History, Diagnosis, and Management of NMOSD

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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: [00:00:58] Hello and welcome to the ABCs of NMOSD podcast series. Today's podcast is entitled, "History, Diagnosis, and Management of NMOSD." The ABCs of NMOSD is an education podcast series to share knowledge about neuromyelitis optica spectrum disorder. My name is GG deFiebre from the Siegel Rare Neuroimmune Association, and I will be co-moderating this podcast along with Jacinta Behne. Jacinta, do you mind introducing yourself?

Jacinta Behne: [00:01:25] Sure. Thank you so much, GG, and welcome, everyone. It's indeed an honor to co-host this podcast with GG. I'm the Executive Director of the Guthy-Jackson Charitable Foundation and really happy to be here with you today. Back to you, GG.

GG deFiebre: [00:01:40] Great. Thanks so much. And 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. This podcast is being recorded and will be made available on the SRNA website and for download wherever you get your podcasts.

[00:02:00] The 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 and courage to bring clinically meaningful therapies to patients. Horizon believes science and compassion must work together to transform lives.

[00:02:25] For today's podcast, we are pleased to be joined by Dr. Brian Weinshenker. Dr. Weinshenker is a Professor of Neurology and Consultant at Mayo Clinic in Rochester, Minnesota. His interests are in inflammatory demyelinating diseases of the central nervous system, including NMOSD, and he was involved in the discovery of the biomarker for NMOSD, which we will discuss today as well.

[00:02:45] So welcome. And thank you for joining us today, Dr. Weinshenker.

Dr. Brian Weinshenker: [00:02:50] Thank you, GG. And thank you, Jacinta. It's a pleasure to be here on this extended holiday weekend. I hope everybody had a good Independence Day.

GG deFiebre: [00:02:59] Yes. Thank you. So, to start, do you mind just talking about kind of the, the history of NMOSD in terms of when it was first described and maybe its history with MS or people with MS diagnoses and that kind of, you know, how they were separated, you know, in the past?

Dr. Brian Weinshenker: [00:03:16] Sure. Most people would say in 1894, we had the first description by a French physician who lived in Leon, France by the name of Eugène Devic. He described a single patient who experienced optic neuritis, so that would be vision loss that occurred sequentially in both eyes, in a very short period of time. And then the patient developed paralysis and spinal cord inflammation, and, within a few months, sadly passed away. So, it was a fatal disease. His student, Gault, wrote a thesis at that time and reviewed 16 other what they felt were similar cases.

[00:03:59] And that's really what we knew about neuromyelitis optica for a long period of time. It was recognized that it had some similarities with multiple sclerosis that I think we'll talk about in a minute, in the sense that there were attacks that caused blindness in the eyes and paralysis. Devic realized he'd seen only one case. He did not really suggest diagnostic criteria, but really for the next nearly a century, people just try to figure out what was unique about Devic's case.

[00:04:30] And some people said, 'well, they have optic neuritis and myelitis and had no further relapses.' So, not having further relapses became a very key part of making the diagnosis and differentiating it from multiple sclerosis, which was known to cause recurrent relapses and attacks. But, in fact, that proved to be a very poor predictor.

[00:04:54] I think Devic would have recognized that his patient died within a few months. So, he would have probably said, 'how could I know if this patient was going to relapse because the patient died?' So, for nearly a century, there was a lot of controversy about whether this was some unique form of multiple sclerosis. Was it part of the multiple sclerosis spectrum, or was it in fact a separate disease?

Jacinta Behne: [00:05:21] Let's go on then. Thank you, Dr. Weinshenker. Was LETM alone ever considered NMOSD?

Dr. Brian Weinshenker: [00:05:29] So, there, there is an entity called transverse myelitis, and it had been recognized for some time that some patients would develop attacks of paralysis. And I think for a long time, people tried to find some unitary explanation about why people developed transverse myelitis.

[00:05:49] They thought, you know, probably some cause. And one of the key clues was the fact that some people who got vaccinations safe to rabies virus or smallpox would develop what looked like transverse myelitis and some people, after they had rubella, German measles, would get this. And it was recognized that the transverse myelitis didn't come on when the patients had a rash and fever and during the acute symptoms, but it was somewhat delayed.

[00:06:20] So, without a lot of understanding of the immune system, it was thought that maybe this could be a secondary reaction, maybe an immune reaction, that was occurring. And, you know, that's what was thought of, of transverse myelitis. And then of course, people recognize that multiple sclerosis, which was recognized at the time also caused attacks of paralysis, but they tended to be less severe, and they weren't associated with long spinal cord lesions.

[00:06:50] So, those patients who got severe transverse myelitis with long spinal cord lesions were recognized to be different than the patients who had the milder transverse myelitis with multiple sclerosis. And the more severe transverse myelitis was just called idiopathic transverse myelitis. Things really changed after we recognized neuromyelitis optica and discovered an antibody marker that we'll talk about in a minute that we use to diagnose neuromyelitis optica.

