

# Neuromyelitis Optica Spectrum Disorder (NMOSD)

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[00:00:00] **GG deFiebre:** Thank you for joining this session on NMOSD. We are pleased to be joined by Dr. Justin Abbatemarco who is Staff Physician at Mellon Center at Cleveland Clinic. Dr. Abbatemarco, do you mind joining us?

[00:00:21] **Dr. Justin Abbatemarco:** Hello and welcome, everyone. So again, my name is Justin Abbatemarco. I'm a staff physician at Cleveland Clinic, and I am super excited to be giving this talk. It's a really exciting time to be talking about neuromyelitis optica spectrum disorder. We're in a completely new era with regards to treatment and management, and so we'll kind of go through that a little bit today together. Just a quick outline on what we'll be dealing with. We're going to talk a little bit about the history of the disorder, some symptoms that we commonly see especially in context to the diagnostic criteria, and then we get into the both short-term and long-term treatment options in NMOSD. We'll end on symptom management. We'll see how much time we're at. I know we're a minute or two behind, but we'll be okay, and I do just want to make sure that we will kind of defer discussions on MOG or MOG-associated disorders, MOGAD, because it's a completely different disease, and I think there's a different session about that.

[00:01:18] No disclosures. I do not have any relationships with pharmaceutical companies, but we have borrowed some of their nice graphics to help kind of get our point across today. So, let's jump right into it. So, what is neuromyelitis optica spectrum disorder, NMOSD for short? Some other terms you may have heard, Devic's disease or just neuromyelitis optica. These are all synonymous terms, but this is, NMOSD is the latest term used in the diagnostic criteria, and this is an inflammatory autoimmune process with an antibody mediated kind of disorder that affects the brain and the spinal cord, and so the body is producing these antibodies which is attacking the brain and spinal cord, and so that, at its most fundamental level, is what NMOSD is.

[00:02:08] Just a little bit of history, it's kind of nice to know how this came about. That seminal paper actually on this disorder came out in the 1800s, and that's where the name came, Devic's disease. It was Eugene Devic that kind of first described this disorder, but I can't overemphasize the importance of this piece. So, in 2004, we discovered the aquaporin-4 autoantibody, and this transformed the whole field. It not only gave us a biomarker for the disease, allows us to differentiate it from multiple sclerosis, but it also helped kind of

lead the way for some international treatment trials which we get to discuss at the end. So, this was really a huge discovery.

[00:02:51] I think this is where it gets to compared to MS a lot, and we'll kind of make some comparisons as we go along here. I just wanted to highlight a few differences in the demographics for this disorder, so NMO usually affects females. It's almost a 10-to-one ratio of females to males affected with the disorder which is very different from MS. MS also has a female predominance, but it's not as strong. It's like two-to-one, and MS commonly affects Caucasians whereas NMOSD actually is very common in the Asian continent along with the African Americans, Afro-Caribbean kind of populations. These are areas actually where MS is less common, so a little bit of a different demographic that we kind of see with this disorder, and this is a topic that we'll cover throughout this talk. The attacks vary, and NMOSD is much more severe when we're comparing MS, and the relapse recovery is usually incomplete which is very different from MS. Usually, that has complete recovery with time.

[00:03:57] So let's talk about them. What are the typical symptoms we see for relapses in NMOSD? One of the most common ones that we'll see is optic neuritis, and this can cause visual disturbances, so we can see that up here, in one or both eyes at the same time. This can be mild, but a lot of NMOSD patients can have really significant disability here and have complete blindness sometimes. Other symptoms that we'll see, other relapses that we'll see in NMOSD, include inflammation of the spinal cord, also called myelitis, and this can affect the arms, so you can have weakness in one arm or both arms along with sometimes the legs, and this disability could be really significant to the point where patients are wheelchair-bound and unable to ambulate anymore.

[00:04:48] Another less common, maybe a little less discussed symptom in NMOSD is this area postrema syndrome, and that just means like this intractable nausea and vomiting, so patients will have symptoms for days to weeks of just this constant upset stomach to the point where they sometimes need an IV for fluid resuscitation, but this doesn't always get to the neurologist, right? People are thinking of the GI tract, and then it takes a little while for the diagnosis to be made, and I'm sure some of you guys have experienced that. I wanted to break down two terms maybe in a little bit more detail because we may hear about them a lot, but I wanted to make sure we kind of understood what they really meant, so optic neuritis, again, is one of the most common symptoms. This means inflammation of the back of the eye, and this little diagram here highlights the structure, so here is your lens and cornea.

