The audio of this podcast is available at: https://youtu.be/7CKpKo05hdI

Intro: [00:00:00] ABCs of NMOSD is a 10-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 Viela Bio.

[00:00:59]**GG deFiebre:** Hello, everyone, and welcome to the ABCs of NMOSD podcast series. Today's podcast is entitled "I have NMOSD. Now What?" My name is GG deFiebre from the Siegel Rare Neuroimmune Association or SRNA. For today's podcast, we are pleased to be joined by Dr. Michael Levy, associate professor of neurology at Massachusetts General Hospital and research director of the Division of Neuroimmunology and Neuroinfectious Disease. He completed the MD PhD program at Baylor College of Medicine in Houston, Texas with a focus on neuroscience. Dr. Levy completed his Johns Hopkins internship in the Osler Medicine Program, residency in the Johns Hopkins Neurology Program and a fellowship in Neuroimmunology at Johns Hopkins University.

[00:01:44] In 2009, he was appointed to the faculty as assistant professor at Johns Hopkins where he started the neuromyelitis optica clinic and research laboratory. And in 2019, he moved to the Massachusetts General Hospital and Harvard Medical School to develop the research program in neuroimmunology. Um, so welcome today, and thank you so much for joining us. Dr. Levy.

[00:02:07]**Michael Levy:** Thank you for having me. Uh, well, I'd like to welcome everyone to the first of these 10 podcasts. I think this is a, a great effort and thanks to the sponsors for putting it on. The first of these discussions is about the very basics of NMO, of neuromyelitis optica, and I'm going to talk about what NMO is and where it came from, maybe what triggers NMO, how NMO usually presents in patients, how we make the diagnosis, a little bit about the treatment of NMO including what we do when you're actively inflamed, and then what we do during your healing period and how, how you're supposed to feel during that period of time.

[00:02:53] And then following that, just touch on a little bit of the other kinds of treatments that we use to prevent attacks and to treat symptoms from, um, the damage of NMO attacks. So, let's start with the very basic. What is NMO? This is a very important question and it, it can be confusing at first, but the very basic idea of NMO is that in some vulnerable patients, the immune system will turn against you. Um, and the target of the immune attack is a small harmless water channel called aquaporin-4.

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[00:03:35] An aquaporin-4 is a, is a water channel that's found throughout the body, but when the immune system decides that the aquaporin-4 water channel is for whatever reason harmful, then it attacks. But it only attacks the aquaporin-4 water channels in the nervous system. 90% of the time, it's in the optic nerve and spinal cord, and the other 10% of the time, it's in parts of the brain. But it's never outside of the nervous system.

[00:04:03] So even though aquaporin-4 is found in the stomach and in the lung and in the stomach, uh, in the, in the kidney, those organs are never targeted by the immune system. And so, NMO patients don't get inflammation in those organs, only in the nervous system. That's the very basic concept of what NMO is. It's basically an immune attack of these water channels that are doing no harm. In fact, for NMO patients who, who, who are in the throes of an attack, you have to remember your aquaporin-4 water channel has been functioning normally for years and years and years and doing nothing wrong. And then all of a sudden, your immune system decides to attack it.

[00:04:45] Now, we don't know why the immune system turns on the water channel, but when it does, it results in an attack usually of the optic nerves and spinal cord, like I said, about 90% of the time, or some other place in the nervous system. So, a lot of times, you might hear the term aquaporin-4-opathy or aquaporin-opathy, and that basically refers to the idea that, that the immune system is targeting the water channel.

[00:05:15] A lot of my Mayo colleagues will call this a water channel disease, for example. You might hear that term thrown around, but the idea is the same, and that is that it's an autoimmune process that somehow got triggered, um, in, in adult life. You weren't born with NMO, okay, but you were born with the predisposition to develop NMO because there was something in the environment that interacted with something in your genetics that then led to the immune system thinking that the aquaporin-4 water channel was foreign and needs to be attacked and destroyed.

[00:05:51] And on normal surveillance of the spinal cord and optic nerve, it might ignore it for a period of time and then at some point in your life, it says, "Nope. This is harmful. I'm going to attack." And then, it attacks. And it attacks in the same way that aquaporin-4 is a bacterium. It recruits all the components of the immune system to help it in the attack and that results in damage just like you were damaging a bacterium that had invaded your body. That's what the immune system is doing in NMO.

[00:06:22] Now, NMO has been around for a long time. Um, it- we have reports from back in the 1800s. I have colleagues from Germany who, who found reports early in the 1800s and then some reports, uh, in the 1870s, but ultimately was 1894 and 1895 that the term neuromyelitis optica was coined. That came from a series of cases probably 14, 15, 16 cases put together by a graduate student. And what they all had in common was that they all had a, an optic neuritis, an attack of the optic nerves and a transverse myelitis, an attack of the

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spinal cord within closed chronology to each other, so close in time. And they all seem to have spared the brain.

