ABCs of NMOSD Podcast Series
Am I Having a Relapse?

The audio of this podcast is available at: https://youtu.be/1dDeio2fPoU

Intro: [00:00:00] ABCs of NMOSD is a ten-part 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. 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 VielaBio.

GG deFiebre: [00:00:59] Hello everyone, and welcome to the ABC's of NMOSD podcast series. Today's podcast is entitled, “Am I Having a Relapse?” My name is GG deFiebre from the Siegel Rare Neuroimmune Association, and I will be co-moderating this podcast along with Jacinta Behne from the Guthy-Jackson Charitable Foundation.

Jacinta Behne: [00:01:21] Hi everyone. This is Jacinta. GG, thank you so much for inviting me to join you today to moderate the podcast. I'm very, very honored to do so. Back to you.

GG deFiebre: [00:01:31] Thank you so much for joining us. 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 Viela Bio. Viela Bio is dedicated to the development and commercialization of novel, life-changing medicines for patients with a wide range of autoimmune and severe inflammatory diseases. The company's approach, which targets the underlying molecular pathogenesis of the disease, is aimed at enabling the development of more precise therapies, identifying patients more likely to respond to treatment, and pursuing multiple indications for each product candidate. For additional information about Viela, please visit vielabio.com. For today's podcast, we are pleased to be joined by Dr. Sean Pittock and Dr. Dean Wingerchuk.

[00:02:27] Dr. Sean J. Pittock is Professor of Neurology, Director of the Neuroimmunology Laboratory and the Center for MS and Autoimmune Neurology at the Mayo Clinic. Dr. Dean M. Wingerchuk is Professor and Chair of the Department of Neurology at Mayo Clinic in Phoenix and Scottsdale, Arizona. Welcome, and thank you both so much for joining us today.

Dr. Pittock: [00:02:49] Thank you very much for having us.

Dr. Dean Wingerchuk: [00:02:50] Indeed, thank you.

GG deFiebre: [00:02:53] Thank you. So to start, I know this is a complicated topic, but if we could just begin by talking a little bit about how a relapse is defined, and how this might be different from something like a pseudo relapse. Dr. Pittock, do you mind starting?

Dr. Pittock: [00:03:10] Sure. Well, NMOSD is really characterized by having relapses of neurologic dysfunction. And we really define a relapse as a kind of a new area or episode of inflammation in the central nervous system that results in symptoms. And in NMOSD, the types of relapses that we generally see are mainly three types of relapses: areas of inflammation of the optic nerve, which can cause vision loss and pain in the eye; areas of inflammation in the spinal cord, which would cause what we call myelitis or difficulties with motor function or sensory function in the legs, sometimes bladder and bowel problems; and then areas of inflammation in the back of the brain, in an area called the area postrema, where patients can sometimes have relapses of intractable nausea and

vomiting. And these relapses are really related to new areas of inflammation, presumably caused by the antibody targeting the water channel and the astrocytes in those areas. When you get right down to blood brain barrier and get information.

[00:04:20] And these relapses are kind of considered true relapses. Whereas when we talk about pseudo relapses, what we're talking about really is just the development of symptoms that oftentimes relate to an older or previous area of damage. But that area of damage is irritated by something systemically happening in the body. For example, if somebody has an infection and their temperature goes up, they can sometimes develop symptoms that they had when they had the relapse. But once the fever or the urinary tract infection, etc., is treated, then those symptoms resolve. That's really what we mean between relapses and pseudo relapses.

GG deFiebre: [00:05:02] Thank you. And then Dr. Wingerchuk, do you have anything to add to that?

Dr. Dean Wingerchuk: [00:05:06] That was a great introduction. I think as neurologists, the distinction is extremely important because a relapse means the disease is active, that there's active inflammation, and that's usually actionable. You need to do something about that. But if we conclude that it's a pseudo relapse, then it's not. And we'll probably go into more detail about that.

Jacinta Behne: [00:05:34] Great. GG, ready for the next question?

GG deFiebre: [00:05:35] Yeah.

Jacinta Behne: [00:05:40] Okay, great. The next question, one of the patients writes in, what are the symptoms a person with NMOSD should look out for that may indicate they're having a relapse? And, Dean I'll turn to you this time to go first, please.

Dr. Dean Wingerchuk: [00:05:54] Okay. Sure. Well, Dr. Pittock has introduced this a little bit. But most of the time, what tells a person with the disease and tells us as neurologists that a person may be having a relapse is the emergence of a new symptom or new pattern of symptoms that's consistent with the activity of the disease. So, Dr. Pittock outlined the three most common types of attacks affecting the optic nerve, the spinal cord, or the brain stem, this area called the area postrema and also called the vomiting center sometimes.

[00:06:36] And so, usually the first indication that something is happening is the person recognizing that a brand new symptom or brand new pattern of symptoms has started. Now, one of the things about an attack or relapse, and I guess it's important to know that those terms are used interchangeably. People usually talk about attacks, relapses, sometimes exacerbations, they all essentially mean the same thing. But a new symptom that develops and persists.