[00:07:23] We did a study at Mayo Clinic that was published in 2006, looking at patients who just had a first episode of severe transverse myelitis, the kind that we said was different than MS. And, to our surprise, even though these patients had not had optic neuritis or anything, we would have called them idiopathic or of unknown cause longitudinally extensive transverse myelitis, longitudinally extensive meaning have a very long lesion in the spinal cord, often which correlated with severe transverse myelitis, that 40% had a positive blood test for this antibody marker, aquaporin-4 antibodies, that we found that was specific for neuromyelitis optica. And all of a sudden, we had a link between these two conditions. That is longitudinally extensive transverse myelitis, or the severe transverse myelitis, and NMO.

[00:08:20] And in fact, in our follow-up studies, we found that, if this antibody was present in a patient who had symptoms of transverse myelitis, it predicted that half of them, within one year, would have relapses, mainly transverse myelitis, but some of them had optic neuritis. And if they had a negative blood test, then they did not seem to recur. We did not find one patient who recurred, even though 50% of those with his blood test did get these relapses. So, suddenly, the whole concept of idiopathic, we don't know the cause of, transverse myelitis changed and almost half of adults with that syndrome seemed to have a type of NMO.

[00:09:06] And currently, with our international criteria, and I think this is being accepted pretty much around the world, if you have a first episode of transverse myelitis and a positive test for these aquaporin-4 antibodies, you qualify for a diagnosis of neuromyelitis optica, but not if you do not have a positive test.

GG deFiebre: [00:09:29] Thank you. And so do you mind just talking a little bit more about, I mean, you mentioned briefly about how this antibody was discovered, but do you mind talking about kind of when this happened and what the process was in terms of getting this, you know, learning more about this antibody?

Dr. Brian Weinshenker: [00:09:43] Sure. Yeah, and I, feel like I'm somewhat of an insider. The antibody was discovered by my colleague, Dr. Vanda Lennon, and some of her colleagues in her lab. In the late 1990s, I started studying this condition that is neuromyelitis optica and came up with criteria that were able to differentiate it from multiple sclerosis.

[00:10:07] And I would say, at that time there, the acceptance was only so so. A lot of people still said, 'no, I think this is just a type of multiple sclerosis,' but we were fairly confident in it. And I was giving a lecture at Mayo Clinic attended by Dr. Lennon, who was particularly intrigued by the fact that a high percentage of patients with neuromyelitis optica have other autoimmune conditions, like lupus and Sjögren's and other conditions. And she was very interested in antibody mediated autoimmunity and so, she thought this condition might be somewhat different and asked me to send serum, that is blood, from my patients with neuromyelitis optica to her lab.

[00:10:54] And, a couple of months later, she told me, 'you know, I am finding in a fairly high percentage of these patients an antibody marker pattern.' She used a kind of technique where she put the antibodies on rodent, that would be, say, mouse tissue slides and looked at the pattern by which those antibodies bound to human tissues.

[00:11:17] And she found a very characteristic pattern that she said she'd seen before in other samples sent to her, although she wasn't sure what the clinical association was, but she was seeing this in these patients

with neuromyelitis optica. And I said, 'well, why don't we find out what was the clinical diagnosis in those other cases where you had this antibody pattern where you would pick up this antibody pattern?'

[00:11:42] And so, I contacted those physicians who had sent in those samples where she found this and, really to our surprise, virtually all of them had symptoms of either optic neuritis or myelitis or both. So, that really led us to think that this must be some kind of specific antibody marker. And in 2004, we publish this, and I'm doing work on several cohorts of patients, including Japanese patients, with what had been called Asian or Japanese opticospinal MS, which is very much like a neuromyelitis optica that we currently perceive. They had felt, in Japan, they had two different kinds of MS, a more typical MS, like we see in the West, and then they talked about an Asian version, but I thought that looked really very, very much like the neuromyelitis optica we were seeing in the west.

[00:12:42] So, working on those two populations of patients and doing blinded studies, comparing to MS, we found that there was more or less a perfect correlation between the criteria that we had developed to separate NMO and MS and the presence of this antibody, as detected in Dr. Lennon's lab.

[00:13:05] Dr. Lennon would just do the antibody tests. We would do the clinical analysis and, even working with our Japanese colleagues who shared none of their clinical data until after we shared the antibody results, we found a perfect correlation. And, within one year, Dr. Lennon was able, by a variety of techniques, to definitively establish that the target of that antibody was this protein, aquaporin-4.

[00:13:33] So, then not only did we have an antibody marker pattern that was kind of cumbersome to test for, to put the serum on top of rodent slices, we had the specific protein, and we could develop tests that were molecular and based on taking the gene that expresses this aquaporin-4 protein and putting it in cells and specifically testing for that protein.