[00:07:17] And this was different from MS or multiple sclerosis. Multiple sclerosis was well known at the time. There were multiple sclerosis centers al- all across Europe and the US. And it was well known about as a disease. And this one just seemed to be different. NMO patients were already recognized back then to be particularly severe in their attacks, to be... to involve optic nerves and spinal cord a lot more than the brain. And that's really what distinguished them even over a hundred years ago.

[00:07:53] And so, Dr. Devic, Eugene Devic who was the senior neurologist at the time who was mentoring Frederick [Gault 00:08:01] who put together these cases. It was Dr. Devic who recommended the term neuromyelitis optica. Neuro is obviously neurological, myelitis the spinal cord, and optica, optic nerve. So for about a hundred years, that's how we re- refer to it. Neuromyelitis optica is a disease that wasn't immune-mediated kind of like MS disease that preferentially involved optic nerves and spinal cord.

[00:08:27] So if you look back at all the case reports and series over the past hundred years, that's what they all had in common. And it wasn't really until, uh, the late 90s when my colleagues at the Mayo Clinic, uh, decided that they could put together. They figured out a set of criteria, clinical criteria that help distinguish NMO from MS and from other related diseases. And they used things like the preferential involvement of the optic nerve and spinal cord, but also sparing of the brain which was not typical for MS. MS almost always involves the brain.

[00:09:04] And so, when the brain is not involved but the optic nerves and spinal cord are heavily involved, that, that pushes MS down the list of things... of the list of possibilities. And so, my colleagues at the Mayo recognized that in the late 90s and also some features on, uh, cerebral spinal fluid and MRI that tended towards NMO as opposed to MS, uh, but it wasn't until 2004 when Dr. Van Der Linden at the Mayo Clinic and her colleagues, Brian Weinshenker, and, and others. Everyone deserves credit up there in Rochester and other Mayo branches who put- brought these case series together, brought the serum to, to Dr. Linden to wash over slides of mouse brains and, and smooth muscle tissue and stomach tissue and basically a panel of, of tissues from mice, and she would wash the serum over and the antibodies from the serum would stick to aquaporin-4 in the mouse tissue.

[00:10:06] And she recognized this pattern of staining and helped put together, um, these series and, and proclaimed that there was an antibody in NMO patient serum that bound in this pattern. And then within a year, um, she figured out, and again all the colleagues at the Mayo Clinic deserve the credit, figured out that the antibody binds aquaporin-4. And shortly thereafter, every MS and neuroimmunology center around the world was reproducing that test and picking out their NMO patients from among all of their other MS, uh, clinics and recognizing that, yeah, they really are a different group of patients.

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[00:10:53] Their immune system is targeting aquaporin-4 as opposed to MS where the target is, is different. And then, more recently, those who tested negative for aquaporin-4 but really seem to have a disease that preferentially involved optic nerve and spinal cord, um, they are now tested. A lot of them up to half are testing positive for yet a different antibody called MOG, myelin oligodendrocyte glycoprotein.

[00:11:22] Now, MOG is different from aquaporin-4. MOG is a protein that's expressed on myelin. The aquaporin-4 water channel is expressed on the supported cell called an astrocyte. MOG is only an essential nervous system. Aquaporin-4 is found throughout the whole body. So they're, they're different immunological targets, but MOG patients have a lot of the same clinical features. So, for example, I just saw a patient came into the hospital blind in one eye.

[00:11:51] I said, "Look. Your brain, e- your brain MRI looks great. I don't see any evidence of MS, but among the, the other causes of recurrent disease are NMO which is an aquaporin-4 disease or MOG which is a different immunological target. We don't know which one you might have. We'll send off for both tests, and then we'll see you in clinic. And if you have a recurring disease, you're, you're highly likely to test positive for one of these antibodies." And, sure enough, it was MOG.

[00:12:20] And one of the other features we noticed about MOG is when they do come back to clinic, they are often seeing much better than my aquaporin-4 patients who tend to sustain a lot more damage and don't do as much healing as MOG patients. So we're already recognizing differences between aquaporin-4 disease and MOG disease that we may not recognize early, but once the antibody test comes back and helps distinguish them, we al- we also know that their future is different in terms of how well they heal and how many times they're likely to recur and things like that.

[00:12:55] Now, it's not just MS aquaporin-4 and MOG. We have a, we have a range of other diseases. On my Facebook page, there are dozens of people who test negative for everything. They test negative for aquaporin-4. They test negative for MOG. They have spinal fluid that's not consistent with MS or brain MRI that's not consistent with MS. And tha- so, there's still a lot of work to do to find these other diseases that may look similar to NMO or may look similar to MOG or to MS. And, and I'm sure those markers are there. We just need to find them.