[00:05:40] Then you have this retinal nerve fiber layer on the outside, and all of those nerve fiber layers kind of converge into the back, into the optic nerve, and the optic nerve is sending the signal them from the eye to the back of the brain, okay? That's shown here, and this is where the inflammation that we see in NMOSD happens, and so the issue is that the signal does not get from the eye to the back of the brain, and people ask all the time, "Well, can I use glasses to correct that?" And unfortunately, there's no trouble with the eye itself. It's able to receive the signal. It's getting the signal from the eye to the back of the brain, so glasses do not help, but that is optic neuritis. That's what that term means. The other term that maybe you'll hear about is called myelitis, transverse myelitis, or longitudinally extensive myelitis. All of those terms are equating to inflammation within the spinal cord, okay?

[00:06:37] And you'll see a couple cartoons here. Doug Anchorman is a MS patient diagnosed in the '90s, but he's a comedian as well and has terrific kind of captions and cartoons, and here, he's talking about what's called an MS hug because sometimes when we have inflammation of the spinal cord, patients will experience this sensory level, and it can feel like a hug coming across the chest or belly, and it can have a variety of other

symptoms associated with it, but this is kind of a nice way of illustrating that point. So, these are two of the most common symptoms we'll see in our relapse for NMOSD. I don't want to get down too much into the weeds. I just wanted you guys to be aware of the diagnostic criteria for NMOSD, and it is really central with the aquaporin-4 antibody, so if you have that antibody positivity, it doesn't take very much. One symptom, and you're able to kind of make the diagnosis. You can make the diagnosis without those autoantibodies, but it becomes a little bit more challenging and requires a little bit more evaluation, and then we could talk about that maybe at the end if there are further questions about that.

[00:07:44] Okay, so here, you have this relapse. What do we do about it? What do we do in the acute setting, the immediate setting, to make patients feel better? The bedrock of our treatments usually centers on corticosteroids. IV methylpred or methylprednisolone is the most commonly employed medication usually given over 3 to 5 days in an IV. Sometimes, we pair that with this therapeutic plasma exchange. Other synonymous terms are PLEX or apheresis. They kind of all mean the same thing, and what that is, that is filtering the blood to get rid of some inflammatory mediators to help reduce inflammation. Steroids do the same thing, but this kind of comes at it in a different way, and so these are our two kind of main work horses for acute treatment. IVIG, which is used for other disorders, other neuroinflammatory disorders, is not commonly utilized in NMOSD, and early treatment is imperative. We try to get to these relapses as soon as we can so we can prevent disability accrual.

[00:08:48] And it kind of brings us to our next kind of point, and I wanted to contrast this idea with multiple sclerosis a little bit, so how do NMOSD patients develop disability over time, right, the thing that we're trying to prevent? This is a diagram of what multiple sclerosis looks like, so a patient will have a relapse maybe right here. This is the orange box kind of suggesting they have some symptoms. They stay there for a couple weeks, and they get better. Usually, they go right back to baseline. This can happen over and over if they're not properly treated, and so multiple sclerosis has a little disability related to a relapse, but they also have this neurodegeneration, and we're not 100 percent sure what causes that, but MS has this kind of multifactorial kind of disability accrual. NMOSD is very, very different. NMOSD disability comes from incomplete recovery from a relapse, and again, NMOSD patients usually have very severe, so this box would probably be much bigger, and they don't always recover back down to baseline, so we'll have this incomplete recovery, and this leads us to our next point.

[00:09:52] I can't overemphasize the importance of preventing relapses because that's how we prevent disability and keep patients functionally independent, doing the things they want to do, and this kind of leads us into this point about, which medications do we utilize to help prevent disability accrual and help prevent relapses? And that's with long-term immunosuppressant medications. This is another cartoon, and I think a lot of my patients feel this when we're in clinic, right? It says, "These ads for prescription meds are ridiculous, one page of benefits and three pages of side effects. Why not the other way around?" You know, I try to set the stage in my visit to weighing risks and benefits. These are big medications that we're talking about in this disease. We're talking about a big disease that we have to be aggressive managing, and so we're weighing those two pieces, but I know it can definitely feel this way in kind.