Jacinta Behne: [00:13:59] Goodness, Dr. Weinshenker, this is so incredibly interesting, understanding and hearing how this evolution has occurred. Could you just share just a little more about how our understanding of NMOSD has changed over time from the original, you know, diagnosis from Dr. Devic to today?

Dr. Brian Weinshenker: [00:14:19] Well, of course, Devic's single patient had optic neuritis, the attacks of blindness, and myelitis, the attacks of paralysis and numbness in the legs due to spinal cord involvement.

[00:14:32] And I would say that still is the dominant kind of attack, probably 85 to 90% of attacks that occur in neuromyelitis optica are of those types. We now recognize there are other kinds of attacks that can occur that target various spots in the brain. One of the most characteristic is one that causes a very unusual symptom and that's nausea, vomiting, and hiccups.

[00:14:59] And that occurs in about 20% of patients, and often it'll occur months or even years before the first symptoms, the first typical symptoms, the optic neuritis and myelitis, occur. But with this antibody marker, which has turned out to be very, very highly specific, that's the antibody to aquaporin-4, we find it in that group of patients. So, that instantly linked that condition with the other symptoms. And, furthermore, we now recognize that patients with this vomiting and hiccups that can go on for months and doesn't respond to standard treatment for nausea and vomiting, but steroid treatments, which are anti-inflammatory treatments that we use in neuromyelitis optica, more or less stopped that condition in its tracks. So, we've recognized that as another characteristic syndrome.

[00:15:56] And there are some others that occur that are kind of unusual syndromes that target an area of the brain called the hypothalamus and thalamus, which can include unusual eating disorders, sleepiness

disorders, like narcolepsy, other hormonal disorders, things that we don't see in MS. And now, if this antibody is positive, we can be pretty confident that these are syndromes linked to neuromyelitis optica and we have to treat the patient for neuromyelitis optica, not only to deal with these, the symptoms they're experiencing now, but to prevent further attacks of optic neuritis and myelitis.

GG deFiebre: [00:16:39] Thank you for that overview. I think the history is really fascinating and shows, you know, how far, you know, knowledge about NMOSD has come over the years and even fairly recently. And, you know, all your work on this as well is super important. So, thank you.

[00:16:52] And so, moving on kind of from the history and what we've learned about NMOSD over the years to the diagnosis and how a diagnosis gets made for NMOSD. So, do you mind just talking a bit about what the radiological, clinical, or pathologic findings are of NMOSD? So, how someone kind of gets this diagnosis? And whether this differs between someone who tests positive for the aquaporin-4 antibody or not?

Dr. Brian Weinshenker: [00:17:16] Well, things practically always start with symptoms. So, patient has to have symptoms. And the two major ones that make us concerned are optic neuritis, which is typically blindness, most often in one eye at a time but in some patients, it may occur in both eyes, and attacks of paralysis and numbness, usually below a certain level.

[00:17:43] So, patients might report, 'I had weakness in my legs and then numbness spread up right to my middle abdomen. And from there down, I couldn't feel properly, or I perhaps couldn't feel it at all. Often the bladder and bowel stop working or don't work properly. Usually, in almost all patients with neuromyelitis optica, these symptoms come on quite rapidly over hours or days, rarely over weeks, usually more over hours to days.

[00:18:16] So, those are the key things we're looking for. I've mentioned other unusual conditions. In those situations, the main mimic would be either multiple sclerosis or what we call, and it does exist, is still idiopathic transverse myelitis, another kind of maybe temporary, single event attack, perhaps because someone's had a flu or a vaccine that's triggered an immune response and something that won't recur.

[00:18:53] Obviously, that's very important to treat, but those are not patients that we would need to treat with medications on an ongoing basis for prevention. So, to differentiate from multiple sclerosis, there are a number of things. The severity is much worse with neuromyelitis optica. So, that's an important consideration. The lesions we detect both in the spinal cord and optic nerve tend to be longer and more extensive, which is very, very helpful. Spinal fluid testing can be very helpful, especially testing for something called oligoclonal bands, which is an indication that clones of immune cells have set up colonies in a long-term basis in the brain and central nervous system.

[00:19:44] And when we detect that marker, it's highly suggestive of MS. It does occur in a small percentage of patients with neuromyelitis optica, but a much smaller percentage. So, although many tests are not a hundred percent perfect, picking up oligoclonal bands would be a strong indicator for MS.

[00:20:05] There are other spots in the brain that occurred that are very typical for MS. That often occur. Even if there are no symptoms from them and we don't see them in neuromyelitis optica. So, those would be the key ways to differentiate from MS.

[00:20:20] With regard to transverse myelitis, I think the important point to make is neuromyelitis optica is a disease. It is not just a set of symptoms. It indicates a prognosis for the future and expectation that there will be further relapses. Transverse myelitis just means that there's an episode of weakness and paralysis below a given level. So, I would call that a syndrome, a collection of symptoms and signs. It's not a diagnosis.