[00:13:31] Now, what causes NMO in the first place? That's a, a really difficult question for us to answer because we don't really understand f you're not born with a disease, what triggers the immune system to suddenly turn on itself. If you were living with aquaporin-4 in your body and in your optic nerves and spinal cord and living with your aquaporin-4 water channels in peace, ha- having caused no harm, then why suddenly at age 42 does your immune system say, "You know what? I don't like aquaporin-4 water channel anymore. I'm gonna attack it in the optic nerve."

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[00:14:06] And then, you wake up and you can't see out of one of your eyes or both eyes or can't walk or can't pee. This, this is all too common in, uh, stories that patients tell me about how NMO started in them and they're, they're asking themselves, "Well, what caused it to happen in the first place?" I don't, I don't know the answer to that. What I can tell you is what we think is going on is that, is that your immune system might be predisposed to believing that aquaporin-4 is foreign as opposed to other people who have a very strong feeling that aquaporin-4 is not foreign, okay.

[00:14:46] And, and that genetic predisposition to something you heren- inherited from your pa- your parents, but why didn't they develop NMO? Well, because they weren't exposed to the same things you're exposed because it's not just your genetic predisposition. There must be something in the environment that then comes in and says, "And then it's time to attack." And, and it has to be something specific enough that it says, "It's time to attack your aquaporin-4 water channels."

[00:15:14] So I have colleagues at University of California San Francisco who have narrowed in on a gut bacteria, w- bacteria that lives in your intestine that has a water channel that's very similar to the human aquaporin-4 water channel. And it has a region that's very, very similar, in fact, I think something like 80 or 90% similar in one part of that water channel. So, maybe, maybe your immune system was interacting with that gut bacterium. It recognized that it was a bacterium. And it was, it, it was noticing that that water channel was very similar to the water channel it was surveilling in the spinal cord or the optic nerve.

[00:15:59] And so, when it goes back there, it says, "You know what? This water channel looks just like that bacteria water channel. Let's attack just in case, you know, because we don't want any bacteria in the optic nerve and spinal cord. That could be detrimental." But, then of course, in making that mistake, it actually causes a lot more damage and a lot more harm. So we don't want this immune process to take place, um, especially since it tends to recur over and over and over again.

[00:16:28] And so, it doesn't really learn its lesson as, as there are a lot of other, um, processes like, for example, idiopathic transverse myelitis. Those are patients who have a single attack to the spinal cord, but for whatever reason, the immune systems apologizes. It doesn't do it again. It leaves. It has... There's a limited capacity to heal, but then, they don't have to worry about recurrent attacks in the future because, for whatever reason again, the immune system says, "Yeah. We attacked and, and we didn't mean to." And they apologized and then leave, but with aquaporin-4 and with MOG, it's recurrent. So the immune system is convinced that not only is aquaporin-4 foreign, but even after it attacks and it sees as a result of the damage, it still thinks aquaporin-4 is foreign. And so, it's gonna attack again and again and again if, if we don't do anything about it to prevent that.

[00:17:20] Now, that genetic predisposition is a, is a malfunction of a process we call tolerance. So what is tolerance? Tolerance is a, is a new buzzword you'll hear a lot in the

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research world because it's something we're trying to restore. So, patients who have broken tolerance are those who have decided that some part of their self is foreign. And so, when you break tolerance to aquaporin-4, your immune system decides that it's no longer self, that it's now foreign, and it's going to attack.

[00:17:54] Now, how does tolerance get broken? Well, we can break tolerance in mice, for example, by activating their immune system to a very high degree. So, a lot of you may have had your first attack after a vaccine or after an infection, and that may be because your immune system is activated. You have to activate the immune system in o- in order to break tolerance. So, that's one component. Then, there has to be a specificity to it towards that water channel, and that's where those mimics come in, those, those other water channels maybe on bacteria or viruses that look like aquaporin-4.

[00:18:30] And so, the combination of the two, an activated immune system and a broken tolerance to something that looks just like aquaporin-4. The combination is what we think triggers the, the disease in people. So, we can recreate the disease in mice, and all we have to do is we take aquaporin-4, and we mix it with an immune adjuvant that basically hyper-activates the immune system. And we break that tolerance just by over-activating the immune system.

[00:19:00] Um, you know, there's very specific features, um, in mice that allow us to do that. One is that we, we can take mice that don't have aquaporin-4. So, they, they believe aquaporin-4 is foreign. And in those mice, we can recreate the immune response that we see in people. And when we transplant those... that immune system to a regular mouse, that immune system then triggers optic neuritis and, and transverse myelitis just like in people. So we know how to break tolerance in mice, but we don't know exactly how that happens in people.

[00:19:38] Now, how does NMO usually present in people? Well, the most common presentation if you're under 35 is optic neuritis. And so, what is optic neuritis? Optic neuritis is inflammation of the nerve that connects the eye to the brain. That nerve is about 50-millimeters long, 5-centimeters. It goes from the back of the eye through the orbit, through the skull, and into the brain. And it can be inflamed anywhere along that path. It's most commonly inflamed in the bone or closer to the brain, and it can inflame both optic nerves.

