Community Q&A

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[00:00:04] **Krissy Dilger:** How about we just get started with, do you mind just describing how NMOSD is initially diagnosed?

[00:00:18] **Dr. Elias Sotirchos:** Yeah, definitely, that's a great question. So, I think that usually with NMOSD, people will present with an initial attack of neurological and an initial neurological acute event that will bring them to the attention of the neurologist or ophthalmologist—depends kind of on what the nature of the presentation is. The most common of those being either optic neuritis, which is characterized typically initially by onset of pain behind the eye, usually, worse with eye movements.

[00:00:53] That then can progress over a period of usually a few days to blurry vision, color vision can be affected, and depending on the severity, it can lead even to complete loss of vision in one or even both eyes. If it's occurring simultaneously in both eyes, which, if it's occurring simultaneously in both eyes, that is more consistent with NMOSD rather than multiple sclerosis or bilateral simultaneous involvement is not that common. So, that's the one, I think, common presentation. So, initial presentation of optic neuritis that will bring people to attention.

[00:01:29] The second being an episode of myelitis where there's spinal cord inflammation, which will also kind of develop over a similar time frame. So, days to one to two weeks at most is the time frame to the need or the neurologic dysfunction. And that will be characterized often by a variety of symptoms, including [inaudible] the spinal cord, including back pain, weakness, which can be in the legs and/or arms, depending on the level of the spinal cord that is affected, numbness, and paresthesia.

[00:02:03] So, like, tingling or electrical sensations that people may describe, as well as bowel and bladder dysfunction. Those are the two most common. And then there are some rarer presentations of NMOSD, including what's called area postrema syndrome, where people develop this syndrome of intractable hiccups, nausea, vomiting. That one sometimes will be seen initially by gastroenterology because it's thought to be a GI issue and may even elude diagnosis. But sometimes these things improve on their own, even without steroids or other interventions that we use.

[00:02:35] And sometimes then people will have a second event, either optic neuritis or myelitis, that will bring them to the attention. I think that one additional issue to discuss is, with the newer recognition of MOG antibody disease, like, what is NMOSD, what is MOG antibody disease? I think that it's a distinction that is confusing not only for patients, but even for a neurologist to some extent, just because of the terminology that's often used historically.

[00:03:03] And there are actually efforts going on now to revise the diagnostic criteria since the NMO diagnostic criteria was last published in 2015. And so, they don't really account for the MOG antibody disease, which

can present similarly and affect the optic nerve and spinal cord. And so backing up historically, neuromyelitis optica means myelitis and optic neuritis, essentially, is the origin of that word.

[00:03:31] So, saying that a disease that affects the optic nerve and spinal cord, but that doesn't really mean that it's necessarily one disease because MOG antibody disease, what we're calling NMO which, when I'm saying NMO, now I'm going to be referring mainly to people who are aquaporin-4 antibodies, seropositive or negative for both antibodies, which is this seronegative category, can have kind of similar manifestations. But we know that fundamentally the diseases are different, this is a different underlying cause. And we know that the course, the responsive treatments can differ depending on what the cause of the NMO and the attacks is.

[00:04:13] **Krissy Dilger:** And so, somebody submitted a question. Judy asked, "I'm antibody negative, and my neurologist says there are new developments in treatments but not for antibody negative." So, I think she's referring to the new FDA-approved drugs. So, can you just talk about the difference between positive and negative in these ongoing treatments? And if there's any trials or anything on the horizon for antibody negative patients?

[00:04:51] **Dr. Elias Sotirchos:** Yeah, no, definitely. That's a really great question. I think it's really important to address. I think that—so to clarify, the clinical trials that were done in NMO of the three newer therapies that are now FDA-approved, which are Soliris, also called Eculizumab; Uplizna, also called Inebilizumab; and ENSPRYNG, also called Satralizumab. These clinical trials demonstrated effectiveness of these medications and preventing relapses in people with NMOSD.

[00:05:25] Now, the trials were all a little bit different in their design with the Soliris trial only enrolling, for example, people who were positive for the aquaporin-4 antibody. The other two enrolled antibody negative patients, but the conclusion was that the number of antibody negative patients was too small to make a conclusion about whether the drug actually worked in that population.

[00:05:50] So, when the FDA approved these three new therapies, the labellings of the FDA specifically says that they are indicated for aquaporin-4 antibody seropositive people. And so, because of that, these therapies are less accessible to people who are aquaporin-4 antibody seronegative. They still can be prescribed, although it's off label and it's much more difficult to obtain insurance approval.