You can have transverse myelitis due to MS, due to NMO, due to MOG associated disease, due to vaccine reaction. So, many, many different things can produce that syndrome. And that's when you have to do the whole medical evaluation based on the nature of the symptoms, blood tests, and so forth, looking at the MRIs, in order to put a patient in the correct diagnostic category.

Jacinta Behne: [00:21:20] This is so interesting. And let's say that you suspected someone might have NMO, what diagnostic tests and tools would you use, or other physicians use to confirm that diagnosis?

Dr. Brian Weinshenker: [00:21:35] Right. Well, the single most helpful one, I would say, especially for the majority of patients with neuromyelitis optica, is this antibody test, aquaporin-4. It's present often at the time of the very first symptom. There may be rare patients where it's not present right at the very first symptom, but the level goes up and it becomes detectable over time. So, it might be worth retesting, if it's negative. But that test is very highly reliable and specific. It's rarely present in any other situation, except for neuromyelitis optica.

[00:22:13] So, fortunately our concerns about false positives is, is quite low. Of course we like to see compatible symptoms. If the symptoms don't look compatible or the MRI doesn't look right, looks very suspicious for MS, we always have to have some skepticism. But, fortunately, these days, with our current level of testing, if you have a positive test for aquaporin-4 antibodies, that's very, very reliable.

[00:22:46] The problem is when you do not have a positive test, what do you do then? So, we've learned that other antibodies, and this is something we didn't really know confidently until about the last five or six years, that there is one other antibody called MOG-IgG. And this is an antibody that reacts to a myelin protein.

[00:23:09] I didn't mention, but the NMO antibody, the aquaporin-4, reacts to a different cell in the brain called an astrocyte supporting cell. The MOG antibodies react to the myelin producing cells called the oligodendrocytes and specifically target a component of the myelin. And, people with that antibody may have a syndrome that looks a lot like the aquaporin-4 antibody syndrome, but there are differences. Now it's possible that a patient may have symptoms that could fit either way and it's the antibody that makes a critical difference.

[00:23:49] The most important differences that we see compared to MOG is, firstly, the attacks tend to be less severe and recover better. So, that's certainly a good thing for those patients who have MOG. They tend to be younger. Optic neuritis, the loss of vision in an eye as the presenting symptom tends to be more common and getting both eyes involved simultaneously also tends to be more common. But these are not kind of absolute things because in both of these conditions, you can get both eyes involved and, you know, it's, sometimes a bit of a judgment call. And, with the first step episode in one event, it may not be very easy to tell the difference. And that's why detecting these antibodies, if things seem compatible, can be so helpful.

[00:24:39] The problem we have with the MOG antibody test is that that test is not quite as good. This has nothing to do with the labs that are doing the test. It's just that that antibody is a little more sticky and there's more tendency to get false positives. And that's mainly a problem when the level of the antibody is on the low side. When the antibody has very high levels, it seems to be quite reliable, but when it's low or borderline positive, we've learned that some patients with MS, some patients with other conditions, may have those kinds of low borderline antibodies and we have to be somewhat careful.

GG deFiebre: [00:25:20] Got it. Thank you. And so, then how can someone get tested for these two antibodies, the MOG and then the aquaporin-4? What is that process like?

Dr. Brian Weinshenker: [00:25:28] Fortunately, the process is very simple. All it involves is a blood test. It can be tested in the spinal fluid, as well. And occasionally that can be helpful, but the chances of getting a

positive test are actually much higher in the blood because we think that's where the antibody is produced and the antibody leaks from the blood into the spinal fluid. There may be some production right in the spinal fluid, but most of the antibody is produced in the blood and that's where the highest levels are.

[00:26:00] So, basically, it is a specialized test and it's done by specialized labs. Many, even expert centers, would send these blood tests to a specialized center to do this. And I think that is valuable because it is, as I suggested, especially for the MOG antibodies, a bit of a tricky antibody to test, it's a bit of a sticky antibody. You can get false positives. So, having a lab that has coordinated its testing and checked its results against the results from other labs that have developed a high degree of reliability and testing, I think, is very straightforward.

[00:26:39] But the process is really quite straightforward. The test itself runs in the hundreds of dollars. So, you know, it's not an inexpensive test having said that, once you've got a positive, convincing positive result once, usually there is no need to retest. So, I often tell people that, you know, say compared to an MRI scan that's often used on a yearly basis to follow MS, this is a lot less expensive and the significance and how it alters treatment is much, much greater.

Jacinta Behne: [00:27:17] Thank you so much, Dr. Weinshenker. Next question, if a person is negative for aquaporin-4, but has optic neuritis and transverse myelitis, how is the diagnosis determined?

