you know, have that patient tested for the aquaporin-4 or the MOG antibodies. What I will say is that, you know, another thing that can be a useful distinguisher is that the MS lesions, when they occur, tend to leave a moderately sized scar. So, what patients will see when they come back to their doctor after they recover from their episode is they'll see a few spots on their brain MRI or on their spinal cord MRI that shows a scar.

[00:33:29] And in fact, with the MOG antibody disease, what we've recognized is that they tend to recover completely and don't leave as many scars within the brain. And that might be part of the reason that they don't have that progressive course. So, that's another useful distinguisher. But, you know, with optic neuritis and transverse myelitis, in this patient's scenario, you know, multiple sclerosis would be high on the list as well.

[00:33:51] So their doctor would want to consider maybe a spinal tap to look for oligoclonal bands, those kind of things that might help with the diagnosis of MS, realizing we don't have a blood test for MS, unfortunately. But it might be unreasonable to test them for the MOG and the aquaporin-4 antibodies.

GG deFiebre: [00:34:08] Got it. And then, can someone have a MOG or even, I would say, NMOSD with aquaporin-4 positive or negative, that affects the brain and spinal cord without affecting the eyes, or do people always lose vision with every attack?

Dr. Eoin Flanagan: [00:34:24] No exactly right. It does- It can sometimes, with the aquaporin-4 positive in particular, we'll see recurrent episodes of transverse myelitis. And that's why they changed the name from NMO, which is neuromyelitis optica, to NMO spectrum disorders, because we know that it's a spectrum and not everybody has the inflammation within the optic nerve and the spinal cord. So, some patients can have inflammation in different regions. The other thing to mention that's interesting with the aquaporin-4 antibody is some of those patients will develop inflammation in an area called the area postrema, which is in the brainstem and it's the vomiting center.

[00:35:00] So some of those patients will present with vomiting or hiccups and nausea, and sometimes they go to see a gastroenterologist and they don't realize it's a neurologic problem, but that could be a pretty common manifestation of the aquaporin-4 positive NMOSD that patients should watch out for, because that, sometimes that gets confused with gastroenteritis or gallbladder problems or other GI issues.

GG deFiebre: [00:35:26] Got it. And then, we have gotten a few questions about the COVID-19 vaccines. If you don't mind, if we just kind of talk about them a little bit. So, one, you know, obviously we've gotten a lot of questions about the efficacy or the effectiveness of these vaccines kind of in the general population or in those on potential immunosuppressants that are used in MOG or aquaporin-4 positive NMOSD or seronegative NMOSD. How effective are these vaccines? Do we know? Or are we still looking at it?

Dr. Eoin Flanagan: [00:35:56] I think this is something we're still looking at. You know, we're strongly recommending that all our patients get the COVID-19 vaccination because it seems it will give at least some protection.

[00:36:06] And we don't know, particularly with the treatments that target the B cells like the rituximab, inebilizumab, they target the antibody-producing cells. So, we don't know if patients will make as strong an antibody response to the vaccination. But I think it's something that's under further study. But there are other ways that the vaccine helps you protect against the infection with T-cells and other things.

[00:36:31] So, certainly it'll give some protection, and we just don't know exactly how much or if those patients will need additional boosters. I think it's something that we're trying to study further. And it's been studied quite well in the MS field where we have more patients in the United States to learn from. And we can probably extrapolate some of those findings towards the MOG and the aquaporin-4 positive NMOSD patients down the line.

GG deFiebre: [00:36:56] Got it. And then, someone has a relative who has MOGAD and received the COVID-19 vaccine and also took the spike protein antibody test. So, obviously not just the regular antibody test, but the spike protein, which is what the vaccines are, people immunity towards. So, but it came back negative. So, what does that kind of mean in terms of how effective the vaccine might've been? How accurate is this test? Are there other tests like T-cell tests that might be available to look at this as well?