[00:06:26] But that's kind of why that situation has come up. Now, currently, what's going on is there are phase three clinical trials going on in MOG antibody disease. Because, again, some people who are seronegative NMO are actually MOG antibody seropositive. And so, for those people there are these two phase three trials that are attempting to demonstrate the efficacy of two treatments for MOG antibody disease and ultimately obtain FDA labels.

[00:07:00] But that doesn't mean that we don't have treatments for people with seronegative NMO who are seronegative or both antibodies. It's just that we typically will use more of the older, more traditional therapies that have been used extensively in NMO. Things like Rituximab, Mycophenolate mofetil, also known as CellCept, [inaudible], for example, is an option Tocilizumab, also known as Actemra.

[00:07:29] So, there are a variety of options, even IVIG, and one of the issues, I think, with seronegative NMO is that it's not entirely clear if this is just, let's say, a third antibody that or something else that we just haven't discovered yet. And it's actually a distinct population, a distinct disease that's different than aquaporin-4 IgG seropositive NMO or MOG antibody disease.

[00:07:55] Or if there are multiple things going on, like maybe there's two or three diseases that we just haven't discovered yet, or are there other features going on and they're in the same family of disease. But we just, let's say, happen to test these people at the wrong time because we know that levels of the antibody in the blood can fluctuate. Or if we test people after they've already been on treatment, it could be that the treatment made the antibody negative, and then your test is going to be less sensitive at that stage.

[00:08:21] Other features that can occur is—that depends on what test you use. Some tests are better than others. And so, if somebody was tested only by an older assay, it might have less sensitivity and not pick up the antibody. And then if you test somebody by a newer assay, it might be positive. So, there are a lot of caveats to this. And I think that it's an area of ongoing discussion.

[00:08:43] Definitely, I think it's something that research will be targeted towards—this double negative population that are negative for both MOG antibodies and aquaporin-4 antibodies. We definitely need to understand, first of all, what exactly these people have, and maybe they have more MOG antibody disease or aquaporin-4 antibody disease, and also to develop new treatments.

[00:09:04] But, I mean, currently in terms of clinical practice, when I see somebody who's negative for both, I try to say, okay, you're negative for both, but do your clinical features or imaging features fall more within aquaporin-4 antibody NMO, or do they fall more into MOG antibody disease? And then try to use that to guide what treatment I'm going to choose. Or do you look like something that can mimic NMO? Like, there are conditions like sarcoidosis or other that can kind of look like NMO, but they're not NMO. And so, do we have to do a further work up.

[00:09:43] **Krissy Dilger:** Yeah, those are great points, and I think it's interesting. I know there's a lot of talk of, is there a third disease in there, antibody in there, that might be discovered for these double seronegative people? So, that's something—I'm interested to see where it goes from here. So, Dana, I see your hand is raised. Would you like to ask a question?

[00:10:09] Audience Member: Yeah, thank you very much for taking the time this afternoon. I just got a cheeky couple of questions, but they are related. I developed transverse myelitis December '22, and I'm AQP4 positive. Have I always had that? Has that antibody always been in my body? And just something triggered it at that moment, or did it appear at that time with the transverse myelitis? And it may not be an answerable question but…

[00:10:43] **Dr. Elias Sotirchos:** No, that's a great question. It's actually a very interesting question because it gets up to the fundamental question of: When do people develop NMO exactly in their lifetime? And is it at the time of the initial event or could it be something that was brewing for a few years before that may have just come to light at that time? And the same is true of other diseases actually.

[00:11:08] For example, in MS there's now increasing evidence that there's something called, like, the MS prodrome where people years before they're diagnosed actually have had MS. And if you actually did an MRI at the time, you could see some lesions, but they weren't really having a lot of symptoms or a clinical attack. And that led to this recognition of something called the Radiologically Isolated syndrome, where people have a lesion on the MRI that looks like MS, but they don't really have symptoms.

[00:11:34] And we know that a lot of those people will go on to develop multiple sclerosis. Now focusing on NMO, I think this is a really, really interesting question. I think that first of all, no, we don't think that it's

something that everybody has their whole life. It's not something that somebody is born with. So, we do think that it's definitely acquired at some time in somebody's life.

[00:11:52] On the other hand, it's actually something that—it's difficult to answer because we don't really have blood stored on people years before they develop attacks. However, there is actually an interesting report from Japan where they had a patient who developed aquaporin-4 IgG seropositive NMO, and they were a blood donor, and they had blood bound years before they actually had their first attack.