[00:07:14] Now sometimes you might hear or read that a symptom has to last for 24 hours for it to meet the criteria to be an attack. And that's an arbitrary definition, and it's one that sometimes is helpful, but I'll give you a couple of examples. So, if somebody awakes one morning and they have pain and significant visual loss in one eye. Well, that would be something that would certainly raise concern of a new attack of optic neuritis.

[00:07:49] It's new, it's consistent with new activity of the disease. I wouldn't advise waiting 24 hours to see whether that would resolve before seeking a medical care. On the other hand, somebody

might have a history of having optic neuritis, and let's say their vision got partially better and they were left with visual blurring or visual loss.

[00:08:24] And if they notice that that same eye is affected with the change in vision, but it's a pattern of visual change that they haven't experienced before, really distinctly different than what happened to them the first time, then that's potential symptom of a relapse. So overall the most common symptoms are going to be related to vision, they're going to be related to weakness, numbness, sometimes pain or change in bladder or bowel function. That's all related to the spinal cord.

[00:09:01] And then sometimes those attacks in the brainstem that can cause nausea, vomiting, or sometimes hiccups. Those are typically symptoms that need to persist longer before you would necessarily reach the conclusion that they were NMO, because being nauseated is something that we all experience occasionally. So it's a little bit different for each symptom and how it develops in the pattern. But those are by far the most common general presentations.

Jacinta Behne: [00:09:42] Thank you so much, Dr. Wingerchuk. Dr. Pittock, would you have something, anything you'd like to add please?

Dr. Pittock: [00:09:52] No, I think Dean covered that question very nicely.

Jacinta Behne: [00:09:56] Okay.

GG deFiebre: [00:09:59] Great. Thank you. And so, we talked a bit about the potential symptoms of relapse that are related to the central nervous system, but are there any sort of symptoms of relapse that might not be related? For example, stomach issues, I know you talked about nausea, but gut issues or fever, increased heat or cold sensitivity. Dr. Pittock?

Dr. Pittock: [00:10:24] Yeah, so, well, when we started doing a lot of the studies on intractable nausea and vomiting at Mayo, and in Japan they've been studying this for many years before that, a lot of these patients when they were having attacks of area postrema - in other words, they're having episodes of intractable nausea and vomiting - many of these patients underwent extensive workup. In fact, most of them presented to gastroenterologists for evaluations and had upper GI endoscopies, lower GI endoscopies, CT scans, etc.

[00:10:59] And generally it was ultimately found that these episodes of intractable nausea and vomiting were generally related to attacks that were occurring in the area postrema, not relating to local gut problems. The question of whether or not there could be gastrointestinal dysmotility because of autonomic dysfunction in NMOSD has been raised and potentially could be playing a role.

[00:11:23] But certainly gut symptoms can be present in patients with NMSOD, but not related to relapse of the central nervous system inflammatory disorder, but related to potentially side effects medications. For example, use of steroids on a regular basis can cause gastritis or even stomach ulcer and abdominal pain. Cellcept, for example, can cause diarrhea and abdominal pain at about 5 to 10% of patients.

[00:11:51] So, those need to be considered in the setting of gut symptoms. And then also remember that in patients with NMOSD, there's a very high frequency of coexisting other autoimmune

conditions. So for example, patients with NMSOD have a higher risk of ulcers of colitis. And that also can be a presentation, but not necessarily related to the NMOSD per se, but to a coexisting autoimmune condition. In respect of pain, we do sometimes see pain in the setting of a relapse. For example, sometimes patients can report interscapular pain as the first symptom of transverse myelitis.

[00:12:32] Sometimes patients can develop tonic spasms that can be painful in their limbs. That can also occur in the setting of a relapse. But pain generally is a big problem in NMOSD, but it's generally more of a neuropathic pain relating to kind of damage and irritation of neurofibrils in a damaged area in the cord from a relapse.

[00:12:54] In terms of heat and cold sensitivity, again, this is very much patient dependent. Patients with multiple cirrhosis can have very significant heat and cold sensitivity. Some patients can become very lethargic or have worse symptoms in the setting of heat, oftentimes in the summer, sometimes we have patients wear cold vests, etc., or ice vests.

[00:13:14] That's less of a problem in NMOSD, but it does exist. And it may certainly relate to the fact that when you become overheated, that there is an effect on the transmission of the electrical impulse through damaged areas where potentially there's a lack of myelin. And so those are certainly things to think about in patients with NMOSD.

GG deFiebre: [00:13:45] Good. Thank you so much for that overview. Dr. Wingerchuk, do you have anything to add as well?

Dr. Dean Wingerchuk: [00:13:51] No, I don't think so. Not to that question.

Jacinta Behne: [00:13:55] Then we'll go on to the next question. Dr. Wingerchuk, any side effects from NMOSD drugs mimic relapse?

Dr. Dean Wingerchuk: [00:14:06] Well, the usual situation with side effects of medication is aggravating some pre-existing symptoms. So the kind of pseudo-relapse or pseudo-attack that Sean Pittock described earlier. So, for example, sometimes medications, and this is especially true of medications that have an effect on the brain itself - so anticonvulsant medications that might be used for pain or spasms, for example, or spasticity medications. They can sometimes aggravate or bring out symptoms that people were having before. So, it can make a previously weak leg seem temporarily weaker, or maybe a previously affected eye seems more blurry. So, usually that's the case is that it's essentially causing a pseudo-relapse.

