Pediatric NMOSD | Part 1

History and Diagnosis

You can listen to the audio of this podcast at: https://youtu.be/Pn4AokvyEdU

Intro: [00:00:00] ABCs of NMOSD is an education podcast series to share knowledge about neuromyelitis optica spectrum disorder, or NMOSD, a rare relapsing autoimmune disorder that preferentially causes inflammation in the optic nerves and spinal cord.

[00:00:22] ABCs of NMOSD podcast series is hosted by SRNA, the Siegel Rare Neuroimmune Association and in collaboration with the Sumaira Foundation for NMO, The Connor B. Judge Foundation and Guthy Jackson Charitable Foundation. This education series is made possible through a patient education grant from Horizon Therapeutics.

Rebecca Whitney: [00:00:51] Hello and welcome to the "ABCs of NMOSD" Podcast Series. "ABCs of NMOSD" is made possible through a patient education grant from Horizon Therapeutics. Horizon is focused on the discovery, development, and commercialization of medicines that address critical needs for people impacted by rare, autoimmune, and severe inflammatory diseases. They apply scientific expertise and courage to bring clinically meaningful therapies to patients. Horizon believes science and compassion must work together to transform lives.

[00:01:32] My name is Rebecca Whitney from the Siegel Rare Neuroimmune Association, and I recently had a conversation with Drs. Jayne Ness and Silvia Tenembaum on "Pediatric NMOSD – History and Diagnosis."

[00:01:45] Dr. Jayne Ness is professor of pediatric neurology at the University of Alabama at Birmingham (UAB). She has directed the UAB Center for Pediatric Onset Demyelinating Disease since its founding in 2006. The center is based at Children's of Alabama, the children's hospital adjacent to UAB's medical center. Dr. Ness has been involved in clinical trials for pediatric NMOSD and she is especially interested in long-term outcomes of children and adolescents with demyelinating disease.

[00:02:16] Dr. Silvia Tenembaum is a pediatric neurologist who received her MD with honors from the University of Buenos Aires and acquired further training and certification in pediatric neurology in Argentina. She serves as Associate Professor and Chief of Clinics at the Department of Neurology, National Pediatric Hospital Dr. J. Garrahan, a tertiary referral pediatric hospital in Buenos Aires, Argentina. Dr. Tenembaum is the Director of the Pediatric Neuroimmunology Program at the same institution. She has had a longstanding interest in a wide range of CNS neuroimmune disorders with pediatric onset and has established a Comprehensive Care Clinic for children and adolescents with multiple sclerosis, neuromyelitis optica, acute disseminated encephalomyelitis, MOG antibody associated disease, autoimmune encephalitis, and related disorders.

[00:03:11] Her research interest focuses on the identification of novel biomarkers of autoimmune neurological disorders in children, the identification of clinical and neuroimaging characteristics of pediatric multiple sclerosis, and autoimmune disorders targeting AQP4 and MOG antibodies, and optimizing treatment approaches for children with these diseases.

[00:03:34] Welcome, Dr. Ness and Dr. Tenembaum, and thank you for joining us today. We are here to discuss the pediatric NMOSD. Dr. Ness, if you want to start us off with just a brief history of NMOSD in children? Maybe when was it first recognized in kids?

Dr. Jayne Ness: [00:03:56] I think that we have not recognized it in children as early as we did in adults. And then, in adults, NMOSD was recognized in the mid 1800s. I'm not going to have the exact date, Silvia, if you've got it there, but and then it was, you know, identified by Dr. Devic and, actually, I believe it was his student, as being the combination of both eye and brain involvement.

[00:04:25] And the first case in children, I'm actually not entirely sure when the first case in childhood was. I think it was in the mid 1960s, but I'm going to, Silvia, do you know for sure? That's one part I didn't get looked up.

Dr. Silvia Tenembaum: [00:04:40] I looked for that, and I found that the first published case was in 1995. And, actually, that was a young girl, aged 11, described as a pediatric MS, previously diagnosed as having ADEM. But, looking at the images and the clinical phenotypes of relapses, this young girl had NMOSD.

[00:05:05] So, the title of the paper was, "A Pediatric MS Case Previously Diagnosed as ADEM," but actually that was an NMOSD case. And in 2000, there was an additional pediatric case at four years of age from Rabat, Morocco.