Dr. Brian Weinshenker: [00:27:30] Well, I would say the first thing that I would think about is, is the diagnosis really neuromyelitis optica? Those are always conditions where we think very hard. Could it be multiple sclerosis, which is much more common? We take a very careful look at the MRI to make sure we're not missing MS-like spots. And if the patient had these oligoclonal bands in the spinal fluid that I mentioned are much more typical for MS, we might reassign the diagnosis to multiple sclerosis.

[00:28:01] But there are about 30% of patients who have what we think typical MRI findings, the long spinal cord lesions and severe attacks, and we really think it is neuromyelitis optica and they don't test positive for the aquaporin-4 antibodies. It seems that somewhere, depending on the part of the world where this is being tested, 20 to almost 50% of those patients may have the MOG antibodies. So, that's certainly worth testing.

[00:28:35] And, in fact, many places now, including Mayo Clinic, where we do this testing, offer a panel. So, you can have both antibodies tested at the same time and I think there is some value to that because we're recognizing the MOG antibodies are actually more common in the general population then the aquaporin-4 antibody. So, just based on the detection rate of the antibodies, it makes some sense to test both.

[00:29:05] But some patients are negative for both and the 2015 international panel criteria, and maybe I'll digress and just mentioned that, in around 2010, under the sponsorship of the Guthy-Jackson Foundation, we assembled a committee of 19 individuals. I believe they were from nine different countries, almost every continent in the world, except for Africa was represented.

[00:29:31] And we, over a course of a couple of years, sat down and hammered out diagnostic criteria. And basically the final product said there was one group that we're very confident about who have the aquaporin-4 antibodies and then there are patients who don't have the aquaporin-4 antibody. So, at that time, MOG was just being recognized. So, we didn't create a separate category for them. Although, I think we kept in mind that we could easily create another silo with patients with MOG antibodies, but there were patients who had neither antibody. And then we were more rigorous about the MRI characteristics. Did they have typical MRI characteristics?

[00:30:16] We weren't as liberal. Now, I think I mentioned that, with the aquaporin-4 antibody, all the patient needs is one clinical syndrome, like transverse myelitis or optic neuritis. If they have the antibody, we can

make the diagnosis and those where the antibody isn't present, we require more than that. And we require these additional MRI characteristics and other things to make sure that we're not including some patients with multiple sclerosis because we don't really want to mix in patients with multiple sclerosis because we would treat them quite differently.

Jacinta Behne: [00:30:54] Just real quickly, so, is that when NMO became NMOSD, a spectrum disorder?

Dr. Brian Weinshenker: [00:31:03] Right. So, we often refer to this disease now, instead of neuromyelitis optica or NMO, as NMO spectrum disorder, we proposed that in 2007, when we started seeing more and more syndromes like the vomiting and hiccups and other brain lesions. And we said, 'Gee, these are patients that might otherwise be excluded, unless we broaden the spectrum.' So, we called it NMO spectrum disorder. And in 2015, when the international panel discussed it, the recommendation made was that should be our new term for this condition because we didn't really think it was a different disease, if the patient had vomiting and hiccups or other things, aside from optic neuritis and myelitis. We thought it was all part of the same condition. So, we recommended changing the official term to NMO spectrum disorder. So, I suppose, Jacinta, in answer to your question, that was the time when that term became formalized into our entomology into our use of terms to describe this condition.

Jacinta Behne: [00:32:13] Thank you.

GG deFiebre: [00:32:14] Thank you for that. And so we did get a question come in about the MOG test. Do you mind just speaking about what titer level might be considered low? Is there like a particular cutoff where that's the case?

Dr. Brian Weinshenker: [00:32:25] You know, different labs report things differently. So, it's hard for me to give you one number that would apply across all centers. Many of the tests that are done are run at Mayo Clinic and based on work of my colleague, Dr. Eoin Flanagan, who leads our research effort on MOG diseases at Mayo Clinic. He found that a titer of 1,000, which is the amount that you would dilute blood and still get a positive test, was very reliable.

[00:32:57] If the level was one in 40, or you dilute the blood 40-fold, and you get a positive test, but, if you dilute it anymore, you lose it, he found it was only 50/50. At one in a hundred, it was intermediate. So, I would say anything over one in a hundred, as tested at Mayo Clinic, is quite suggestive.

[00:33:20] If it's in the range of one in a thousand, it's highly suggestive. But if it's one in 40, it's about 50/50 of it being correct.

Jacinta Behne: [00:33:32] Okay, well onward then please. We're going into treatment and symptom management. What are the treatments that are generally used for NMOSD?

Dr. Brian Weinshenker: [00:33:42] I always start by categorizing the treatments into three groups. There are the treatments we give acutely, when a patient comes with a sudden attack and has a neurologic deficit. And there, our goal is to rapidly get recovery of function. So, that's number one.