Jacinta Behne: [00:15:10] Thank you so much. Dr. Pittock, anything you would add?

Dr. Pittock: [00:15:16] No, I have nothing to add to that.

GG deFiebre: [00:15:21] Thank you both so much. So are there any common triggers for a relapse? For example, do relapses often follow viral illnesses or bacterial infections? Can something like weather or temperature have an effect on relapses, Dr. Pittock?

Dr. Pittock: [00:15:39] Well, that's a good question. It would be really nice if we could identify definitive triggers for relapse in patients, because then we could be ready to deal with them.

Patients will report their own observations that, for example, they developed a clinical attack soon after a vaccination or soon after a viral illness, or even a bacterial infection.

[00:16:03] It's very difficult to say definitively because this is a very difficult area to study or investigate because as you know, vaccinations are very common, viral infections are very common, and to make that definitive link between one and the other is difficult. But I suspect that anything that stirs up the immune system, I suspect has the ability to potentially trigger a flare of an immune-mediated disorder. I think that a lot more work needs to be done in this area. But I don't think we can definitively say that one does lead to the other. But I suspect it does.

GG deFiebre: [00:16:52] Thank you. And then Dr. Wingerchuk, any additional thoughts on that?

Dr. Dean Wingerchuk: [00:16:58] Well, one thing that came to mind, first of all, I agree with everything that Dr. Pittock just said, but is, just today I was asked by a patient whether stress triggers relapses, and I think that's a particularly common question. It's also quite a difficult one to answer for reasons that you might already appreciate, because what's stressful for one person might be not particularly bothersome to another. And there are some people who thrive on sort of the adrenaline of whatever uncertainty or their work environment, and other people might look at that and think, gee, that looks extremely stressful.

[00:17:46] I think there's good stress and bad stress. And, I think for people who can eliminate as much of the bad stress as possible, that's helpful. I do think sometimes we see stress as a cause for fluctuating symptoms. So, symptoms that might be left over from a prior attack, and when someone gets very anxious or very stressed, that those symptoms worsen, and that leads them to worry whether they're having an attack. Generally the answer of course is no.

GG deFiebre: [00:18:20] Thank you so much. Jacinta, do you want to ask the next question?

Jacinta Behne: [00:18:25] Thanks so much, really appreciate it. Next question: a patient writes in, what should a person with NMOSD do if they think they're having a relapse? Should they go to the emergency room, their general practitioner, their neurologist, etc.? Let's ask you, Dr. Wingerchuk, to comment first.

Dr. Dean Wingerchuk: [00:18:48] Sure. Well, I think it depends a lot on the specific scenario. Because the best situation of course is if somebody has an established relationship with a neurologist who is knowledgeable about the disease and can be contacted. Somebody has new symptoms that they've noticed for a couple of days and they want to get advice. I think contacting neurologist is a very reasonable thing.

[00:19:22] If somebody has a more acute event or something like loss of vision, something that's progressing quickly, maybe doesn't have somebody that they can communicate with very easily or very quickly, or maybe doesn't have consistent care at all, then I think the emergency room might be the best place to go. This is always, well, this is sometimes a difficult decision. I suppose these days in the midst of a COVID pandemic, that's another factor to consider before making a trip to the emergency department.

[00:20:03] But, sometimes that if there's an important symptom that's progressing and causing some significant impairment of function and is consistent with the kinds of symptoms of NMOSD that we described before, the emergency room may be the best place to go.

Jacinta Behne: [00:20:25] Thank you so much, Dr. Wingerchuk. Dr. Pittock?

Dr. Pittock: [00:20:28] Yeah, I agree. And I think it is important to try and get medical attention early, because we know that the earlier we get in with treatment, the more potentially we can reverse and improve outcome. And also, it's very important to be able to have a neurologist be definitive that an attack has occurred, because that will play into decision-making as to what attack preventive medication the person should be on, and whether or not such medication should be changed.

[00:21:01] So, one, you want to get the diagnosis early; two, you want to get treated early; and three, you want to use the knowledge of whether or not you have, or haven't had an attack to make decisions relating to attack prevention therapy.

Jacinta Behne: [00:21:16] Thank you so much.

GG deFiebre: [00:21:9] Thank you. And so I know we talked a bit about this at the beginning. But at what point of experiencing symptoms of a relapse should someone with NMOSD seek medical attention? I know we mentioned the 24 hours. But, are there certain symptoms that maybe warrant going to see a physician earlier or not? Dr. Pittock if you'd like to start?

Dr. Pittock: [00:21:43] Yeah, I suppose I would have the opinion that if you have NMOSD, it's a serious condition. And we know that in NMOSD that it is the attack that causes the disability. And so I think it's very appropriate for patients to be very vigilant and to get the appropriate medical care as quickly as possible.

[00:22:13] NMOSD patients are very educated and informed about the types of symptoms that they should be looking out for. And so, if you have NMOSD and you develop pain in an eye and your vision starts to blur, I wouldn't tend to be waiting for a long period of time. I would say, I want to be seen, and I want to get on steroid therapy as soon as possible.