[00:05:24] But I have to look to Jock Murray's book, Multiple Sclerosis: The History of the Disease. And there was the story of Ludwina of Schiedam in Holland that was considered the first MS case, that was a pediatric case in a younger of 16 years. And I'm sure that was an NMOSD case, because she started with a spinal cord involvement and left her with a paraparesis with severe spasticity.

[00:05:57] And after that, some episodes of visual loss, so optic neuritis involvement, but with no recover. She was blind in one of the eyes. And this is not the typical evolution of the optic nerve in an MS patient. So, I think that Ludwina of Schiedam in Holland is the first pediatric one, and that was exactly 1380.

Dr. Jayne Ness: [00:06:23] Wow. Yeah, I think a number of cases that we have, you know, called quote, quote, ADEM, or quote, quote, you know, then MS when we finally felt brave enough to call kids with MS. I think in retrospect, they'd be diagnosed as NMO.

Dr. Silvia Tenembaum: [00:06:41] It is evident of many pediatric neurologists around the world before those first published cases, including me in Argentina and Jayne in Alabama, United States were diagnosing, and we were treating children with a clinical picture resembling something that adult patients had like NMOSD. Although we were not publishing those cases, but we were discussing experiences in the meetings with expert colleagues, and we were treating those kids as if they were NMO.

[00:07:16] Later, we had the opportunity to request for the NMO-IgG test and serum and confirm if those cases have actually the antibody positivity. The first published characterization of NMOSD-IgG seroprevalence in pediatric patients was published in 2008. There was a paper with, we wrote with Brenda Banwell where 87 pediatric patients and Dr. Vanda Lennon offered to test all these kids.

[00:07:55] Most of them were from Buenos Aires. So, our teen NMO patients were included in addition to 14 patients with optic neuritis, 13 with transverse myelitis, 3 ADEM patients with longitudinally extensive transverse myelitis, and 41 MS cases. And Dr. Vanda Lennon blind tested all of them with the test she had just discovered. And seven out of the nine NMOSD patients who were relapsing, showing relapsing disorder, were positive for the test. Some of the optic neuritis patients as well, and a single patient with a transverse myelitis.

[00:08:37] None of the pediatric MS patients. So, that was the first published characterization, published in a cohort of children with NMO, with the Mayo Clinic, with Vanda Lennon performing, herself, the test in those kids. That was a wonderful experience.

Rebecca Whitney: [00:08:58] Thank you very much.

Dr. Jayne Ness: [00:09:00] That was a seminal paper.

Rebecca Whitney: [00:09:01] And how common is it to see NMOSD in children? And how does it compare to the other rare neuroimmune disorders like TM, ADEM, MOG that we are now aware of? And also, as compared to pediatric MS? Dr. Ness, go ahead.

Dr. Jayne Ness: [00:09:20] So, that is actually something I did actually look up ahead of time that is there, I think one of the nice papers looks at, there's papers from Denmark, Korea, Taiwan Germany, Austria. And then, then many of these are also reviewed by Dr. Tenembaum and Dr. Yeh, that they've just published this paper, that, you know, the incidence ranges from, you know, 0.05 to 4 per hundred thousand patient years or per year, and the prevalence is 0.5 to 4.4 per 100,000, actually it'd be patient years.

[00:10:04] And, and where in comparison, MS, you know, in some of the papers we looked at, some of the, in others, the specific studies, for example, in Denmark can be, MS can be five times more common, five to 10 times more common. So, they're rare. I mean, very, you know, one per 100,000 person years. But it can be, you know, if, if you've evolved, you know, would be at for a max of, you know, MS, or even a half of that, and then children are, you know, children with NMOSD are perhaps a fifth of that. So we're really talking one, do the math, you know, one in a million, one in, one in 500,000. Silvia, would you, have I done my math right?

Dr. Silvia Tenembaum: [00:10:54] No, I, I think that there is a difference if we compare North America, for example, with South America. So, there is a race difference. That's the reason that, yeah, in the Canadian cohort of Brenda, there were only three NMOSD cases and the rest, the 17, were from Argentina.

[00:11:16] So, the disorder is much frequent here in South America because we are not Caucasian. We have European ancestry, but we have a mixture with natives, so we are mestizos with rather more darkened skin. And in Brazil, for example, more Black population than in Argentina. So, it's even more frequent in Brazil than in Argentina. But generalizing, in South America, there is more prevalent than in North America, because this is exceptionally seen in Caucasian NMOSD. It's more frequent in mestizos or Black population and in Asian population, that's the, high frequency in Japan and South Korea.