[00:12:22] And that person was actually found to be positive for the aquaporin-4 antibody years before they developed their first attack of NMO. Now, again, it's not like we have this on all NMO patients. But this is, I think, a very interesting and thought-provoking case that tells us that people can have the aquaporin-4 antibody years before they actually develop their first attack.

[00:12:48] And I think this also is consistent with what we know about the course of NMO. So, even before we had treatments, people with NMO, it's not like they would have an attack and then they have an attack continuously. They would go into remission kind of spontaneously and can go even years without an attack, even without treatment sometimes.

[00:13:07] And so that tells us that the antibody can be circulating. But if it can't gain access to the spinal cord or to the optic nerve, it can't really cause damage potentially. And so, I think, though, on the flip side, though, we based on the studies that have been done of the antibodies, like testing people for controls who don't have any myelitis or optic neuritis or anything like that, we essentially never, almost never see it be positive.

[00:13:38] And so, on the flip side, it's not like there are thousands of people walking around who have the aquaporin-4 antibody in their blood and are never going to get NMO. So, we do think that if somebody has it, they're almost certainly going to have an attack. But the data—that case from Japan demonstrates that there could be a lag of years between having it in your bloodstream and actually having an attack.

[00:14:04] And we don't know exactly what triggers these attacks. So, the antibodies in general are in the bloodstream. They're not in the brain or spinal cord, and our brain and spinal cord is protected from our blood by something called the blood-brain barrier. That keeps a lot of our—it tries to protect our brain and spinal cord because it's so precious from toxins, from bacteria, viruses from our own immune system to some extent.

[00:14:31] And so, but we think that somehow that can break down intermittently at some point, infection, trauma potentially, or just randomly, and somehow the antibody gains access to the central nervous system and they can cause attacks.

[00:14:47] Audience Member: That's really interesting. Thank you. Well, connected with that. In 2015, I was diagnosed with a primary immune deficiency, and I'm IgG and IgA deficient, and that's a genetic thing, which something triggered that. But I always had the propensity for it. And my sister also turns out to have it. So, I've been on Ig immunoglobulin replacement therapy since then.

[00:15:14] I've also over the years collected a little collection of autoimmune conditions. And then of course, this erupted in 2022. Is there any connection between the primary immune deficiency and the collection of autoimmune disease and what has happened? So, there seems to be—some immunologists do think so, but…

[00:15:41] **Dr. Elias Sotirchos:** Yeah, no, that's a great question. I mean, I have to say most people with NMO typically do not have immune deficiencies. But on the flip side, there is—we do know that people with the

most common, what's called common variable immunodeficiency or CVID, which can be characterized by low antibody levels. Like, you have actually paradoxically, you would say, “Okay, these people are immune deficient, but paradoxically, they are more susceptible to autoimmune diseases in general.

[00:16:08] “Including things like inflammatory bowel disease, inflammatory arthritis, autoimmune muscle or lung conditions and other things like that.” And so, generally, I do think that there likely is a potential linkage there. Although on the flip side, most people with NMO typically don't have an underlying genetic immune deficiency, but it definitely can predispose people to autoimmunity.

[00:16:31] Audience Member: Okay, lovely. Thank you very much. That's really helpful. Thank you.

[00:16:37] **Krissy Dilger:** We have gotten a few more questions in the chat. So, starting with Caroline's question, “Why do viruses/infections lead to deterioration in NMO symptoms, e.g. nerve pain, increase in neuropathy/muscle weakness? Is it because of stimulation of the immune system? If so, does that suggest the immunosuppression being used is not fully effective?” She says, “I've found that COVID induced deterioration is not improving after three months.”

[00:17:11] **Dr. Elias Sotirchos:** Yeah, that's a great question. And we definitely have seen this, we see this quite a bit in clinical practice. I have to say, we generally don't think of it as being because the immunosuppression is not fully effective. Because it is a phenomenon that we see not only in people with autoimmune neurological conditions, but we see it, for example, with people who have had stroke or people who have myelopathy due to compressive [inaudible] or other things like that.

[00:17:45] And so, of course, we also see it a lot in of autoimmune conditions like multiple sclerosis, like NMO. And I have to say, I mean, it's difficult to answer this question definitively, but generally, the way that we perceive of it is that there is a systemic stress occurring on the body. And in somebody who has already had a neurological event that has left scarring, for example, in the spinal cord or in the optic nerve, there is decreased reserve.