[00:22:38] Now obviously, there are caveats to that. If you're somebody who has NMOSD and you also have ocular migraines, and then if you're just having typical visual symptoms of ocular migraine, then you probably can weigh it out a little bit to see if that goes away. So, I think each individual patient needs to consider their symptoms within the context of other things that they may also suffer from. But I think the earlier you get evaluated, the earlier you get diagnosed, and the earlier you get treatment, better.

GG deFiebre: [00:23:17] Thank you. And Dr. Wingerchuk, any additional thoughts on that?

Dr. Dean Wingerchuk: [00:23:22] Yeah, I agree. And, I recognize too that, especially for people that are newly diagnosed, this can be a big challenge, right? Because you receive a diagnosis after having gone through some neurologic symptoms that got you there, and then you start learning about the importance of relapses. And the natural tendency is to pay extremely close attention to everything that happens with your body.

[00:23:52] And that can be hard to kind of calibrate in to understanding what's normal in this spectrum of numbness and tingling that comes and goes and visual blurring that comes and goes and when to act. But that's why the education and kind of the descriptions that Dr. Pittock was giving of different types of symptoms and how they evolve is so important to help you understand when to make the call.

Jacinta Behne: [00:24:20] Thank you so much, Dr. Wingerchuk. Next question. This patient writes, are there specific tests used to determine that a patient is having a relapse? And if so, what are they, can you tell us a little bit about them? And Dr. Wingerchuk, I'm going to turn to you first.

Dr. Dean Wingerchuk: [00:24:42] Well, I'd say the three main tools that are used to determine a relapse are, number one, the story. So listening to the symptoms, the particular symptoms and how they developed a pattern and the pace over time, etc. Number two is the examination. So the neurologic examination to determine whether those symptoms have an associated change in function that's detectable by the neurologist. If it does, and those two things fit together, that may be all that's required in diagnosing a relapse.

[00:25:00] The third is MRI. MRI isn't always required. It's very helpful information to have. And in some circumstances, it is the arbiter. It does really provide the objective visual evidence that, yes, there's a new lesion, or there's a lesion that's lighting up, that's in the right place to cause these symptoms, this is an attack.

[00:25:43] But those three things are all interrelated. We know for some patients that they'll have, for example, an optic neuritis attack. They have very typical symptoms and we may be able to detect an abnormality on their exam, but actually we don't find an abnormality on the MRI just because the MRI is not a very sensitive tool for visualizing an optic nerve, which is very small. So, that's why it's particularly important to look at the story and the examination, and then use the MRI with appropriate judgment. Those by far are the most important instruments that we use to determine if someone's had an attack or not.

Jacinta Behne: [00:26:29] Thank you so much. Dr. Pittock, anything you would add?

Dr. Pittock: [00:26:33] No, I agree. I mean, I think sometimes you don't necessarily need an MRI to make a diagnosis of a relapse. The MRI potentially can help because it potentially can show you areas of inflammation that may not be relevant or coincide with the specific symptoms of the patients. For example, sometimes a patient will have an optic neuritis, and when you do the MRI scan, you sometimes can see a lesion in the spinal cord that may be asymptomatic.

[00:27:03] And what does that tell you? Well, it's telling you that there's more of an active inflammatory process going on. And again, that might inform the decisions relating to ultimately what type of attack preventative medication you want to use. Because at the end of the day, yes, it's all well and good to deal with the relapses, and it's very appropriate to diagnose them and treat them earlier. But the most important thing we can do is to try and stop them happening in the first place.

[00:27:30] And so, getting a sense of the type of relapse the patient is having, and also the extent of information that's current, that's present, I think also informs, in terms of making decisions relating to attack prevention therapies.

GG deFiebre: [00:27:48] Great. Thank you. And then just as a follow-up to that, I know you said that MRI isn't necessarily always warranted, but at what point should someone push for an MRI if their physician is reluctant to give them one or take their symptoms seriously? And what do you look for in an MRI during a relapse? Are you looking for new lesions or reactivation of old ones? Dr. Pittock, if you want to expand?

Dr. Pittock: [00:28:12] I suppose if I had NMOSD and I thought I was having a relapse, I'd be pretty demanding of an MRI. In multiple sclerosis, we do MRI scans essentially on a yearly basis, even if patients aren't having any symptoms. And, I would argue that imaging in NMOSD is even more warranted.

[00:28:39] So, I think it's very reasonable and appropriate if you feel that you've had an attack, and if your doctor actually thinks you may be having an attack, that you have imaging, because as Dean said, it really does firm up the diagnosis. If you're kind of not sure, and you see an area of new enhancement in the spinal cord that coincides with the symptoms the patient's having, then I think that certainly can be very, very helpful diagnostically.

GG deFiebre: [00:29:05] Thank you. And Dr. Wingerchuk, anything to add to that as well?

Dr. Dean Wingerchuk: [00:29:09] No, I think it really depends on the presentation too. And there may be a very good explanation about why certain symptoms are not related to NMO and why an MRI may not be needed. I think it's very specific to the actual symptoms and what's developed.

Jacinta Behne: [00:29:31] Thank you so much. For Dr. Wingerchuk, does the change in aquaporin-4 antibody levels indicate a relapse?