[00:12:04] So, I think that we should, we cannot give a fixed number if we not related that number within the geographic location of the cohort, for example. In my pediatric cohort, I work in a pediatric hospital, NMOSD patients are three to one, compared with MS patient. It's less frequent. Multiple sclerosis is more frequent than NMOSD. That's interesting. I think it's a different ratio in North America, for example, Canada or United States.

Dr. Jayne Ness: [00:12:39] Could I have you, so did you just say that your, it was three to one, it was three MS to one NMOSD or the other way around?

Dr. Silvia Tenembaum: [00:12:47] Exactly. Yeah.

Dr. Jayne Ness: [00:12:48] Okay. Okay. I just wanted to, because again, that's, that is striking. And again, I would say that we, you know, it is not... So, in our population, that's, from Alabama, that's about 25% African American across the south that are the numbers that, you know, we probably have two MS to one NMOSD.

[00:13:13] If you have the whole spectrum, you know, that fulfills the 2015 criteria. You know, you know, so it's still, it's still more MS, but, you know, NMOSD is not as rare as everybody tells us it is. Certainly, it's more in African Americans.

Dr. Silvia Tenembaum: [00:13:33] Yeah.

Rebecca Whitney: [00:13:34] Very interesting. Thank you. Moving on to some of the diagnostic information related to NMOSD. As far as what you may see on the imaging, what you find in your clinic exams and also pathologic findings, what we do through the different tests. Do you find that they're different in children than what is in adults? Does it differ by age of the child? If it's a very young child with longitudinally, extensive transverse myelitis versus a 13-year-old who may have an onset of optic neuritis, can you talk a little bit about that?

Dr. Jayne Ness: [00:14:17] So first of all, for full disclosure that I see only children, you know. We see them up until 18, and so I really have limited adult experiences since I've completed my training. I mean, we certainly meet with our adult neurologists and have conferences. So, I'm not, you know, so I'm not going to have the clinical experience to answer that smartly. But the presentation I think often in younger children can include more encephalopathy than the older, than the, you know, even, you know, teenagers and, and certainly adults. And I think that can make it really challenging to under-, you know, and especially a very young child who may be encephalopathic or are they just, you know, do they hurt? You know, are they, you know, that they can't communicate to you. It can be very hard to, to identify even where all the, even where all the lesions are.

[00:15:12] I mean, one of the things I trained our residents is that, you know, if you suspect demyelination, you have to scan from stem to stern because you may have silent optic nerve lesions because a child can't tell you that they can't see. Or they may have, we certainly identify kids with spinal cord lesions that fulfill criteria for neuromyelitis optica, but they weren't moving much in bed, and they were, you know, it was, I don't think anybody would necessarily identify them initially as having a cord lesion if, you know, because they were just so irritable and didn't feel good. So, I think it's the age that often makes it more challenging.

Rebecca Whitney: [00:15:52] And how about you, Dr. Tenembaum? Do you have some experience with adults that you would like to discuss?

Dr. Silvia Tenembaum: [00:15:58] No, because I work in a pediatric hospital, the same as Jayne, but I learn from the other colleagues showing in the meetings and experiencing results and the publications. And what we saw in the paper I mentioned with Brenda Banwell, and what I am seeing now with the evaluating all my pediatric cohort, that the single most useful diagnostic feature associated with NMOSD in an adult patient, and which have the distinction from MS, is the longitudinal, long involvement in the spinal cord.

[00:16:38] And that is less predictive for NMOSD in children than in adults, because more frequently they start with an encephalopathic picture like Jayne described or with an optic neuritis, uni- or bilateral involvement of the optic nerves. And only when they grow up, they may show the typical longitudinal spinal cord involvement or within the relapses are showing that when they suffer from relapses of the disorder. It's different from the other biomarker, which is the MOG-IgG - myelin oligodendrocyte glycoprotein - that in a small number of children, may develop a disorder resembling NMOSD. So, the brain involvement is more frequent, particularly in the younger patients, more frequent than in AQP4-IgG positivity.

Rebecca Whitney: [00:17:37] Great. And are children more likely to be AQP4 positive NMOSD versus AQP4 negative? Do you see a difference there?

Dr. Silvia Tenembaum: [00:17:49] In my experience, they're very more frequent, the seronegative for AQP4. It's exceptional that children with NMOSD, who fit all of the diagnostic criteria to be AQP4 seropositive.