[00:18:18] And so, that systemic stress that is being put on the body by the infection can lead to a deterioration through a variety of mechanisms. I mean, one is actually fever, it has been well described. So, this is a very well-described thing in especially multiple sclerosis. But also we see it in NMO and MOG antibody disease.

[00:18:38] Where, when the body is overheated, the conduction of electrical signals can be slowed down, especially in axons or nerves that lack myelin, which is the sheath around it. And so, that's thought to be one of the basis, for example, of the phenomenon, when people who are having an acute infection have this pseudo-relapse is called, “pseudo” being there. Not because we don't think it's real, but because it, we don't think it's due to a new inflammation at the time, because if you do an MRI in these people, you're not going to see a new lesion that's active and taking up [inaudible] or anything like that.

[00:19:16] And then I think that, and I'm really sorry to hear that three months after COVID you're still experiencing this. I think that this is also an issue that's not unique even to people who have an underlying condition to begin with because we know that, like with Long COVID now, which has emerged as something that's affected a lot of people, including people who are immuno-competent and don't have pre-existing neurological issues before they get COVID.

[00:19:44] And the basis for that is still not fully understood, I would say, whether there's inflammation, whether there's other kind of processes going on. So, I personally, when I encounter this from a practical perspective,

when we encounter this in clinical practice, my approach would not be to say, “The immunosuppression is not working, let's bump it up or be more aggressive,” because you can also see how that can potentially result in unintended consequences.

[00:20:12] So, an infection led to this immuno-suppressing more being more aggressive, could put somebody at an even higher risk for more severe infections. And so, I think that there's a risk to doing that, but we definitely have to make sure that we're not missing an attack because on the flip side, we know that infections can rev up the immune system, and sometimes we can see attacks occurring in the setting of a systemic infection.

[00:20:36] So, in order to try and distinguish these things, we might do an MRI. The other thing that's very important is whether the symptoms that people are experiencing are completely new, or if they're symptoms that they've had before. Because if this is just a, I'm not saying, I don't mean “just,” I mean, it's obviously—it's causes a lot of symptoms to people that can be very debilitating. But if it is a worsening in symptoms that people have experienced before, it's much more likely that it is a this pseudo relapse that is just the infection, the fever, or the systemic stress that the body is under leading to a worsening.

[00:21:13] But if it's a new symptom, something completely new that somebody never experienced before, then that would be concerning for an actual new inflammatory event that would need to be worked up and treated as such. So, it's quite a complicated discussion. But I think that overall, we have to be careful with overly immuno-suppressing people when we're in these situations.

[00:21:35] **Krissy Dilger:** Okay, thank you. We have another question: “Are there any talks in progress between the US and other countries regarding the future roll out of the new NMO preventatives to those living elsewhere?” This person is in the UK and is just wanting to see if the new therapies might make their way over there?

[00:22:00] **Dr. Elias Sotirchos:** That's a great question. So, I mean, the first thing that I have to say is that is that this is not the way that generally the approval—this is a great question. I'm not actually not familiar exactly with the full landscape of treatments that are available in the UK because I think that it is somewhat separate of course from the other European countries.

[00:22:18] And so, the way that it works in general is that the company, the pharmaceutical company that's the manufacturer of the drug and who typically has sponsored the clinical trial, has to submit an application for the approval of the medication in each country or jurisdiction in which they intend for it to be used. Now, I'm not actually entirely from—so what would have to happen is that the companies, the three different companies that make these now FDA-approved therapies would need to apply to the UK.

[00:22:53] And then the UK would need whoever, like the organization that would be the same as, like, the FDA here, or what's called the EMA, the European Medicines Agency, would need to approve it. And then I think that there's a separate issue, which is that in the setting of a public health care system, there would need to be a decision on whether it would be covered, which is somewhat a separate decision.

[00:23:17] For example, here in the United States, Medicare may decide that it's not worth covering a medication, even if it is FDA-approved. That happened, for example, with one of the recently approved Alzheimer's drugs last year; Medicare said, “We don't think that we would cover it.” So, the NHS would also have to say, “We're going to cover it.” So it's a little bit complicated, but it's more up to the sponsor rather than the US. The actual pharmaceutical companies applying.

[00:23:46] **Krissy Dilger:** Thank you for the knowledge, and SRNA will continue to monitor everything going on with them. And if there is an announcement to be made that these drugs will be coming to more countries. We're

happy to—we'll definitely relay that news to our members. Another question, and I think this was in response to something you had been talking about earlier with the diagnosis, but how do you test for sarcoidosis?