Dr. Dean Wingerchuk: [00:29:42] Yeah, that's a great question. And I know Dr. Pittock has studied this a lot and he can tell you the real answer, but I'll tell you my take first. And that is that some studies have shown that there can be an increase in the titer, the level, of aquaporin-4 antibodies detectable in blood shortly before a relapse or an attack.

[00:30:11] However, the overall data suggests that this is not a useful way to monitor the disease for an individual person. And that for most attacks even if you had that data, when you do have the data, you don't see the titer increase. Now, Dr. Pittock can tell you the real story.

Jacinta Behne: [00:30:33] Okay. [laughs] Dr. Pittock.

Dr. Pittock: [00:30:38] I think that's, I know it's again, in the last year, two groups, both Kazuo Fujihara from Japan and our group, have published papers saying that antibody levels are not very helpful in the day to day management of patients with NMOSD. And now there have been papers where some people have reported that at the time of severe attacks, there are increased levels of antibodies in the blood, and that those levels correlate, those increases correlate with the length of the legion of the spinal cord, etc.

[00:31:12] What I can tell you is we looked in, we looked at quite large numbers of patients where we were basically, we had serial samples, in other words blood samples collected at different times along the duration of their illness. So sometimes samples collected with intervals of many years in between.

[00:31:30] And then we were also actually able to take blood samples and actually know what was actually happening in that individual patient at the time of the blood sample. So for example, we might have a blood sample from a patient when they had an attack. We might have a blood sample from a patient when they were in remission. And we might have a blood sample from a patient that was drawn, say a couple of weeks before they had an attack.

[00:31:52] And by putting those, taking those samples and measuring the levels of the antibodies at all those different time points and correlating them with the clinical phenotype of the patients, what we found out was that generally it was all over the place. Generally, patients sample levels, their titers actually remained quite steady throughout the course of their illness.

[00:32:13] And then there were some patients where they start on an immunosuppressant medication, they get a drop and some get a very significant drop and others don't get much of a drop. And some patients go negative and others don't. And even some patients that go negative continue to have clinical attacks. So it's kind of all over the place, but overall, there's not a very good correlation between the antibody levels and the clinical course of the patient's disease. And that's kind of the bottom line.

[00:32:44] Now, the other problems with some of these assays is that we're looking at very big changes in titers. So for example, if you're kind of diluting a person's sample and you're doing like 10-fold dilutions, then you may not see a change. And we didn't see a change when we did that. But, if you look at smaller dilutions, look at smaller changes in antibody titers, sometimes you can see changes. But overall, I don't think changes in antibody titers indicate a relapse.

GG deFiebre: [00:33:16] Thank you so much for that overview. And so the next question is about how often relapses happen. So to start, what percentage of patients who are diagnosed with NMO will go on to have relapse versus those who don't? And then how often do people with NMO have relapses if they don't use immunosuppressant medications versus when they do? Dr. Wingerchuk?

Dr. Dean Wingerchuk: [00:33:44] Yes, those are excellent questions. And so, part of it depends on the data that one's looking at. Historically, NMO was considered what we call a monophasic disease, meaning people typically were described as having the disease if they presented with spinal cord inflammation and optic neuritis affecting both eyes.

[00:34:12] And that's a particularly rare type of presentation and one that sometimes in certain circumstances seems to be a single attack. But where we are now, especially diagnosing NMOSD with the help of the aquaporin antibody, we know that the vast majority, we think 90 plus percent of people, if they have a typical presentation and they have that antibody and were observed without treatment, that they would eventually relapse.

[00:34:46] The relapse frequency is highly variable though. There are some people who have clusters of relapses, maybe three or four relapses in a several month period and good information that, or good objective data showing that those were relapses. And other people who even without treatment have gone many years until their next relapse. What we're looking for as part of research in the field is to understand whether we can, we're pretty good at diagnosing this disease, but need to be better at predicting how it's going to behave over time.

[00:35:27] And the last question was asking about aquaporin-4 levels. Well, those levels don't appear to be very good on an individual level for predicting attacks. But there's a lot of work going on now to try to understand whether other markers, for example other blood tests, might be able to do that.

GG deFiebre: [00:35:49] Thank you. Dr. Pittock, do you have anything additional?

Dr. Pittock: [00:35:52] Yeah, I agree with Dean. Actually, last year we did a large study, was a multicenter study where we looked at 441 patients with NMOSD in the USA, the UK, Japan and Martinique, which is one of the French, one of the Caribbean islands. And we actually studied 1,976 attacks in 441 patients.

[00:36:22] And what we did in that study is we worked with these mathematicians and we kind of created a mathematical model that allowed you to predict, depending on the characteristics of an individual patient, what the likelihood of an attack is. And I can just tell you a little bit from that study here, I'm just looking at the table here, because I knew that this question would come up, but I just thought it might be interesting.

[00:36:46] So this is an interesting paper because it provides these predictive tables where you could actually go down and look based on what type of attacks you've had, etc. What the likelihood of you having an attack in one year, five years, or 12 years is. And these data were based on people that were on the immunotherapies that were available at that time.