[00:18:04] I think it's less than 10, 8 to 10% of my cohort. So, it's more frequent that they are seronegative and probably 60% of those seronegative or more. But there is still a good number of children with double seronegative results. And I think that's amazing because there's still some auto antibodies that are waiting to be discovered.

Dr. Jayne Ness: [00:18:35] Yeah, absolutely.

Dr. Silvia Tenembaum: [00:18:39] And it's different from adults. Adults, 90% of NMOSD fulfilling 2015 diagnostic criteria will be seropositive for AQP4-IgG antibodies. And that's not the finding we have in children. That's a striking difference.

Dr. Jayne Ness: [00:18:56] So, actually I want to ask the question is how many, and this may be preempting what you were going to ask, is how many children end up seroconverting after initially, in your experience, after initially being negative? Do you have many that have seroconverted later, you know, they were pre-pubertal and then later in puberty?

Dr. Silvia Tenembaum: [00:19:18] I have none patients seroconverting from seronegative to seropositive for AQP4. And I have two or three children starting seronegative for and becoming seropositive after the second or third relapse. Those who were seronegative from the start to AQP4-IgG antibody still were seronegative during the follow up, even having suffering from relapses.

Dr. Jayne Ness: [00:19:48] Interesting. Because we've, we've experienced the same with the, with the NMOSD, for the aquaporin-4 antibody, that I haven't had anybody seroconvert. But I also wondered because some of these children I have on rituximab and so I don't entirely trust that result.
Dr. Silvia Tenembaum: [00:20:09] You're absolutely correct. After starting immunosuppression, I don't test any more the antibodies, because I'm not going to get a positive result or useful results. You are absolutely correct.

Dr. Jayne Ness: [00:20:23] Although interestingly, we've had, you know, when the MOG antibody became more widely, commercially available from Mayo, I did have patients who are, you know, "seronegative" - if you could see me do my air quotes - and then ended up becoming MOG, you know, but were found to be MOG positive. So, rituximab doesn't wipe out all the MOG, but I've seen it wipe out aquaporin-4.

Rebecca Whitney: [00:20:44] Interesting, good to know. That was a question I did have listed, is if those immunosuppressant therapies do impact the levels of the antibodies. So, thank you very much for bringing that up. Is there a general age range for when NMOSD is diagnosed in children? Can it happen in an infant? Are there known triggers that may be that initial attack in NMO?

[00:21:09] And I know we talked a little bit about race and ethnicity and that being a factor in the number of NMOSD diagnoses. Are there other possible predispositions to a child having NMOSD, like a family history of autoimmune issues or MS? Dr. Ness, do you want to start us off on that one?

Dr. Jayne Ness: [00:21:32] So, there is some data from the US network that children with autoimmune, demyelinating disorders, including NMO, have a higher frequency of family members with autoimmune disorders, not necessarily all demyelinating, but can also have, you know, some family history of lupus,

that's probably the one that I see the most frequently. So, there probably is, there is definitely some genetic predisposition.

[00:22:02] There is probably that, certainly in MS, there's talk about the Epstein-Barr virus. You know, history of having had that to the point that if a child is negative for the Epstein-Barr virus, it's almost something that you need to think about, like, are, is there something else than MS. And then there's a question of, you know, are there preceding, you know, what people worry about immunizations.

[00:22:26] We haven't seen anything in our own group that really specifically acts as a trigger, that I've been able to associate, you know, that we've been, you know, these are small numbers, so it's hard to, you know. But I don't think that's it, you know, immunizations sound pretty reassuring. And it's often, you know, is there other viral triggers? Certainly, I think, you know, there is, probably your genetic and, you know, ethnicity is probably your biggest predisposition. But we're still talking about an extraordinarily rare disease that, you know, on the back of the napkin numbers.

[00:22:58] And even when there's you know, aren't good epidemiologic studies, you know, even one less than far, far less than one in 100-, you know, 1 in a million.

Rebecca Whitney: [00:23:05] And as far as when you are seeing this come up in children, what age does it typically happen? What do you see? Dr. Tenembaum, what is your experience with diagnosing?

Dr. Silvia Tenembaum: [00:23:17] For the beginning of the disorder, it's more frequent around the age of, from 10 to 14 years of age, probably. That's the interval where most cases are seen, are being seen. And looking for the youngest, it was 18 months of age, a single one.

[00:23:40] And after that, we're at 21 months, probably three or four kids. And above the age of two, more frequent. But I think the peak is between 10 and 14. Under that age, there is the same prevalence looking at girls and boys. And in adolescence of post-puberal patients, it's more frequent in girls.