Dr. Eoin Flanagan: [00:37:28] Yeah. I, I don't think we fully know yet. That suggests, if they don't have antibodies to the spike protein, that they didn't make as good an antibody response as we would like. But we don't know for sure, you know, if the T-cells are enough to prevent against the infection or other processes. So, it's an excellent question. We don't know yet. You know, sometimes it may take longer for the patients to make antibodies to the vaccination. So, the spike antibody could be repeated down the line and I've, I've done that in some of my patients and found it to, you know, initially be negative and subsequently be positive. And, you know, I suppose as we learn more, it may be that those patients need an extra booster kind of thing.

GG deFiebre: [00:38:10] Got it. Thank you. And then, we did get another question that if someone tested positive for MOG, how often should they be retested? And then, I would ask the same thing of the, of aquaporin-4.

Dr. Eoin Flanagan: [00:38:21] Yeah. Yeah. So, if I start with the MOG antibody and, you know, generally these antibodies are best tested as a diagnostic marker. And at that point, that is the most useful thing. And then we usually base our treatment decisions on how they're doing clinically.

[00:38:37] So if they've had only one relapse, because many of, up to 50%, can be a one-off episode, we don't want to put a patient on a long-term immune-lowering medication that puts them at risk if there, you know, if there's a 50/50 chance they may never have another attack. So, we tend to base our treatment decisions on, more on the clinical grounds.

[00:38:56] So, I think it requires more study for most patients. You know, repeating the antibody is not going to be quite as important, but it may give you a sense of how closely you want to observe. If a patient has an attack, you repeat it six months later and it's negative, they may be less likely to go on to develop further attacks, while if it's still positive, you might want to watch them more closely.

[00:39:17] But really most of the decisions are based on clinical grounds, so there's not that much usefulness right now in repeating the antibody test. But from a research standpoint, we are studying some of these things and trying to figure out more. With the aquaporin-4 antibody test, again, this one is not really very useful to follow.

[00:39:34] And we've looked at that to see if, you know, the titer would go, if the level would go up at the time of an attack or predict that it's going to, you're going to have an attack, and it doesn't really seem to be that useful. So, I think for that one in particular, once positive, always positive, don't need to probably retest.

GG deFiebre: [00:39:52] Got it. And then, we did get a question about someone with MOGAD and then FLAMES, which is, I believe, is an acronym for a subset of MOG antibody disease. If they have persist-, if, I guess if you could talk a little bit about what that is first. And then, if they have persistent encephalopathy or status epilepticus, would you consider testing for another antibody, the NMDA receptor antibody?

Dr. Eoin Flanagan: [00:40:18] This is an absolutely excellent question. So, the FLAMES is a term that describes the patients who have inflammation in the brain that's usually just on one side and it involves the cortex, which is the gray matter of the brain. As many of you know, the brain has gray matter around the outside.

[00:40:37] And then, we have parts of the deep gray matter where a lot of the cells are. And then we have white matter where we have a lot of the fibers connecting different parts of the brain. And, you know, these diseases are generally tend to be more of a white matter disease, because that's where that myelin, the insulation of the cables is, that is located most of all. But there is some myelin located in the gray matter.

[00:40:59] And what we recognize is that some patients can have this inflammation in the cortex just on one side, where they may develop seizures, status epilepticus, headache, fever. They may develop weakness on one side. Sometimes it gets mistaken as a stroke. And the MOG antibodies are usually quite positive in that situation.

[00:41:18] But some patients can also have other auto-antibodies, and the NMDA receptor antibody is an important one that can be tested in the spinal fluid, is best tested in the spinal fluid, unlike the MOG, which is better tested in the blood. So, it wouldn't be unreasonable in a patient with that kind of syndrome to test both of those antibodies.

[00:41:37] Because sometimes patients can have more than one antibody. It's just like a patient who's more prone to autoimmunity in the body. If they get diabetes, they might be more likely to get autoimmune thyroid disease or other, rheumatoid arthritis, that kind of thing. Sometimes we can see patients who have two brain autoimmune diseases, but it's rare.

GG deFiebre: [00:41:55] Got it. And so, we did get a question, you know, we've talked about these two different antibodies, and so sometimes people are positive for one or the, or the other. But where does someone who's a double negative, so doesn't test positive for either of these antibodies, fall in terms of long-term treatment?