[00:10:44] So this is a table for medications, and I have randomized clinical control data, so that's kind of like our gold standard that we use to kind of evaluate the efficacy of a medication, and I want to go through those in a little bit detail. So, our first one, and the most widely prescribed medication, our clinic and my practice, is rituximab, so rituximab is an anti-CD20 medication which just means it targets a very select portion of the B cells, and it's infused after its starting dose every 6 months, so very, very convenient, and it is very well-tolerated. Most patients do really well during infusions with a little bit of pre-medications. All of

these medications are going to have some increased risk for infection in some way, shape or form because they're all suppressing the immune system, and there is a chance to have this reduction in immunoglobulins if you're on this medication for long-term, but we can usually manage that.

[00:11:44] One point that I just want to make really quick is that this is an off-label use, so this is not an FDA-approved medication, but that is not uncommon. I think that's a little confusing for patients in my practice as many others. We commonly utilize off-label or non-FDA-approved medications for different indications. We're borrowing this medication actually from rheumatology and hematology because they've been using it for well over 20 years. The other medications, these are FDA-approved. These are the newest medications that have come out over the last year to 2 years. Inebilizumab, which is very, very similar to our rituximab. You can see it as a similar mechanism at dose for an anti-CD19 marker which is, again, for B cells, similar infusion schedule and similar side effect profile, but very effective, had great clinical data as well as the rest of these medications which actually have very different mechanisms.

[00:12:39] Satralizumab is an anti-IL-6 medication, and IL-6 is an important inflammatory mediator in the blood, and so we're able to reduce inflammation through this kind of mechanism. This is a subcutaneous, so this is a self-injection that patients are using instead of an infusion-based medication with the rest of these, and again, well-tolerated. The last medication I wanted to kind of end on is eculizumab. This medication is a complement inhibitor, and so when the aquaporin-4 antibody binds to somewhere on the nervous system, it stimulates the complement system to mediate damage, and we're able to block that process with eculizumab. This, an infusion is every 2 weeks, so it's very frequent infusions but well-tolerated. You just need to have a meningitis vaccination before getting it. I just wanted to make sure we brought up these two other medications, azathioprine, mycophenolate are older medications used for the treatment of MS. I think now that we have so many other treatment options, we've moved many patients to the first page of medications that we have available.

[00:13:47] And I really want to make sure that we have time for questions, so I will end on this slide, and we'll open it up and make sure that we can answer any specifics, but I think one of the more confusing pieces that I see in my clinic for patients is this idea of a relapse versus symptom management because these things can overlap. So, when we talk about a relapse, right, we talked about the common symptoms you'll see there. We're talking about new inflammatory disease, and the reason we make that distinction is that new inflammatory disease means that we need to be thinking about changing or adjusting your disease-modifying therapy, the medications we just discussed, right?

[00:14:28] The problem is that patients can have symptoms outside of relapses, and they can overlap, which makes it confusing, but the reason we make this distinction and really harp on this is that symptom management doesn't require a change in DMT. It just means that we have to kind of focus in on which of these symptoms is bothersome. It could be fatigue like that cartoon was showing, neuropathic pain, burning sensation, numbness, and tingling, feeling you're walking on glass, weakness, numbness or tingling, loss of bowel and bladder or bowel and bladder difficulties.

[00:14:57] It really ranges, and so I just want to make sure that distinction is kind of mentioned because it's hard to get your head around especially given the overlap but vital when you're seeing your kind of treatment team. GG, I want to open it up. I know that we started a minute or two late, and I can always adjust and talk about some other things, but can we open it up for questions so that everyone has an opportunity to kind of ask theirs?

[00:15:24] **GG deFiebre:** Sure.

[00:15:24] **Dr. Justin Abbatemarco:** Do we have some already?

[00:15:26] **GG deFiebre:** Yeah, so I have a few, and then if anyone wants to add more to the chat or the Q and A, I will grab it from there.

[00:15:34] **Dr. Justin Abbatemarco:** Okay.