[00:20:17] And the way that usually feels is it starts off with pain. It could be like, like a soreness behind your eye like you've been punched in the eye. It could also be pain with eye movement. So, when you move your eye side to side or up down, that's when it hurts. And most commonly, it'll be associated... It'll start that way with pain. And then a few days in, then you start to lose vision.

[00:20:40] The vision could be lost in a spot like in a central gray area that's called a scotoma, or it could be lost like a curtain coming down or going up on your field of view. So,

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it could look like a curtain is coming down and half of things are black. They can't see anything above a certain line or below a certain line, or it could be... it could involve your entire field of view, but it looks like you're looking through water or through glass. And that's, that's all how optic neuritis presents. And it, it evolves over hours to days. It could be even a couple weeks, as long as a couple weeks, I've heard a few stories. And then, when you start treatment, then things may start to reverse and improve. That's one presentation.

[00:21:27] The next most common is transverse myelitis. And if you're over 35, it's the most common presentation. So, that's an attack of the spinal cord. And both the optic nerve and the spinal cord are very small. The optic nerve is probably the diameter of a, of a pencil, and the spinal cord is about the diameter of a quarter. And there's not a lot of redundancy in those areas meaning that if you knock out or remove or cut or destroy any part of those nerves, you're gonna notice whereas in the brain, when an MS patient has a small lesion in the brain, sometimes, they don't even notice because there's enough redundancy in the brain and the communications between all the different parts of the brain, they can reroute and recircuit. You can't do that in the optic nerve and spinal cord. It's a straight wire. There's not a lot of redundancy.

[00:22:18] So if you have an attack in the optic nerve or the spinal cord, you will probably notice it. In the spinal cord, you may target different tracts. There are tracks that go from the brain to the limbs. Those are motor tracts. And if you target one of those, you'll become weak or you may target a tract that goes from the limb to the brain that carries sensory information, and then you may not notice, uh, if something is hot or cold or sharp. You may not notice vibration coming from your toes. Um, you may not be able to carry proprioceptive information. So when you close your eyes and try to stand up, you're gonna fall over 'cause you don't know where your, your joints are in space. That's proprioception.

[00:23:02] You may not be able to urinate or have normal bowel movements because those nerves are also targeted in the spinal cord. So, all those things can happen. Now, the most common thing that starts first is pain, and it starts with pain in the back, and it kind of spreads around the body. And if, if your, if your attack is in the spinal cord in the neck, then you'll feel it going around your neck or into your scalp or into your shoulders. And if the attack is in the thoracic spinal cord, it'll be a band around your thorax or band around your abdomen or a band around your leg.

[00:23:37] So those are all features of how NMO presents in the optic nerve and spinal cord. That's 90%. Then, the other 10% involve parts of the brain. And the most common part of the brain that's involved in NMO is called the area postrema. It's a small part of the brainstem right above the top of the spinal cord, and its job is to sense when you need to vomit. It senses the blood. There's a part of the, uh, the vasculature there that's open to the brain, so the brain needs to be able to sample the blood and decide whether or not to trigger a vomit attack. And that's a normal part of how your brain keeps track of what's in

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your blood and whether you need to... whether you just ingested something that needs to be vomited.

[00:24:25] If that part of the brain is attacked in the NMO, you get this two to three-week episode of nausea, vomiting, and also hiccups. And it's intense. Most attacks are very intense. For those of you who experienced it, you can tell me how horrible it feels, but then it almost always goes away. It goes away quicker if you treat it, but if not, it goes away on its own anyway. And it's not something you ever wish on your enemies, but once it's gone, it's usually gone permanently. And that's an area postrema attack. Most people have just one. If they have it, very rare could you have a second attack like that.

[00:25:02] Now, if you involve other parts of the brainstem which connect the spinal cord to the brain, you may have symptoms very similar to a transverse myelitis, but in addition, you may also have eye movement abnormalities, double vision or problems with your, with your eye movements which are coming with brainstem attacks. And then, there are other parts of the brain, and these are very rare, but they're classic for NMO to involve parts of the brain that control your endocrine function, your hormone function, your sleep cycles, it- body temperature. Um, and these are, these are basic parts of the brain that are very close to the brainstem. And all of them are susceptible to NMO.

[00:25:46] Now, how is NMO diagnosed? The, the way it used to be done is if you had an optic neuritis and transverse myelitis, then you are already on the NMO list, and all you had to do was make sure it wasn't another disease like MS being most common so that the task was to rule out MS. Now, since we have the aquaporin-4 antibody, that antibody turned out to be so specific that even patients who were thought to have MS, if they test positive for aquaporin-4 antibody, now are much, much, much, much, much more likely to have NMO than MS just by virtue of the antibody.