[00:37:09] So, it was actually quite concerning because if you looked at the likelihood of relapse in people that were on kind of standard immunotherapy before these trials, these therapies actually only had about a 30% reduction in the likelihood of relapse rate. It was not impressive. But what we found was is that if you had, for all patients, all NMOSD patients, regardless of how many attacks you've had in the past, 34% of patients will have an attack in the following year. And 54% of patients will have an attack in the following two years.

[00:37:46] So, that's quite significant. And one of the things that was interesting was is that people that have had a shorter duration of disease, whether it was less than five years, those patients have a higher likelihood of having an attack, than people that have had the disease for longer. So, it's a significant risk, at least based on the older therapies. And, again, this paper I think was what really reinforced us in our endeavors to complete these three phase-three trials, which was ultimately to identify drugs that really have a proven robust benefit in terms of stopping relapses.

Jacinta Behne: [00:38:30] Thank you so much, Dr. Pittock. The next question, if I had a relapse, will the new damage to my optic nerve and/or spinal cord be permanent? Let's start with you, Dr. Pittock, this time.

Dr. Pittock: [00:38:45] So, generally with relapses in NMO, at least traditionally, and Dean and Brian Weinshenker did most of the work, showing that relapses in NMO are really a lot worse than relapses in MS. In multiple sclerosis, patients tend to make near full recoveries in the early relapse/remitting phase of their illness. Whereas in NMO, the relapses are more severe.

[00:39:11] Having said that, if you get in very early with steroids or even plasmapheresis, some are using that as their first line therapy, we do know that there is reversibility. And many patients will

get a good recovery from their attacks. Unfortunately, some patients are left with significant disability. So, and we really haven't made significant advances in our ability to reverse disability from a relapse, because the treatments are pretty much the same. There are some obviously that use steroids first and others that are arguing that plasmapheresis should be considered as a first line therapy.

[00:39:51] But regardless, we don't really have significantly new medication approaches to the management of relapse. So I think generally, the fact that relapses in NMO do cause damage and that that damage can be permanent. That again reinforces the argument and the reason to really try and aggressively stop clinical relapses.

Jacinta Behne: [00:40:19] Thank you so much. Dr. Wingerchuk?

Dr. Dean Wingerchuk: [00:40:24] Yeah, that's a great summary. It is one of the things that we have difficulty predicting. And there are some attacks that are quite severe and recover very well, and other attacks that are more moderate but don't seem to recover very much. We're not very good at predicting what the outcome is going to be using tools, for example, such as conventional MRI scans. Because they're not really showing us, they're showing us where the lesion is or where the inflammation is, but they're not able to tell us whether there's permanent injury to the neurons or not.

[00:41:10] Usually, what we're just looking at is a white spot that indicates there's more water in that area. That's it. But there's a lot of interest in new techniques, new imaging techniques in particular, that might be able to help that. And, certainly will be useful to do the kinds of research that Sean was just referring to new treatments for attacks themselves.

GG deFiebre: [00:41:40] Thank you both so much. And so, with these attacks, does nerve damage worsen over time? And if so, how do you distinguish between worsening nerve damage and a relapse with the condition without something like a fever or severe weakness? Dr. Pittock?

Dr. Pittock: [00:42:00] Well, that's a very good question. In fact, so one of the questions is, in between attacks of NMOSD, do people have ongoing nerve damage? Is there a kind of ongoing irritation or immune-mediated destruction of the nervous system? I think this is an extremely important question. And in fact, Dean Wingerchuk actually wrote a paper showing that generally in NMOSD, we don't see, at least in the vast majority of patients, progressive disability in between relapses.

[00:42:40] And that's very different, as you know, from MS, where in MS the disability generally accrues because of the progressive neurodegenerative component, whether it be secondary progressive MS, or primary progressive MS, but not necessarily from the relapsing component of MS. And in fact, if you look at the drug studies, and you read between the lines, you'll see that generally, in patients that don't have clinical attacks in the drug studies, we don't generally tend to see progression, at least over the short term, one or two years of those drug studies.

[00:43:17] So, I think generally, we don't see progressive nerve damage in between clinical attacks. Or if it does occur, it's occurring on a very subtle level that probably warrants quite detailed and maybe more sensitive analysis than using kind of the crude measures of disability that we use. So I

think it's certainly something that warrants a further investigation. But generally we think that once the attack is kind of finished, that in between attacks, things remained relatively good.

[00:43:56] Now can people have kind of subtle attacks? I suspect that they can. One of the things that I was thinking about when Dean was just talking about the last question was in the drug trials, we tended to see attacks that were not as severe as we thought they'd be. In fact, in the drug trials, there were a lot of attacks that physicians thought patients were having, but at the end, the adjudication committee, when they looked at those attacks actually felt that they weren't attacks.

[00:44:26] And that raises the question of, when patients are on immunosuppressant therapies, maybe if they have an attack, their attack is actually milder than you would expect. So that being on an immunosuppressant medication to prevent attacks, if an attack occurs, it might actually dampen down the severity of that attack. So I think there's still a lot obviously to learn. But, relapses, yes, we need to stop them, they do cause nerve damage. But whether there's kind of an ongoing irritation that's occurring sub-clinically is a good question.