[00:15:34] **GG deFiebre:** But a question that I think we get pretty frequently is, someone might present with optic neuritis and transverse myelitis. We started on steroids and then get tested for aquaporin-4. Do any of the kind of acute treatments impact antibody levels or showing that someone is positive or not?

[00:15:54] **Dr. Justin Abbatemarco:** Yeah, it's such a great question. They can. This will reduce the inflammation, and we do try to get those testing done before, but those medications are all short-term and only affecting things for a couple days to weeks, and so I would say most of the time, it's not interfering with that testing, and it's easy to kind of redo a week, 2 weeks after that kind of period of time, but it's a fantastic question and one that we get a lot in the clinic as well.

[00:16:22] **GG deFiebre:** And then relatedly, so I know you kind of very briefly talked about the MOG antibody, so when someone tests positive for aquaporin-4, is that, unlike MOG, mean that someone has NMOSD for sure no matter kind of when it occurs or if they test negative later? How does that work?

[00:16:43] **Dr. Justin Abbatemarco:** And that gets a little confusing, but there's been a lot of studies about how the aquaporin-4 antibody kind of can fluctuate throughout the disease. The aquaporin-4 antibody is a biomarker and, it actually causes the disorder. It's pathogenic in and of itself because sometimes, antibodies can just be markers for autoimmune diseases, and so the antibody is fairly specific and sensitive. It's very good at kind of picking up this disease. It's in stark contrast to the MOG or a MOGAD where we're still trying to learn and figure that one out. For example, that MOG antibody doesn't itself mediate some of the neurological symptoms that we see.

[00:17:27] The second part of that question about, what happens with that antibody as you go along? It does; there are times when that antibody can disappear. Sometimes, if you're treating, let's say, with rituximab, that can make that antibody go away. We talked about it with steroids. That would be a transient thing, but rituximab could cause that antibody to go down. Sometimes, there's just the natural fluctuations with it. I do not commonly follow that antibody over time. The titer doesn't usually change my treatment approach, and usually, we're talking about long-term lifelong immunosuppression for this kind of disorder, though we are still trying to figure out that last part.

[00:18:05] Is there a safe time to come off this? We're actually doing studies in MS for taking people off the disease-modifying therapy around 55 to 60, but I'll tell you, the prelim evidence for NMOSD is probably not. There's a chance for relapse even as you get a little bit older, and so I don't usually follow the antibody, the antibody titer after that kind of diagnosis is made.

[00:18:32] **GG deFiebre:** Got it. Thank you. And so, I know you talked very briefly kind of about some of the symptoms that might occur, and we will have dedicated sessions on both bladder and bowel issues, but we did have a question come in that asks about suggestions for bladder and bowel control for those diagnosed with NMOSD.

[00:18:52] **Dr. Justin Abbatemarco:** Yeah, it can be a really challenging thing, and it's commonly seen with

patients with that transverse myelitis. So, inflammation of the spinal cord very commonly can affect the bowels or bladder, and one of these slides I didn't get a chance to show is how important it is to kind of have this kind of multidisciplinary team involved, right? Is a neurologist important? Absolutely, but at our center, we have experts coming from all over including our urology and gastrointestinal team members to kind of help because there are testing that we can do to kind of see how the bladder is reacting. Sometimes, it can be contracting too much. Sometimes, it's not contracting enough, and there are some medications to help with either one of those things.

[00:19:34] There are also a few things that can be done lifestyle-wise, being a little bit more mindful about how much you're drinking, when you're drinking, making sure you're double-voiding, so that's going to the bathroom and then trying to void right again to make sure the bladder is completely empty, so that is a big topic, but I just want to stress that multidisciplinary kind of team approach to those things because it can be challenging to get them under control so it doesn't interfere with day-to-day activities as much.

[00:20:07] **GG deFiebre:** Got it, okay, and I have a question that also came in, so we haven't talked too much about those who are potentially double negative or didn't test positive for the aquaporin-4 antibody, so someone asked if the medications listed are available for those who are diagnosed with NMOSD but not necessarily aquaporin-4 positive.