[00:42:12] And is this thought to be a kind of different illness altogether, maybe something we haven't found an antibody for yet? And do they tend to have repeated attacks? Where, where do those who are double negative, you know, kind of fall in all of this?

Dr. Eoin Flanagan: [00:42:24] Yeah. I think the double negatives are hard. You know, they probably, you probably require a, you know, good neurologist to look through that. The first thing you want to do if you're double negative is ensure that you don't have multiple sclerosis, which is going to be the most common reason to be double negative. And your doctor should be able to assist with that. Otherwise, they're areas where we're trying to discover more. We're looking to see if there's other antibodies that we could discover that may be markers of new diseases.

[00:42:50] And otherwise, you know, we know with these immune diseases that if you lower the immune system with some of these treatments, they tend to work regardless of what the antibody is or if we don't know. So, sometimes using some of those immune medications targeting the B cells with rituximab or azathioprine, mycophenolate.

[00:43:06] So, a lot of times we just have to use what we can to try and diagnose them. But the first thing will be to determine if it's MS, then if it is MS, then we would use one of the approved medications for MS. And if it's not MS, then we would try one of the medications that we use for the MOG antibody or for the aquaporin-4 positive NMOSD, similar medications.

GG deFiebre: [00:43:27] Got it. And then, I just want to talk a little bit about kind of the, the history of how these disorders were categorized. So, you know, I believe in the past, anyone who is potentially diagnosed with longitudinally extensive transverse myelitis or, you know, lesion in the spinal cord that extended more than three segments was maybe diagnosed with NMOSD. You know, and then obviously prior to the MOG antibody, being kind of, you know, a test being widely available, you know, maybe those individuals were clumped into either MS or NMOSD.

[00:43:57] So, do you mind just kind of talking a little bit about the history kind of what maybe happened in the past and then how we've gone from there until now?

Dr. Eoin Flanagan: [00:44:05] Yeah. Yep. So, you know, back I think it was in the late 19th century, Devic who sometimes this disease, the NMO disease, is called Devic's disease was the first to describe this condition. And in the late 1990s, Dr. Brian Weinshenker and Dean Wingerchuk, who were neurologists at the Mayo Clinic, realized that this was a different disease to MS. And in 2004, really the key was the antibody test because that now allowed us to distinguish the aquaporin-4 positive NMOSD from the other disorders - MS and other inflammatory demyelinating diseases.

[00:44:42] And then, the discovery of the MOG antibody, which was Kevin O'Connor and a group were able to discover that. And, you know, the availability of that now has helped us. So, the way I think it's best to consider these diseases is we have three definite clear diseases. One is multiple sclerosis, where we don't have a blood biomarker, but we have pretty consistent findings on the MRI and in the spinal fluid that can help us. The second disease is the aquaporin-4 positive NMOSD. And the blood test is very reliable for that. We very rarely see any false positives.

[00:45:18] It's a very good test. And that's its own disease. And then the third disease we have is the MOG antibody disease. And again, the MOG antibody is very useful, but a little bit sticky. So, sometimes a low positive we can see with other diseases. We have to be a little bit careful, and we can occasionally see some false positives there.

[00:45:35] So that's, you've got your three defined diseases and then all of the others are kind of more discovery for patients who have, you know, MOG antibody negative, aquaporin-4 antibody negative NMOSD, or they might have recurrent optic neuritis, recurrent transverse myelitis, ADEM, where all these antibodies are negative.

[00:45:53] They're all areas for further discovery. And, you know, there might be multiple different diseases in there, but we have to kind of work harder to discover those. So, I think for now it's best to think of it as three different diseases. The MS, the aquaporin-4 antibody positive NMOSD, and the MOGAD, or MOG antibody positive disease.

[00:46:13] And I don't know if you wanted to mention a little bit about the disease entity, been described itself as its own entity, but we can cover that too.

GG deFiebre: [00:46:21] Yeah, that was actually, that was my segue into the next kind of set of questions about, you know, in terms of, you know, I know people have kind of been lumped into one category or the other, but I know that, you know, our partners over at the MOG project have worked on submitting to get a separate ICD 10 code, for example, for MOGAD. And so, do you mind just talking a little bit about what has to be done to make this happen? If, you know, what steps have been taken? And how making MOGAD its kind of own disease might impact patients, researchers, or pharmaceutical companies?