[00:34:04] Number two is prevention, prevention of attacks. Once you make a diagnosis of neuromyelitis optica, let's say the patient has a positive antibody test, you're quite certain that, in the absence of treatment, the patient is going to have further relapses, what can you do to prevent further relapses?

[00:34:25] And the third is to deal with various symptoms that the patient might experience, either acutely in the setting of a relapse, there are all kinds of symptoms that may occur acutely, and sometimes in the long-term, due to leftover damage in either the optic nerve or spinal cord or other parts of the brain. We call those symptomatic treatments, treating symptoms.

[00:34:52] So, let's start with the acute treatments. The first treatment that we give when a patient comes in with an acute, sudden neurologic syndrome, to reverse the neurologic injury, is corticosteroid, or sometimes known as steroids. And these are usually given high dose intravenously, typically over five days. And often we will then give a tapering course of steroids, generally, well tolerated, but there are a number of nuisance side effects and even some potentially serious side effects.

[00:35:28] An important backup treatment, if the steroids don't work, is a procedure that we really, I would say, did pioneering work at Mayo Clinic. In fact, I led a very large NIH supported study in the 1990s, even before we knew for sure that NMO was a separate condition. We included patients with NMO, but patients with other severe acute syndromes, as well. But it's turned out to be really, really helpful for NMO patients, a procedure called plasma exchange, where the patient is hooked up with a catheter in their vein to a machine that separates their blood and the liquid portion of the blood, which contains antibodies and so forth, from the cells in the blood. And the liquid portion is taken off and replaced with an artificial plasma that doesn't have these antibodies and other inflammatory proteins that lead to the neurologic damage.

[00:36:29] And, in fact, thinking of the SRNA, I think almost at your first meeting, I had just developed that or just completed that plasma exchange study. And I think the first place I had presented it was what was then called the Transverse Myelitis Association. So, Sandy Siegel would remember that well. Then there's preventative treatments. There are many treatments that seem to be helpful. There are three that are FDA approved that I think require special recognition because they were just recently approved.

[00:37:03] And, based on very rigorous scientific study, have been shown to be highly effective. One is called eculizumab, the second one is inebilizumab, and the third one is Satralizumab. And they have commercial names as well. Soliris and Uplizna and Enspring are the three commercial names, three different companies that produce these.

[00:37:27] And I won't go into the details of how they're given, but they're all monoclonal antibodies, highly targeted treatments, that block specific inflammatory pathways and reduce the number of attacks by somewhere between 75 and 95%, summarizing across all these various agents.

[00:37:46] And then symptom treatments, we may be talking about, but they are for, 'How do we manage vision loss? How do we manage the complications of not walking, physical therapy, pain, and so forth?'

GG deFiebre: [00:38:01] Thank you so much for that overview and on the, you know, the different types of treatment, you know, acute versus long-term. And so can the aquaporin-4 antibody levels be affected by acute treatments or these long-term treatments?

Dr. Brian Weinshenker: [00:38:15] They certainly can be affected by the acute treatment, especially plasma exchange. Essentially, we bulk remove antibodies, so the levels might go down well over 99%. Of course, the faster we take them out, patients continue to produce those antibodies, and so, it's a bit of a race with plasma exchange to remove them faster than patients can produce them.

[00:38:39] But, in the short term, it's an effective thing. Obviously, in the long-term, we need to do something to stop the production antibodies. Steroids can also lower the levels. So, the best thing is to test the blood before any steroids or plasma exchange has started. But the main problem is with the plasma exchange, lowering the levels.

Jacinta Behne: [00:39:03] Thank you so much. Let's go on to symptoms, please. If a patient comes to you and there may be a suspicion of NMOSD, are there general symptoms that you would initially look for?

Dr. Brian Weinshenker: [00:39:16] The main symptoms are the ones that I referred to before, the vision loss and the paralysis, loss of function, but there are some other symptoms that are less, perhaps somewhat less common, and less well-recognized. A very characteristic one that occurs after transverse myelitis, the paralysis attacks, is something called paroxysmal tonic spasms. And often this comes on maybe days or weeks after an attack of transverse myelitis and patients will get these attacks where the legs draw up and twist, typically lasts about 30 seconds to a minute, but they may start recurring multiple times an hour.

[00:40:07] Sometimes the hands can be affected, as well, and the hand will go into a claw-like posture. And, unfortunately, quite often patients are told that this is spasticity, which it isn't. What it is, is short-circuiting across the bare nerves that lie close to one another when the myelin gets stripped off, in neuromyelitis optica. And it seems to be, although it occurs in MS and neuromyelitis optica, more frequent, more severe in neuromyelitis optica. And the treatment there is a medication called carbamazepine or Tegretol, which in very low dose will stop those kinds of symptoms. So, that's an example of one kind of acute symptom that can occur.