[00:24:22] **Dr. Elias Sotirchos:** Yeah, it's a great question. So, sarcoidosis is a condition that's also inflammatory, and it can affect the brain optic nerves and spinal cord. So, it sometimes can mimic some features of NMO. But in contrast to NMO, it's actually a systemic disease and that it can affect other organs outside of the brain and spinal cord. And actually, the brain and spinal cord are actually only affecting about 10% of people with sarcoidosis. It usually affects—the lungs are the part of the body that's most affected.

[00:24:56] So, generally the approach to working up for sarcoidosis is usually a CT of the chest is really the first line. Sometimes people might get a pet scan, and then there are features on the MRI like in myelitis, for example, that can provide a hint that this is sarcoidosis rather than NMO. There's patterns of how the lesions may look in the brain or in the optic nerve that can also provide some hint.

[00:25:23] But generally, the most common approach is to look for it in the body because if you find it in the body and you can do a biopsy of a lymph node, for example, that shows features consistent with sarcoid, then you can extrapolate that probably what's going on in the brain and spinal cord is sarcoidosis. Because generally, it's a condition that's diagnosed by biopsy, and we generally avoid doing spinal cord biopsies and brain biopsies unless we really need to.

[00:25:54] One thing is that the diagnosis can sometimes be challenging because as I said, 10% of people with sarcoidosis have neurosarcoidosis, where the nervous system is involved. Of that 10%, about 10% might have only the central nervous system involved with no systemic involvement. And in those cases, it can be pretty sometimes challenging to make the diagnosis since you can't do a biopsy of a lymph node, for example, and you have to make the diagnosis by inferring what's going on in the central nervous system based on imaging, based on the spinal fluid findings or even sometimes doing actually a brain biopsy or a spinal cord biopsy. Rarely, we might need to do that, but it's, yeah, generally with imaging is the most common way to make that initial assessment evaluation.

[00:26:43] **Krissy Dilger:** Thank you. Another person asked, “Is there any research showing a prodromal phase with NMOSD, such as depression, urinary issues? Any other kind of symptoms like they're looking for in MS?”

[00:27:03] **Dr. Elias Sotirchos:** That's a great question. I haven't really, I have to say, I haven't seen studies with something like that. Generally, we consider NMO to be—and the reason for that is that in MS sometimes attacks can be very mild, or people can develop lesions on MRI without having symptoms. Generally, in NMO, when there is an attack, it's almost never asymptomatic.

[00:27:26] Like, we rarely see something on MRI without somebody having symptoms. And generally the symptoms are much more severe. So, because of that, I think that possibly not. On the other hand, though, NMO may be associated with other autoimmune diseases. Actually much more than MS. A lot of people with NMO have things like Lupus or Sjogren's syndrome or other rheumatologic conditions.

[00:27:52] And those conditions can definitely cause things like fatigue, depression, anxiety, joint pains, and peripheral neuropathy, and things like that. And so, it might be that if there is a prodrome, it could to some extent be related to concomitant autoimmune diseases rather than the NMO itself, I think is a possibility. But it's also more difficult, I think, to examine just because NMO is much rarer.

[00:28:20] So, a lot of these studies that have looked at the prodromal phase of MS have looked at kind of, I mean MS is fairly common in general, and they look, for example, at large insurance claims databases and

saw that in the years preceding a diagnosis of MS, people were seeing their primary care doctor more, they were having more lab test order because of these non-specific symptoms of fatigue, joint pain, sensory changes, things like that, that were there but not severe enough to prompt the full MS work up.

[00:28:56] But I think that it's definitely an interesting question. I think I'll have to look and see if there's been anybody looking at that. Off the top of my head, I'm not aware of any literature on that right now.

[00:29:08] **Krissy Dilger:** Thank you. And another question I think this person is just asking, "Have you seen any unusual symptoms in NMO such as sleep behavior disorder or chronic nausea issues after hot flashes, not related to menopause?" This is a younger person.

[00:29:29] **Dr. Elias Sotirchos:** Yes, I mean NMO—in addition to the optic nerves and spinal cord, one area that it can affect as I said previously was the part of the brain stem that controls the vomiting center of the brain called the area postrema. And that can result in the syndrome of hiccups, nausea, vomiting. And so, I think that sometimes that that's affected.