[00:26:27] And it's such a highly specific antibody that we've come to depend on it a lot, so much so that the new criteria that we use since 2015 start with the aquaporin-4 antibody test. And if you're positive in the context of any of six types of attacks, the six I listed, optic nerve, transverse- or spinal cord, area postrema, brainstem or other parts of the brain, with an aquaporin-4 antibody test, the diagnosis is done. It's NMO with one caveat. The aquaporin-4 antibody test has to be a reliable test.

[00:27:04] There- the older tests are not as reliable as the new cell-based assays. So, let me go quickly into how these tests work. The original test depended on the way Dr. Linden did it when she first discovered the antibody which is just putting serum on mouse tissue and looking for a pattern of staining. That has since been replaced by a test called the ELISA, E-L-I-S-A which basically looks for the antibody in a dish. You put proteins at the bottom of a, a plate in the lab. You add the serum, and you look for binding of the antibody to the protein in a dish, no more mouse tissue.

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[00:27:42] Now, it turns out that test is- has a few false positives, and they're in the very low range. So, if you have a very low positive ELISA test, sometimes, we're a little bit nervous to make the diagnose- the diagnosis if the rest of the clinical clues aren't there. Um, and I'll go into what all those clinical clues are, but the new cell-based assay which is offered through the Mayo Clinic and through Quest Diagnostic, and I think ARUP Labs, um, out west. If you, if you're diagnosed through a cell-based assay in the context of one of those core presentations, then, your diagnosis is done.

[00:28:22] If you test negative for aquaporin-4, most people should be tested for MOG to make sure that that's-, uh, to see if that's the, the, the disease. Now, there's some people who should be tested for MOG first because the clinical presentation may favor more a MOG presentation. For example, kids are much more likely to test positive for MOG than they are for aquaporin-4. So you may... If you're gonna send off both, great. If you're only gonna send off one in kids, you're more likely to be MOG positive than aquaporin-4 positive.

[00:28:54] And now, there are other, um, clues, clinical clues that can help distinguish and help decide wh- whether or not the diagnosis fits. So those clinical clues are based on other objective measures mostly the first one, uh, the strongest one is the MRI is if the MRI of the spinal cord shows a long inflamed lesion whether it's the optic nerve or the spinal cord, that tends to favor the diagnosis of NMO or MOG over MS 'cause multiple sclerosis, that doesn't cause huge long terribly inflamed lesions like MOG and aquaporin-4 NMO do. That's a very helpful clue.

[00:29:39] So even if you're low positive on the ELISA test which is not our favorite aquaporin-4 tests, but you have a terrible horrible-looking MRI, then, then that's still probably NMO as opposed to MS. Um, other clues. So there's a test called an OCT, optical coherence tomography. It's a photograph of the back of the eye of the retina. The, the back of the eye connects directly to the optic nerve.

[00:30:06] Damage in the optic nerve reflects in the retina, and we can see that damage on this test called the OCT. There are certain parameters around NMO and around MOG and around MS that can give us clues to the diagnosis. And same with the spinal fluid. Spinal fluid is obtained through a lumbar puncture. That's, uh, for those of you who have not had a lumbar puncture, it's like an epidural for, for childbirth purposes with a stick a needle, yeah, through the vertebral bones and your lower back, to sample the spinal fluid that's bathing the brain in the spinal cord.

[00:30:43] Now, that spinal fluid that's bathing the brain in the spinal cord, they contain clues from any process going on in the central nervous system. And we use those clues to help distinguish among these diseases. S- so, particularly inflamed spinal fluid may, may prep, uh, prep the bias towards a diagnosis of NMO compared to MS, but then there are other MS specific tests in the spinal fluid that are, that are less likely to be positive in NMO and MOG.

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[00:31:16] So we use a combination of all those clues if the aquaporin-4 and MOG tests, um, are not reliable. And so, the order that I would put these tests are, first, is the clinical presentation, optic nerve, spinal cord, optic neuritis, transverse myelitis. Then, the antibody test and the MRI. And then, all of the ancillary clues after that. And then, sometimes, we're left without a diagnosis. There are many cases that I put in my... I, I have a group of patients. I call them the double seronegative group. These are people who are negative for the aquaporin-4 tests, negative for the MOG test, but I know they don't have MS or any other known diagnosis.

[00:32:02] And we're looking for new biomarkers, antibodies or T-cells, that can help diagnose these patients, but right now, there are still quite a few of those patients who don't quite fit. And what do we do for them? Well, we look for the disease that's closest to them. So we have MOG-ish patients where we have aquaporin-4-ish patients or MS-ish patients, and we try to treat them with those same medications that we use for those diseases and hope that they work, um, but if not, keep a very close eye on them 'cause if they, if they don't work, then we need to be able to try something else.