[00:40:54] Of course, there's urine retention, and we may need to put in a catheter in the bladder, but usually that's not going to be a permanent thing and after the patient recovers, there'll be pretty good recovery of bladder function in most. And there may be some ongoing symptoms that require management, but a permanent catheter, unless the patient has very severe damage as a result of a transverse myelitis episode, is usually not necessary.

GG deFiebre: [00:41:24] Okay. So, you mentioned, you know, that there's a certain type of people who get told that that's spasticity. But does spasticity and, you know, as a separate thing, occur in NMOSD? And if so, how is it treated kind of in the long-term?

Dr. Brian Weinshenker: [00:41:36] Spasticity is basically what happens when the reflexes in the leg, I think people know what reflexes are, when the doctor taps on the knee and the leg jumps, but we're hooked up in the factory in a way that, even when there's bad damage in our spinal cord and the brain cannot send down the usual messages to turn off the reflexes, that the reflexes will take over. And when we try to stand on our legs, instead of them being completely paralyzed and limp, the reflexes takeover and hold you up. And that's a good thing.

[00:42:16] So, spasticity is not all bad, but it can be too much of a good thing. The reflexes can really take over and make your legs very stiff and jump. And, when you're sitting in a chair, legs can go into spasm and your back can stiffen up and you can slide off the chair. That's too much of a good thing. That needs to be kept under control and I tell people that treating spasticity is like building a pyramid. We always start with the bottom level of the pyramid, which is stretching, which has no side effects and is probably the most effective treatment, but layered, the next layer of the pyramid going up would be oral anti spasticity medications like Baclofen or tizanidine.

[00:43:00] There are some others, and the combination is usually effective. But other things, like injection of Botox and, you know, in really extreme cases where people are very uncomfortable and maybe cannot stretch because there's too much disability, we have pumps that can infuse Baclofen directly into the spine, which practically always will control this stiffness.

[00:43:26] But, sometimes there may be some loss of function as a result. So, we try to, you know, use that pyramid strategy, always start with the bottom of the pyramid, the stretching exercises first, and then the oral treatments.

Jacinta Behne: [00:43:41] Thank you so much. Regarding pain with NMO, could you talk a little bit about what kind of pain occurs and how it can be managed? In other words, are there commonly used treatments for pain in NMO?

Dr. Brian Weinshenker: [00:43:56] Sure, and, you know, I saw a recent survey about quality of life. It was actually conducted by Horizon Therapeutics, and their findings, I think, would fit pretty well with my own experiences, that most people with NMO do not have permanent pain. The pain occurs in intermittent bouts, often with other disease activity. So, a patient getting transverse myelitis, often their first symptoms will be searing pain across the back, often at the level where the spinal cord inflammation is. And this may go on for days or weeks and can be managed with a variety of treatments.

[00:44:37] Typically, ones that reduce nerve irritability because acute inflammation is coming on. When a patient gets attacks of vision loss in the eye, often they get eye pain, especially bad with eye movement. It's often not incapacitating pain, but certainly significant pain. So, there are these temporary pains. I mentioned those spasms that are treated with Tegretol. They're often quite painful, painful spasms, but some patients have long lasting, often after a spinal cord inflammation, burning and tingling in the legs, what we call neuropathic pain. And again, managed by a combination of physical measures, stimulators, various kinds, and medications that reduce nerve irritability, for example, gabapentin or pregabalin. So, Neurontin or Lyrica are the trade names for those medications.

GG deFiebre: [00:45:39] Thank you. And then, in terms of bowel function, how might NMOSD impact someone's bowel function? What are the main kind of treatment strategies for that?

Dr. Brian Weinshenker: [00:45:50] Right. Well, any patient who has significant what we call myelopathy or spinal cord damage that leads to loss of spinal cord function often will lose the sense that they need to have a bowel movement.

[00:46:06] So, the first thing is they will tend to become irregular and constipated. And sometimes that, especially if constipation is allowed to progress, when they do have a bowel movement, they may get very little warning and they may be incontinent. And, really the main thing is recognition and prevention for most people and trying to cultivate a regular bowel habit. And everybody's got a slightly different formula. What I usually try to encourage patients to do is monitor their bowel movements and try to achieve an every morning bowel habit. Sometimes, taking a little more time after having a hot cup of coffee in the morning, taking extra time, if a bowel movement isn't easily possible, using a glycerin suppository to help stimulate the bowels will achieve that bowel habit.

[00:47:02] And usually, if you train the bowels, they will sort of pick up the regimen and follow along. If it becomes a particular problem, using Senna once or twice during the day, which is a stimulant, may help, as

well. It's important to keep the stool soft. So, using bran, or Metamucil, or a stool softener, or a combination thereof have very few side effects and sort of helps avoid the kind of constipation that can interfere with the success of that treatment regimen.

[00:47:38] But, for most people with this problem, we can get them on a regular bowel habit that avoids incontinence more or less completely and makes their life much more comfortable.