[00:29:57] Actually, typically that improves, though, quite well, even on its own. Which is kind of interesting, but sometimes people might be left with symptoms related to the involvement of the brain stem. The other thing that can occur in NMO is that a structure of the brain called the hypothalamus can become involved. This is less common, obviously than optic neuritis and myelitis, but it can occur.

[00:30:19] And when that is involved, people can have sleep disturbances, including something called cataplexy, which is like a loss of muscle tone, essentially that can occur, or falling asleep, the people can fall asleep all of a sudden, so called narcolepsy. Narcolepsy with or without cataplexy when there's a loss of muscle tone as an episode. That can occur from the hypothalamic involvement.

[00:30:50] The hypothalamus also kind of controls temperature regulation in the body. So, involvement of the hypothalamus can sometimes result in body temperature fluctuations as well. So, it is possible that with hypothalamic involvement in people with NMO or people who have that involvement, that they can have those sorts of symptoms eventually.

[00:31:15] **Krissy Dilger:** We have some questions that were submitted ahead of time. So, I think this is a pretty interesting question: "What is being done to raise awareness within the medical profession for ensuring a swift diagnosis?" I know earlier you had mentioned a few present with some of the more like gastroenterology symptoms. You wouldn't even see a neurologist first. Is that improving? Are there efforts being made generally in the medical field to have more interaction between different specialties to get these diagnoses more quickly?

[00:32:01] **Dr. Elias Sotirchos:** Yeah, no, I think that that's really important because I think that making a swift and early diagnosis is the best way to prevent potential long-term disability because we know that initiating a preventive therapy to prevent further attacks can preserve neurologic function. And so, it's very important to have an early diagnosis to ensure that people are [inaudible] on treatment as quickly as possible.

[00:32:24] I mean, in terms of efforts for that, I think that over the years, we are getting better and better at diagnosing it early. First, the tests are much more widely accessible, at least in the United States now—like most labs, all the commercial labs have it available. And so, NMO and MOG antibody testing even—which just really came out a few years ago commercially now—is much more accessible.

[00:32:52] And I think that ophthalmologists have become aware of this. And so, for optic neuritis, they are starting to be sent routinely. So, there are efforts with things like medical conferences with various speaking lectures and things like that in order to educate people. And these are happening throughout the country in communities in order to educate ophthalmologists, neurologists, especially people who are general neurologists who aren't as subspecialized.

[00:33:26] Some of us are large academic centers because they often are the first line who will see these patients in the community. I think other important things that are being done is training fellows or neuroimmunology. People in neuroimmunology who are subspecialists, because there is an increasing need for people who are specialized in neuro immunology in the community.

[00:33:50] Including the SRNA is funding fellows who are undergoing this training and then go into practice. And so, I think that increasing that resource of people who are available to see these patients and have that expertise is also very important. And so, I think there's a lot going on. A lot of the work is actually done also by the pharmaceutical companies who have received the approval for the medications.

[00:34:16] They organize a variety of meetings and conferences in order to organize talks and lectures for people in the community because they are also interested in getting people diagnosed with NMO promptly as well. And so, I think that there have been a lot of efforts, and we have come quite a way since 2004 when the aquaporin-4 antibody was first identified, but there's definitely still more work to be done.

[00:34:48] **Krissy Dilger:** Thank you for that insight. And I know that that's good to hear for most people who unfortunately didn't receive a quick diagnosis and how much damage that can potentially do. Someone asked, “Why might TM lesions not show up on an MRI in someone with NMO? Could it just be that the MRI machine is not sophisticated enough, especially if repeat MRIs are always done in the same scanner for comparison over time?”

[00:35:21] **Dr. Elias Sotirchos:** Yeah, it's a great question. We encounter this sometimes in clinical practice, I think. The one thing to realize is that, for this imaging, the spinal cord is actually much more tricky than imaging the brain and other parts of the body in general because the spinal cord is actually pretty small. The other thing is that it's not really that stable, it's kind of floating to some extent inside a fluid with spinal fluid around it.

[00:35:48] And so, what happens is during the MRI even a little bit of movement can make sometimes things more difficult to see because there's motion artifact. And even if a patient is absolutely still, there is still to some extent movement because the spinal cord is located right next to the heart, right next to the lungs. When you take a breath, everything is moving to some extent.