[00:32:38] Okay. Now, what do those treatments involve? Well, it depends on whether you're actively inflamed. When the immune system attacks, the optic nerve or the spinal cord or anywhere else, when it attacks, the process that's going on is inflammation. Inflammation is when the immune system reaches the barrier between the blood and the nervous system recruiting other parts of the immune system, and that includes, uh, blood clotting factors. It includes other immune cells. It includes antibodies. It includes the complement system. It includes fluids that are all designed to kill bacteria and viruses.

[00:33:19] And that immune attack is brought to bear on a naïve, uh, harmless part of your body, optic nerve [inaudible 00:33:28]. It is not prepared for that kind of immune infiltration. And so right away, neurological function is compromised. If it's in the optic nerve, almost right away you can't see or it hurts. If it's in the spinal cord, almost right away you start to lose function like strength of sensation. And that's just by virtue of the immune system being bare where it should not be.

[00:33:51] And so, the first goal of treatment in, in... when that happens is to just suppress the inflammation. Try to return the system to what it looked like when the immune- before the immune system attacked. And the first thing we do is we use a, a course of high-dose steroids. Steroids do a number of things to the immune system. First thing they do is they kill immune cells. It just stuns them or kills them. Uh, it tells them to die off. And when the immune cells, when the immune cells are not there causing trouble, um, a lot of the healing can begin, and some of the, um, edema and blood products get taken up by the cleaning crew, and the healing process starts and hopefully function is restored.

[00:34:40] That all depends on whether a- any permanent damage was done 'cause if the immune system has enough time, it'll destroy as much as they can, uh, and it can cause

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permanent damage in some cases. Now, what if steroids are not enough? Well, there's two situations. The first situation is that the steroids i- caused. They, it, it, uh, suppress the inflammation that there's no more inflammation, and you would think that that's a success, but oftentimes, the permanent damage leftover makes you feel like that there was no, no help at all from the steroids.

[00:35:18] And so, we need to be able to distinguish whether or not there's residual inflammation to get rid of or if it feels like the treatment didn't work because, because of the permanent damage, and that we can usually do by MRI because, sometimes, let me give you an example. So, let's say you have a patient who comes in with, with vision loss from optic neuritis. And we use steroids, and i- the information may completely subside, but the patient still can't see out of that eye. Well, what's going on?

[00:35:51] Well, there's two possibilities. Either there's ongoing inflammation, that's one possibility, in which case, we need to do more to suppress inflammation or there was permanent damage done, and there just needs to be some healing time. And so, often, we can't tell which process is going on, but we can get an MRI, and we can try to figure things out. Oftentimes, we'll just jump into escalated treatment. So, we offer more than steroids, and I'll talk about that in a second just in case there's more inflammation that needs to be, uh, sequestered.

[00:36:26] So, our, our first go-to after steroids is called plasma exchange or plasmapheresis. And that's basically a process of filtering the blood. There's IVs either in the arm or a big one in the neck that are used to pull out, uh, about a half a liter of blood at a time. Spin it down, filter it out, put the cells back in, the blood cells back in, but remove all of the, the plasma. The plasma contains all of the, the things that the immune system is using to recruit, the, the complement, the antibody, the, the blood products, the communication signals are all in the plasma.

[00:37:09] So, if you filter all that out, then the immune system doesn't get the, the same drive. And, and, uh, the, the inflammation dies down. And plasma exchange is done over a period of about two weeks. Sometimes, we do the whole thing in the hospital. Sometimes, we can finish it as an outpatient, but, but it takes quite a bit of time to do about two hours every day... every other day, excuse me, for about two weeks. And we usually do that on top of steroids as necessary.

[00:37:41] And, the we ask again, "Is there healing? Uh, are patients feeling better? Is the MRI looking better?" If yes, then we encourage, um, the healing process to continue. I'll talk about that in a minute. And if not, then, we have to do more steroids and more plasma exchange until the inflammation finally dies down.

[00:38:03] We are looking into additional ways of targeting the inflammation, um, and mitigating the damage and preventing any permanent neurological damage. We're using

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experimental therapies to try to do that, but right now, we don't have anything that's sort of a standard of care after steroids and plasma exchange.

[00:38:24] So what happens after the inflammation finally subsides and you get to go home or you go to rehab? Well, the next six months is a period of healing, but a lot of my patients will tell me that it doesn't feel like healing. It actually feels worse because i- if you had an attack in your spinal cord, for example, the healing process can actually be really painful as all of the nerves start to reconnect and the nerves in the spinal cord reconnect with the muscle and starts causing muscle spasms, or the sensory nerves will start sending up signals of pain.

[00:39:01] These can be very painful, and it usually peaks around two, two to three months after an attack. It can be in the optic nerve as well. You'll start to feel pain, uh, all the time or light sensitivity. And this is a... I, I don't want to say a normal part of the healing process, but that's typically what happens when the nervous system is healing, and it's all symptoms from the healing process. Now, we can try to suppress those or, or take the edge off so you're not suffering, but we're not worried about a new attack even though those symptoms feel new to you.