Jacinta Behne: [00:47:53] This is so helpful, I'm sure. What are the possible effects of NMO on bladder function and main treatment strategies for bladder dysfunction in our patients?

Dr. Brian Weinshenker: [00:48:05] Yes, it would be the same group of patients who have the bowel problems, people with spinal cord disorders. And there are different patterns of bladder difficulty, probably the commonest is the spastic or irritable bowel, or the bladder muscle becomes stiff and doesn't allow full filling, and the patient gets these urges that they need to go. There's a constant urge. And the other pattern that's very important to differentiate is the one where the bladder muscle doesn't coordinate with the sphincter that opens up the bladder and the bladder over-fills because the sphincter is just not coordinated right with it, and the treatment is quite different.

[00:48:53] If the bladder's not emptying, the key thing is to try to get the bladder to empty. And there's a number of ways to go about doing that, that we can use conservative measures. But, sometimes, self intermittent catheterization, which I know for a lot of patients might sound very daunting, but is actually very simple, just about all patients can be taught to do, can really give a lot of relief and protect both the bladder and the kidneys from overfilling and pressure that can back up to the kidneys.

[00:49:25] For those that do empty well and have that irritable bladder, there are a number of bladder relaxant medications that we can use, such as Ditropan is a very commonly used one. They often tend to cause some dry mouth, but they can reduce bladder irritability and alleviate a lot of symptoms.

GG deFiebre: [00:49:44] Thank you. And then what about for visual issues? So, if someone has, you know, issues with vision after an attack of optic neuritis and what can be done in terms of managing that?

Dr. Brian Weinshenker: [00:49:55] Well, a very key thing is to, during the acute episode, when the patient gets sudden vision loss, try to do everything we can to save the vision. And that would be the steroids promptly and plasma exchange promptly. If that doesn't work or, in some patients with very severe attacks, there are some that believe giving both treatments simultaneously might give better results. I'd say that's still a bit controversial. But use of plasma exchange is becoming very important.

[00:50:25] Once the vision is lost in neuromyelitis optica, it's very hard to restore function. Of course, we have two eyes. Fortunately NMO affects one eye at a time. We're very careful about getting patients on effective treatment to protect the vision in the other eye. Losing one eye is certainly a bad thing, but not anywhere close to the disaster of losing vision in both eyes. So, those are very important things.

[00:50:56] Of course, we do have low vision clinic. If the patients have some residual vision, often there's a black spot in the center of the vision. Magnification may not be that helpful. We have other kinds of devices to help people manage with low vision. And I won't go into all the details of what might be possible through a low vision clinic, but restoring vision right now is really not feasible for the majority of patients who have

chronic loss of vision in an eye. So, prevention and dealing with the attack very promptly, when there's an acute loss of vision in a patient with neuromyelitis optica, is very important.

GG deFiebre: [00:51:43] Great. Thank you so much for, you know, this overview on the history, diagnosis, and then treatment and symptom management. Before we end today, I just wanted to ask if you had anything you wanted to mention that we didn't talk about or kind of any last thoughts on this topic?

Dr. Brian Weinshenker: [00:51:57] We were very comprehensive, considered many things. I, you know, I just want to end with a general perspective that, for someone like myself, who remembers what neuromyelitis optica was before we really knew that it was different. And before most people got that, I was seeing people who had been misdiagnosed with multiple sclerosis, were on treatments that we now know are actually harmful for them and were getting severe recurrent attacks and we saw quite a high mortality rate because some of those spinal cord attacks could result in difficulty breathing. And so, it was, you know, a terrible condition. Of course, it's still, in a way, is a terrible condition. But I think of it almost like I think of COVID vaccines.

[00:52:44] I mean, COVID was horrible, but at least we got treatments that were 90% effective in preventing problems. And, you know, the same thing kind of for NMO. Terrible as it is, we've got really good treatments now that are somewhere between 80 to 90% effective at preventing attacks. And we've got these treatments that we can apply very acutely, if an attack does occur.

[00:53:10] We still have a long way to go. We don't understand fully the cause of NMO, why people get NMO. We aren't perfect at preventing all attacks. But, you know, we've come a long way and the diagnosis is much, much more hopeful now than it was.

GG deFiebre: [00:53:31] Yes. Well, thank you so much for taking the time today. We did get through a lot and, you know, again also thank you for all the work you did in helping, you know, identify NMOSD and everything. Jacinta, did you have anything to add?

Jacinta Behne: [00:53:45] Nothing. So grateful to you, to SRNA, to you, Dr. Weinshenker, and your colleagues, and, most of all, to those patients and caregivers who are out there listening, and thanks to everyone.

GG deFiebre: [00:53:59] Yes. Thank you so much.

Dr. Brian Weinshenker: [00:54:00] Thank you.