[00:36:12] And so, it's sometimes difficult when something is very small to see it on a spinal MRI, just due to sometimes these technical factors. And so, it's rare, but sometimes we have seen people where, the clinical exam, everything is very clearly consistent with myelitis. But the MRI doesn't clearly demonstrate a new lesion. And so, sometimes it's just a technical issue. Sometimes, I mean, there's disagreement, and I mean, sometimes I might say, “I think there's a lesion,” but the radiologist might not be convinced, and there is a subjective interpretation issue, I think, as well.

[00:36:52] I have to say in aquaporin-4 positive NMO, that would be very, very rare to see somebody with transverse myelitis without a lesion on the MRI. Just because in NMO typically the lesions are relatively large

and extensive. We tend to see that more—still rare, but more—in MOG antibody disease, to see MRI negative myelitis. Although again, even there it's rare, but it occurs somewhat more frequently than in NMO because sometimes the lesion can be shorter or it can involve what the grey matter only. And if there's even a little bit of motion artifact, that can obscure the lesion.

[00:37:40] **Krissy Dilger:** We had two separate questions, but I'm going to try to combine them into one. So, someone asked, "What are some of the potential side effects of taking treatments for NMOSD? What are some things to consider when deciding what treatment or medications might be right for me?"

[00:38:00] And then someone also asked, "How are data being collected and reported on in relation to the success of recently approved specialist preventative treatments for NMO?" So, I guess, can you just speak to, like, what the difference, what someone else who's deciding which treatment to take might decide on that and how the effectiveness of the treatments are being reported on?

[00:38:30] **Dr. Elias Sotirchos:** It's a really important question. I think first of all, now there are again, three FDA-approved therapies in the United States that I went over previously. The names are Soliris, Uplizna, and ENSPRYNG. And then there are still many people treated in the United States and around the world with the generally the most common, I would say, is Rituximab, as well as some of the oral immunosuppressive medications like CellCept, also known as Mycophenolate, and Imuran, also known as Azathioprine are commonly used.

[00:39:07] And one more would be something called Tocilizumab, or Actemra, which is very similar to ENSPRYNG, so that we can kind of lump together with the main difference, I'd say, being the way that it's administered. But overall, the mechanism of action is very similar. I have to say the decision for which treatment is started is a rather complicated discussion because I don't think that—there's no right answer.

[00:39:32] It's not like, "Everybody should go on this one because it's better quote unquote." I would say that in our experience and by looking at the clinical trial data and our experience with some of the off label therapies, like Rituximab generally all of these treatments are rather effective. I would say that some of the oral immunosuppressive might have fallen a little bit more out of favor, especially with the recent options being available.

[00:39:55] Things like mycophenolate and Azathioprine might be used less commonly now. But to some extent, all of these medications are quite effective. It's rather rare for us to see relapses with the FDA-approved therapies and people who are being treated consistently and receiving the medication as indicated, as well as with Rituximab. On the other hand, all of these medications, as any medication, have potential side effects.

[00:40:21] Now the main types of side effects that we're looking at are infections in general, because all of these medications act on the immune system in one or a different way. And so, that risk is across the board with all of them, but it can be different in terms of what types of infections people are at a higher risk for and what people can expect, for example, a thing like vaccine responses because some of these medications can impact vaccine responses.

[00:40:56] And so, it's a very complicated discussion, I would say, overall. I think that it's important to sit down with the patient and go over the medications. And also I think the first thing I think that I have to discuss with patients is the route of administration and whether that's something that would fit with their lifestyle, or work with their personal life.

[00:41:20] Because again, all of these are mixed a little bit differently. We have medication or infusions every six months versus medications that are self-administered as an injection once a month versus the medication that's an infusion every two weeks, for example. So, they're quite different in the route and frequency of administration.

[00:41:39] So, I think that that's an important issue. I mean, then there are a lot of other things that might put them at risk of infection, like a preexisting immunodeficiency, like we were discussing previously, or if somebody's more advanced in age because then the risk of an infection might be potentially higher, as for example, with COVID, as we know where the risk of severe COVID is quite correlated with age.

[00:42:08] So, it's a difficult discussion, but I think that there has to be shared decision making and a lot of considerations end up going into it. I'm sorry, am I forgetting the second part. Was there a second proportion of the question?

[00:42:26] **Krissy Dilger:** It was just, "How is the effectiveness of this data being collected?"

[00:42:33] **Dr. Elias Sotirchos:** Like marketing surveillance, yes. That's a great question. I think to some extent there are now some registries, for example, where people are prospectively collecting data on people who are being treated with these treatments in the real world and assessing outcomes. We're doing this ourselves as well. Looking at people with NMO and looking at outcomes, infections, all of these things long term.