[00:45:00] I suspect that generally isn't happening as much as we think, but we do know that there are patients that have areas of enhancement on their imaging, on their MRI scans, but yet don't have any symptoms. And what does that mean? Does that mean that they have low grade inflammation, but they're not symptomatic? And maybe it means that we really need to start using tools to measure subtle things over a long period of time to kind of get a good sense of whether people are developing some slow burning disability in between relapses.

GG deFiebre: [00:45:37] Thank you, and Dr. Wingerchuk, anything to add?

Dr. Dean Wingerchuk: [00:45:41] Well, that's a great summary. And I think it highlights the importance as was mentioned earlier of attack prevention in this disease. I think by and large, it's very likely to be true that for most individuals, if we were successful at preventing attacks, they would remain stable. They wouldn't get worse. Sometimes people feel like they're worsening or that their disease is progressing, but there's another explanation. Like for example, perhaps they've had myelitis in the past and have been left with some weakness in one or both legs and some stiffness or spasticity.

[00:46:29] Well, sometimes that stiffness or spasticity can get worse and that can interfere with function and maybe make people think that the disease is worsening, but it's actually just an evolution over time of how the nervous system is adapting. It adapts by making the legs stiffer so that people are still able to stand and walk rather than have legs that are like cooked noodles. So, each situation is different, but we think that because the attacks are the hallmark of the disease, that that's the real target.

Jacinta Behne: [00:47:10] Thank you so much. The next question: can inflammation occur repeatedly in the same area, or is it likely to occur elsewhere in the central nervous system? And Dean, I'm going to turn to you. Dr. Wingerchuk, please?

Dr. Dean Wingerchuk: [00:47:25] Okay.

Jacinta Behne: [00:47:26] Thank you.

Dr. Dean Wingerchuk: [00:47:27] Well, yeah, it's interesting. Some people have studied this in the context of both NMOSD as well as multiple sclerosis and found that there actually is a tendency for people to have recurrent events in the same system. So for example, there are people who have NMOSD who have repeated attacks of optic neuritis, and for as long as they're followed, don't have myelitis. And vice versa is also true.

[00:48:02] Now why that is, is not entirely clear, but I think that's a different point than inflammation recurring in exactly the same place or with the same symptoms, because that's what raises the question or the possibility of pseudo-attacks. So what I mean by that is if someone says, I've had 12 attacks this year, but then they tell me that each one of those attacks is exactly the same symptom. You know, my left leg gets a little bit weaker and then the next day it's better.

[00:48:37] It's extremely unlikely that each one of those is actually an attack. That sounds much more like a pseudo-attack. But the scenario of somebody having left optic neuritis, and then two years later, right optic neuritis, and then two years later, another right optic neuritis, that kind of thing happens. And it may be that there are factors, individual factors, maybe genetic or otherwise, that influence how this disease behaves. There must be something that explains why there's an antibody that's present in most people who have NMOSD, yet it can behave differently from person to person.

Jacinta Behne: [00:49:26] Thank you so much. Dr. Pittock?

Dr. Pittock: [00:49:30] Yeah, I know I think Dean makes some very good points there. And actually, I think, in the app that Dean and the Guthys have been working on to help us define whether or not a patient's having an attack or not, I think brings up an important point that Dean was making there, which is that it's very, very important to compare to your pre-baseline. Because as Dean said, if you have a right optic neuritis and say you develop visual loss in the right eye, and then you're kind of presenting a year later complaining of maybe worsening vision in that right eye, it's very important to kind of be able to know what that baseline was.

[00:50:11] And obviously if you have worsened, that would be evident and you could diagnose a new attack there. So just reiterating the importance of kind of having a very good baseline examination, so that you know what to compare these new symptoms to can be very helpful in the clinic. And if you don't have that good baseline, it can be very difficult for a physician to actually define and be more definitive as to whether you have, or are having an attack.

GG deFiebre: [00:50:39] Great, thank you both so much. So then, the next question is, after the first attack, are subsequent attacks progressively worse in terms of symptoms and damage done? And are these relapses kind of treated any differently than that initial presentation? And do attacks, the severity of attacks differ based on whether or not someone is on a medication? Like does medication reduce the potential severity of the attack? Dr. Wingerchuk?

Dr. Dean Wingerchuk: [00:51:17] Yeah. So, generally speaking, attacks themselves are not necessarily worse over time or worse with successive attacks with regards to more inflammation, for example. However, if you have an optic nerve that was inflamed a couple of years ago and took a hit and partially recovered, it's not going to have as much reserve. It's going to be more susceptible to damage from another recurrent optic neuritis affecting that same eye and may not recover as well.

[00:51:57] So, it's kind of like just all of us getting older and not healing or not recovering as well as we go decade by decade. Optic nerves or spinal cords that have been injured when they have another area of injury, then it's a slower and usually less complete recovery. I think the other part of the question was the effect of medications. And this is also an area of active interest amongst all of us who were involved in the project Sean was just referring to, to study the definition and judgments about whether relapses have occurred is relapse severity.

[00:52:43] So it is important to know whether an attack has happened. From the standpoint of studying the disease and studying the effects of medication, it's also very important to know whether we're having an effect on severity of attacks. And we think we are. We think that with probably also the older medications and certainly with the crop of newer ones that we've reduced not only the frequency, but the severity of attacks.