[00:39:37] So those are what we call positive symptoms are pain, muscle spasms, light sensitivity, this is- and, and, um, bladder incontinence for example or spasticity of the bladder. That's what happens during the normal healing process. Um, what's not supposed to happen during the normal healing process is loss of function. So, let's say, um, you're- you, you had an optic neuritis, you couldn't see out of your right eye, and then we managed with steroids and plasma exchange to get you back to at least some blurry vision.

[00:40:11] Well, if you wake up again and you're completely blind in that eye, that's not supposed to happen during the healing process. I, I'll- I never claimed that the healing process is, uh, like a linear line better every day. I tell people that it fluctuates like the stock market. You have a good day. You have a bad day, but overall over time, it should get better.

[00:40:33] So if it gets suddenly worse like you can't see again, that's probably a relapse. And so, you need to get that checked out 'cause you wanna t- start treatment again, acute treatment steroids and plasma exchange. When the attack occurs in the same part of the nervous system where you had a previous attack, it can be a little bit confusing for us because we don't know if you're just fluctuating if it was a particularly bad day or if, if you're having a new attack.

[00:41:01] Um, sometimes, we need an MRI to distinguish that, um, but if you ever have a new attack in a new part of the body, you should know that- notice that right away because you- that part of your body was never involved before. So, for example, let's say, you've had an optic neuritis and you're in the healing phase and I tell you that, you know, two months

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later, the peak of the healing process may cause a lot of pain behind your eye and discomfort, but in that two months' period, then you, you wake up one morning and you can't move your right leg.

[00:41:35] That's a totally new part of your nervous system that's being targeted that's unrelated to your optic neuritis. That's probably a new attack. That's not part of the healing process, and we should start treatment for that right away. So, new symptoms or much worsening old symptoms are things that you need to get checked out right away.

[00:41:57] Now, at the end of that six-month healing process, we don't cap anybody at six months, but usually about 90% of the healing happens in that first six months. At the end of that period, uh, you're often dealing with those symptoms for a longer period of time. So, let's say, uh, let's say you had a transverse myelitis in both legs and you were very weak and could not walk when you came to the hospital, and then after steroids and plasma exchange, we got you to a place where you're using a cane or a walker. And then over the next six months, let's say, we got you to a point where you're only using a cane some of the times, when you go on long distance walks for example.

[00:42:35] Then, after that six months, it's not like I say you can't heal anymore, but I'm not gonna tell somebody that a year after that, they're gonna be, uh, you know, Dancing on the da- on Dancing with the Stars because most of the healing has already occurred, and there, there may be some more healing that happens but not in, not in amazing amount as happens during the first six months.

[00:43:00] After that first six months, we think of most of the biological healing has taken place, but there's still a lot you can do, um, because what you're doing after that six-month period is you're retraining your nervous system. You're rewiring it, so that parts of the brain can try to communicate with parts of your, your... either your retina, your eye, or parts of your, your limbs through this- through a different tract than the spinal cord.

[00:43:26] And if you force your brain to do it, it'll often find new ways of doing it, not as seamlessly as when you were born and learned to walk over the period of the first 12 months of your life. it's not gonna be hardwired the way it was when you're born, but even during that healing period after six months, if you work at it hard enough and reinforce it over and over and over again, you can learn to use different circuits in your brain and your spinal cord to improve your, your walking or improve your, uh, to improve other functions.

[00:44:01] Now, unfortunately, there's no rehab for optic neuritis. There's no way that we can put you in front of a TV screen and flash different lights and rehab the optic nerve. Um, that happens kind of automatically just by vir- virtue of having your eyes open, and we don't have any special, any special tools to do that, but if you have a transverse myelitis, we do have spinal cord injury centers, rehab centers where we encourage you to go and get the best in rehab for the spinal cord.

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[00:44:33] Okay. Um, even after you do all that, okay, even six months later, then you start a, another rehab process and let's say you make even, even more progress after that, I'm still not gonna tell you that you're, you're done because future events whether they're, uh, vaccines or infections or, or particularly stressful time in your life or even just a very hot day may bring out some of your old symptoms, and it should feel like it felt when you first had the attack or during the healing process because the damage that's done is almost never completely healed to the point that it's invulnerable.

[00:45:15] So, oftentimes, what I'll hear from a patient is, "Well, they have fever and burning on urination consistent with a urinary tract infection, but then they're also having neurological symptoms like they had a year or two ago with their NMO attack." So that story is very common, and it's not a neurological problem that's emerging. It's just the infection, and you treat the infection and the neurological symptoms also improve not because there's inflammation again in the spinal cord, but because the old damage that was there and the o- and the new circuits that you used to recover from that damage, they're all vulnerable to, to temperature and to the pH of your blood, and to basically a lot of different things.