[00:20:30] **Dr. Justin Abbatemarco:** Yeah, this is definitely one of our more challenging kind of areas. It's definitely one of the more challenging things in my practice, and so when we're talking about that double negative, usually we're talking about aquaporin-4 and/or MOGAD, and I think there is. MOGAD has only really been described now over the last, I don't know, 4 to 5 years really kind of widespread, so you can just see how quickly this field evolves, right? 2004, we have one antibody. Almost 10 years later, we have another one. I think that there is still a lot of active research to kind of better understand, is there another antibody that we just don't know about right now?

[00:21:06] And so stay abreast on this. Ask your commissions. Come to these kinds of meetings, and we'll make sure we share with you the latest, but when we are making that diagnosis, it just requires us to be really thoughtful about other mimickers, other disorders like multiple sclerosis, but there are other things like sarcoid[osis] that can do similar things, other kind of rheumatological disorders, and so it just requires a really thoughtful approach about other potential disorders, but we can absolutely use the medications we described above to treat seronegative or double negative NMOSD, and really that same kind of mechanism and things apply. I think rituximab treats both MS and NMOSD, and so it's a nice medication that covers us a little bit more broadly when we're a little bit unsure in clinic.

[00:22:01] **GG deFiebre:** Great. Thank you, yeah, because we do get a lot of questions from folks who were diagnosed with NMOSD who initially maybe were not aquaporin-positive but then as the MOG test became available, got diagnosed with MOG, but then there's still that portion of people who don't test positive for either, so we all forget.

[00:22:19] **Dr. Justin Abbatemarco:** I think that's an evolution that's going to happen. We'll have another one, and we'll be able to talk about. I hope it's not in 10 years because it would be really helpful, so hold on. I think it's coming.

[00:22:30] **GG deFiebre:** Right, yeah, so my question was going to be, are there these antibodies that we just don't know yet that we're kind of looking to find that we might then be able to kind of put people in those diagnostic buckets as well?

[00:22:44] **Dr. Justin Abbatemarco:** Definitely.

[00:22:44] **GG deFiebre:** Yeah.

[00:22:45] **Dr. Justin Abbatemarco:** I deal with some other neuronal antibody-mediated diseases, like NMDA is one of them, and there is a new antibody coming out every couple months, and so our understanding of the pathophysiology of these disorders is evolving, and I do. But we're missing a piece to kind of understanding that other, the seronegative group, but fortunately, the medications, we don't always have to have that antibody to be able to initiate treatment and help provide both symptom and kind of DMT medication usage.

[00:23:20] **GG deFiebre:** And then we did get a question too about if, I don't know how to say this.

[00:23:28] **Dr. Justin Abbatemarco:** Kesimpta?

[00:23:28] **GG deFiebre:** Yeah, is that ever used in NMOSD? It's not one I'm familiar with, so apologies for the mispronunciation there.

[00:23:35] **Dr. Justin Abbatemarco:** Kesimpta is an ofatumumab, it is a MS medication, or it's approved within multiple sclerosis, and it's a good question because it's the same mechanism. It's an anti-CD20 medication that's injected. I think we get a little bit into insurance authorization. I don't think insurance would authorize the use because there's no FDA clearance, and it's a brand-new medication, so it's very expensive. In theory, though, right, if we've proven that these anti-CD20s are effective, I think it would be. I don't use that medication, or I don't offer it to my NMOSD patients. That same idea would be there for Ocrevus; Ocrevus, rituximab are equivalent in my book, just a tad different, but again, I don't use Ocrevus because it's not FDA-approved for NMOSD, but we're getting into insurance games, and unfortunately, it's truly what they are. It's an unfortunate reality in our system.

[00:24:37] **GG deFiebre:** Yeah, yep. And then we just very quickly before we go to our next session, I just wanted to thank you for your time and answering questions and everything like that, so we really appreciate it.

[00:24:51] **Dr. Justin Abbatemarco:** No, I appreciate the opportunity to be here and to shed some light on these really kind of complicated disorders, and, yeah. My contact information will be available. I love working with you guys. I thank you for putting this on and all the things you do, and I do apologize for the technical error in the beginning, guys, but it was my pleasure to be here today.

[00:25:12] **GG deFiebre:** Thank you so much, and for everyone, we are going to then now go to the stage area where Dr. Flanagan is going to talk about acute treatments at onset and relapse, so that's currently now. So, thank you so much, and thank you, Dr. Abbatemarco.

[00:25:29] Bye, guys.

[00:25:30] Bye.