GG deFiebre: [00:53:13] Great, thank you. And Dr, Pittock, anything else to add?

Dr. Pittock: [00:53:17] No, I agree. We did look at this, and patients can have a very bad severe attack and then their next few attacks can be very mild and vice versa. It's unfortunate that we just, we can't kind of predict whether an attack will be severe or mild. And, there are some patients that can just have two attacks that are very, very severe and others that have multiple attacks and they're mild. And there's a big difference in the level of disability in those two patients.

[00:53:49] And, it all comes down to the fact that we really don't understand all of the components that are involved in not only causing a relapse, but whether you have a mild or severe relapse. The pieces of that puzzle are eluding us in many ways. I mean, we know that you have antibodies. We know that they bind to the target. We know they cause complement activation. We know they lesion cells. But you can have robust levels of antibody that has a robust ability to damage a cell, and yet you don't have a clinical relapse.

[00:54:30] So, I think these questions are, they're coming from the patients and I think they're really brilliant questions, but they're questions that ultimately remind us of the fact that we really have a lot more to learn.

Jacinta Behne: [00:54:47] Yes, and to that point, oh my goodness, I just looked at the clock. This time has just flown by. This one I will direct to you Sean, to take first. It's actually, the first question was if I'm on medication and I experienced a relapse, should I switch medications? And then we've had one, kind of a follow on to that, that was submitted live. And, the question was, if I've been on an immunosuppressant, yet I still experience an attack, should that particular drug be increased or changed? And what process is taken to come to that decision? So, this is all about medications, relapses, and can you switch or change medication?

Dr. Pittock: [00:55:33] And so, for me that's kind of an easy question. The question that I find hardest is if I'm on a medication and I'm not having relapses, should I switch to one of the newer, kind of proven medications? But in this situation, I would say if you're on a medication and you experience a relapse, for me, that's a big problem. Because at the end of the day, we've got to stop the relapses. We've got to prevent relapses. And if we can prevent relapse, I think we can make a huge impact for our patients.

[00:56:00] So if you're on a medication and you have a relapse, for me, that means that that medication is not working for you. Now, maybe you would have had two relapses if you hadn't been on the medication, but for me, even having one relapse is not acceptable. So, if I had a patient that had a relapse on a medication, then I would look at the medications that are currently available. There are going to be three medications that are proven in blinded randomized controlled fashion trials. These are phase three trials to be a benefit. And I would consider one of those medications for that patient.

[00:56:38] And, obviously again, if they're on that medication, even if they're from these phase three trials and they have an attack, then I would consider switching them to one of the other ones. In terms of vaccinations, I don't think vaccination should be avoided because back on, I believe in vaccinations. I know that there's some people that don't, but I think vaccinations have been very, very important in preventing disease.

[00:57:12] Also there are some therapies that we use that absolutely require vaccinations. For example, if you're considering something like eculizumab, we know that that drug can increase the risk of meningococcal infection. And so you absolutely have to be vaccinated against that, if you want to go on that drug. Now obviously remember that some of these medications that we have patients on, they reduce the ability of your immune system to respond to a vaccine, and that needs to be considered also sometimes.

Jacinta Behne: [00:57:43] Thank you so much. Dean, we're going to turn to you please. Any comments you would add?

Dr. Dean Wingerchuk: [00:57:48] No, that's great points. I mean, it's likely that some people listening are, or know somebody who's on one of the existing older non-FDA-approved medications. And sometimes there's issues there with the pills, for example, of the person not taking all of them or maybe being at a dose that's not adequate. And, in some situations, it does seem that the disease may have broken through just because the treatment wasn't optimized. But other than that I completely agree with what Dr. Pittock said, if the disease breaks through significantly and you've got very good evidence for that, it really should be considering another drug.

GG deFiebre: [00:58:38] Great. Thank you both so much. And, I know we're at the end of our time, but I just wanted to open it up and see if you had any additional thoughts you wanted to add before we close today? Dr. Wingerchuk, do you want to start?

Dr. Dean Wingerchuk: [00:58:51] Well, I really appreciate the opportunity to answer, or try to answer some of these really important questions. Hopefully this overview clarifies, in general terms, what we're trying to target with the disease and the fact that we've got some very exciting data now that for the first time strongly supports the impact that we're having and how much of an impact we're having. And I think the future looks very bright for our ability to build from there and work towards a cure.

GG deFiebre: [00:59:24] Great. And Dr. Pittock, any last thoughts?

Dr. Pittock: [00:59:26] No, I just appreciate the opportunity and I'd like to thank the patients for their extremely good questions. And I think these questions are questions that we as investigators

need to be continually thinking about and trying to move forward so that we can improve our knowledge and try and answer some of these questions better, hopefully in a few years.

GG deFiebre: [00:59:50] Great. Thank you. I just wanted to thank you both so much for joining us and Jacinta for co-moderating with me. We really appreciate your time today.

Jacinta Behne: [01:00:00] Thanks everyone.

Dr. Pittock: [01:00:02] Thanks all. Stay safe.

GG deFiebre: [01:00:03] Thank you.

Dr. Dean Wingerchuk: [01:00:04] Thank you.