[00:45:55] I've had some patients tell me that they have a very, uh, tight window of, uh, where they're comfortable temperature-wise, but they, they can't stand the cold. They get... Their symptoms come out when they're cold, or their symptoms come out when they're hot, or their symptoms come out when they eat gluten or their symptoms come out after they exercise.

[00:46:14] There's a lot of different triggers that will bring out old symptoms even long, long after your attack and your recovery process.

[00:46:23] And so, that's pretty typical in NMO. A lot of it is, uh, just time waiting for the healing process to take place. And then after the healing process is complete, it's trying to avoid those situations that bring out those recurring symptoms. Even after all that, even after you've done your best in rehab, there may be symptoms that we can help with that you just cannot heal from.

[00:46:50] So a spastic bladder, for example. Even after all your attempts to do everything that rehab doctors are telling you to help manage your, your bowel and bladder, sometimes, it's not enough. And there are ways of managing that, for example, Botox injections in the bladder or bowel regimens to help control bowel movements that we can help with in the clinic. And that also includes treatment of pain, neuropathic pain, um, or spasticity or improvements in walking when there are devices like transcutaneous electrical nerve stimulators that help you walk better.

[00:47:24] And so, there are techniques that we can apply in the clinic to help you in the recovery process. Um, I would say that 80% of NMO patients will have ongoing pain after a transverse myelitis attack, and that tends to occupy a lot of the time in our clinic is dealing

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with pain. It's an unmet need. It's something that, uh, our sponsors, Viela Bio and other pharmaceutical companies should pay attention to and help develop new medications for because this is, is a very, uh, difficult problem for patients to tackle. Even a- after they've fully recovered, um, some of their other functions and are doing everything right, they're suffering from a lot of pain and this is a major issue.

[00:48:07] Now, on the preventive side, uh, after going to be these attacks, nobody wants another attack. Uh, that's true for MOG. Even, even though MOG patients tend to recover a lot better than an aquaporin-4 patients, nobody wants another attack. And so, our focus, uh, in the, in the clinic is always to prevent the next attack, and we do that with a variety of off-label drugs. We've been doing it for years with medications like rituximab or mycophenolate also known as CellCept or azathioprine also known as Imuran. These are our go-to drugs for a long time in both NMO and MOG.

[00:48:44] And now, we have the benefit of, uh, one approved medicine, eculizumab, and two additional medications that have proven themselves worthy in phase-three clinical trials, blinded, placebo controlled clinical trials that includes inebilizumab and satralizumab. And I don't have name brands for those yet. I hope they're, they're better than easier to pronounce than the generic names, but all three of these medications will probably be available to you in, in the near future, and you might wanna consider them as preventive therapies if your current therapy is not good enough or if you want to rely more on the science that we have, uh, behind the trials than in the off-label, um, medications that we're using.

[00:49:26] And one of the future podcasts will be around these new trials. So, I won't, uh, tell you too much about them except to say that they were all very beneficial that they have a wonderful safety profile that I'm not too worried about even long-term, and that they're very tolerable.

[00:49:43] Um, the logistics of them can be, um, some more difficult than others. Some are easier to access. Some are less expensive or more expensive. Those are all issues that we'll tackle in future podcasts, but suffice it to say that this is a disease, uh, NMO that went from ha-having no medicines, no drugs that are approved by the FDA to soon to have three.

[00:50:04] And so, that's a wonderful development. 2019 was called the year of NMO because we had three clinical trials that all reported out in a very positive way. And so, I think that's very optimistic for aquaporin-4. And, uh, we have a future trial plan for MOG that I- I'm not gonna talk too much about maybe for a future podcast, but I think MOG is h- is trending in the same direction. We'll have future drugs for MOG as well.

[00:50:30] You can find out all about these different trials and to see if you're eligible for, for participating in a trial by going to our website at massgeneral.org/nmo, and, um, you can contact me through that site as well. And stay tuned for, for more exciting developments.

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This is, um, a, a time. It's- Nobody wants NMO, but at least now, we recognize it. We have a great blood test. We have treatments for it, and we have a lot of advocacy and awareness.

[00:50:58] And so, I thank you for your time and, and attention, and I look forward to participating in future podcasts.

[00:51:05]**GG deFiebre:** [00:51:05] Great. Thank you so much, Dr. Levy. I think those were really wonderful overview about NMO, um, and a great start to this podcast series. So thank you so much. And I would also just like to thank, um, our collaborators. Again, the Sumaira Foundation for NMO, the Connor B. Judge Foundation, and the Guthy-Jackson Charitable Foundation, um, and, of course, this, um, podcast was made possible through a patient education grant from Viela Bio. We'd like to thank them as well. Um, and just for everyone listening, um, this was recorded and will be made available on our website, and you also have nine more, um, that will be scheduled. So, if you're not yet a member of SRNA, I'd encourage you to do so that you get updates about these podcasts. So thank you so much.

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