Dr. Eoin Flanagan: [00:46:57] Yeah, an excellent point. I think it's been really important, and the MOG Project has been very helpful in highlighting this issue. It's really important that we let MOG antibody disease be its own disease. And it's clear it's different from the other diseases. It tends to affect children more commonly, and the antibody is positive, which is a marker, versus the aquaporin-4 antibody is almost always negative. So, it does clearly look like its own disease.

[00:47:25] And on the MRI, it has different features, and on the spinal fluid it has different features, and in the prognosis it has different features. And indeed, we didn't mention this earlier, but when you look under the microscope at the brains of patients who've had a brain biopsy with these conditions, the MOG antibody disease looks different.

[00:47:42] So, there are lots of different reasons that MOG antibody needs to be its own disease because it is its own disease. And, you know, if we're to develop treatments for these diseases, we need it to have its own disease entity so we can enroll patients who have MOGAD into their own clinical trial and not mix them up with our MS patients or our NMOSD patients.

[00:48:03] And also, when we talk to patients, we want to tell them, how are you going to do in 10 years? How are you going to do in 20 years? And we know that the MOG antibody, the outcome is pretty good. So, we

want to be able to tell patients, "yeah, here's, what's going to happen over time, and here's, you know, what we know about this disease."

[00:48:19] And in terms of, before we develop a proven treatment, what sort of treatments we use for the disease, we want to make sure that we, you know, distinguish that, and that we know that the steroids work very well for the attacks, patients can resolve their symptoms, and that we kind of treat it as its own entity.

[00:48:37] So we don't just use MS medications for this disease, which seem to be ineffective, many of the MS medications, or can make the disease worse. So, these are all the reasons why it's really important that this is its defined entity. And we're working as a group with the international classification of diseases to have it as its own disease.

[00:48:56] Because I think this is really important for patients so that they can tell family members, tell other doctors that they see, this is the disease that I have. So, it's really important for all of those reasons.

GG deFiebre: [00:49:08] Great. Thank you so much for that. And then, do you have anything else kind of to add maybe that we didn't cover or anything you want to talk about in a little bit more detail before we end today?

Dr. Eoin Flanagan: [00:49:19] Not, not really. I think we, we covered things. You know, we have the three major diseases, the MS, the aquaporin-4 positive NMOSD, and the MOGAD. And, you know, I'd encourage patients out there if they, if they have questions or they're not sure about their diagnosis, you know, seek out expertise at an expert center.

[00:49:37] There's many expert centers throughout the country who see these cases and who, you know, do research on these cases. And then, finally, you know, I just like to thank all the patients out there. You know, we, we learn so much from every patient. You know, we can learn a whole story about the disease from one patient telling us what happens to them over time.

[00:49:57] And many of these patients give up their time. They offer their blood samples for us to learn more about the disease, and we really appreciate the efforts that patients make to both travel to come and see us physicians who may not be at a convenient location or hook up with us on, on virtual visits to provide samples for research so we can learn.

[00:50:16] And really, you know, I think we all want, you know, what's best for the patient, and, you know, want to develop a treatment for this disease. So, I just can't thank everybody out there enough. We've had some real good success with the aquaporin-4 antibody positive disease with all these new approved medications.

[00:50:32] And I think we can have the same with the MOG antibody disease. And all of this is because of the patients that have given up their time and given samples for research. And it's just, it's really back to the patients who have done so much.

GG deFiebre: [00:50:47] Great. Yes. Thank you so much. And thank you to everyone for joining us. Again, this was recorded, and it will be available on our website, so be sure to check that out as well. So, thank you so much, Dr. Flanagan. We really appreciate it.

Dr. Eoin Flanagan: [00:50:58] Of course. Thanks for the opportunity, and we appreciate everyone listening, and we want to, you know, be able to develop treatments for all of these diseases so patients can live their lives as best as they can. So, thanks again.