[00:43:04] There are other ways to do this as well. People looking into these insurance claims databases that I mentioned previously, where especially in countries that have also public health systems, it's easier to look at this because they have kind of lists of what medication everybody's on, if they were hospitalized at any point with infections or things like that.

[00:43:24] We've seen that a lot coming from Scandinavian countries sometimes, where they have a single health care system and they can look at infection risks and hospitalization for relapses and things like that. But also, there are these post marketing surveillance studies that are being done where often where the people who are enrolled, for example, in the clinical trials are continued to be followed after the main phase of the clinical trial has ended.

[00:43:55] There are a variety of studies that have spun off from the clinical trials where people with NMO who are on these treatments are being followed longer term to see what happens. And if they if relapse, they monitor for risks and infections and all of that information as well. So, there are definitely efforts on going to look at that.

[00:44:19] **Krissy Dilger:** And then we did have two separate people ask about this. And I know it's kind of a typical question and we are near the end of our time. So, I want to go out on this question. Basically, both people were asking about a cure. So, what would that look like for NMOSD? How close are we? Repairing the myelin sheath—is that something that is possible? And we're just curious about your thoughts. I know that there's no cure right now. But just what do you think about the future for NMOSD?

[00:45:02] **Dr. Elias Sotirchos:** Yeah, I think that that's a great question. I think that cure can have multiple meanings here. I think that there are two facets I think to that question. The first, for example, for a cure would be something that you give once and it re-educates the immune system in a way that somebody is cured in terms of that they're not at risk for further attacks.

[00:45:27] So, that's, I think one part of a potential cure. The second part of a cure that I think was what you were alluding to in the latter part of the question was that, can we actually repair the damage that's been done? Which is kind of, I think these are two distinct questions to some extent, because one is more of an immune issue, like stopping the disease process from occurring and stopping the attack from occurring again.

[00:45:53] By the way, we're rather good at this now, I would say, with the medication we have. The problem is that you can't really stop them because we know that, and we've seen this, that if these medications are stopped, the disease can come back, and people can have more attacks. So, I think that for the first, which is kind of the cure in terms of preventing new attacks from happening, I think that there, we're likely closer, potentially.

[00:46:21] And there are efforts ongoing in terms of ways to re-educate the immune system, tolerization strategies to kind of, it's a similar concept to what might be done and people have like a, it's more complicated, but I'm just saying like akin to something that people might—who have a penicillin allergy, and then they're being desensitized to that for people who have a pollen allergy and they're being desensitized to that.

[00:46:44] But in any case, somehow to tolerize the body to aquaporin-4, for example, and try to prevent the immune system from attacking aquaporin-4 or trying to wipe out only the bad B-cells that are attacking aquaporin-4 in a very selective manner rather than what we're doing now, where we're attacking them all with Rituximab or Inebilizumab and trying to do that.

[00:47:08] So, I think that there are a variety of things on the horizon. But I think that everything is relatively early stage, and drug development can be somewhat slow because we have to make sure that something is safe and effective before it's released in the market. And that typically requires a large clinical trial that can take years to complete in order to prove that effectiveness.

[00:47:29] The second part of the question, I think, gets to repair, and that's obviously, I think, that's very, very important. And that's something that unfortunately, we don't have any treatments right now really to augment repair. There is some natural repair that occurred. We know that people have a relapse, and they have severe vision loss, for example, from optic neuritis, and that gets better when we treat with steroids and plaques.

[00:47:59] And we even sometimes spontaneously, but that's more the body healing or remyelinating or doing stuff like that. The body can do that on its own to some extent, but we know that the process is not complete. And so, there are a lot of efforts going on. There's a lot of efforts for this and other diseases, as well as multiple sclerosis to look at remyelination.

[00:48:20] I do think that anything is possible, and there are a lot of potential drugs or approaches that have been proposed to be remyelinating and neuroprotective. I think that it remains to be seen. And there are trials that need to happen in order to show that. But I think that it definitely is possible, but I think that all of these things are at a relatively early phases of research right now. And so, it can take several years from that stage in order for something to actually reach the market and become available to people but I'm optimistic.

[00:48:57] **Krissy Dilger:** Awesome. Well, we've reached the end of our time, I believe, today, but thank you so much for joining us and answering our questions. And we did record the session, so I believe we'll be putting it in our resource library for anyone who wants to view it. And just thank you so much for joining us.