Dr. Jayne Ness: [00:24:04] I agree. The peripubertal age, that 11, 12, 13, is really prime for developing NMO, and the older kids, older than that, it tends to be MS. Younger than that, it tends to be ADEM. And the MOGs we're still figuring out.

Rebecca Whitney: [00:24:24] We're still trying to get to the bottom of that, yes.

Dr. Silvia Tenembaum: [00:24:27] And for adult patients, a female sex is the strongest risk factor. So, that's from the female predominance that the female sex is the more powerful risk factor. It's amazing.

Dr. Jayne Ness: [00:24:42] Yeah, post pubertal. I mean, there's a very strong change after, you know, in our post pubertal kids. And I would also say that, and, for us, you know, ethnicity you know, that NMOSD is more common in our African American patients. And I think that is, that yeah, in our older, older patients are even more strong, you know, like 90%.

Rebecca Whitney: [00:25:04] Thank you very much. And after you're seeing these children, as they present with the symptoms of any of these rare neuroimmune disorders. What are some of the differentiating characteristics that you may look for, whether it's in imaging? Obviously, we do have the AQP4 antibody that we can test for. But how else are you differentiating between the ADEM, the TM, and the MOG for a child with NMO?

Dr. Silvia Tenembaum: [00:25:31] Well, we are making a mixture between what are syndromes or presenting syndromes, which are signs and symptoms that a child might present at the first event, with final category diagnostic, which is ADEM or MS or NMOSD.

[00:25:49] So, at the beginning, optic neuritis is not a diagnosis. It's just referring to the involvement of the optic nerves with something that may be inflammatory. The same for the spinal cord involvement we name transverse myelitis. And the same for an acute encephalopathy with something in the brain MRI.

[00:26:10] And we thought, why taught, we named that an ADEM, an acute disseminated encephalomyelitis. Those are just syndromes and may reflect different diseases. So, a brain MRI is quite different in a kid with multiple sclerosis, compared with the findings you may see in a kid with NMOSD due to AQP4-IgG antibodies or brain involvement in MOGAD, so in MOG antibody-associated disease. Very different. So, more inflammatory, large in the AQP4 and MOG, in the immune-mediated disorders, and smaller and with very clean borders, very well-defined borders, and with a location periarticular in the MS group. So, the brain MRI may be very helpful to think different things. Optic nerves, very different.

[00:27:12] More frequently, they're bilateral involvement in kids, loss of the visual acuity. First in one eye, and very quickly in the other eye. Or simultaneously bilateral, that's more frequent in AQP4 and MOG, and it's exceptional in MS. In MS, it's more frequent involvement of single eye, only one eye. And the MRI is very different as well. In the AQP4-IgG, you may look at the chiasma, the posterior part the optic nerve is emerging, or go into the orbit, and there maybe the involvement of the AQP4-IgG antibodies.

[00:27:53] And in MOG -IgG-mediated disorders, you are going to see more an anterior involvement of the optic nerves, and in the fundoscopy, you will see the edema of, of the papilla. This very exceptional in an MS case. So, the immune-mediated disorders, AQP4 or MOG, are quite different from the brain MRI or the orbital MRI from the kids having or suffering from multiple sclerosis.

[00:28:23] And when looking at the spinal cord, the difference is great, because in MOG or AQP4-IgG are going to see longitudinal extensive spinal cord involvement. So, more than three, four, or five spinal segments with a huge inflammation. And in multiple sclerosis, and the same thing with adults with multiple sclerosis, you will see a short spinal cord involvement, no more than one of two spinal segments.

[00:28:52] That's a huge difference. And looking at the difference between AQP4 and MOG, children with MOG more frequently have bladder control involvement and may be left with neurogenic bladder, because the conus is usually involved in the MRI. And that is not so frequent for AQP4. On the contrary, in AQP4 you will see more cervical, upper cervical involvement going into the middle back. So, the vomiting and nausea or hiccups is another frequent clinical presentation in teenager or adult patients with AQP4-IgG NMOSD. It is the area postrema syndrome. And it's exceptional in MOG and very frequent and suggestive of the diagnosis of NMOSD with AQP4-IgG antibodies.

[00:29:46] So, you can see the pros and cons from the MRI, the clinical point of view between the three disorders, in NMOSD with AQP4-IgG antibodies, MOGAD -the spectrum of MOG antibodies-, and multiple sclerosis. Very helpful to differentiate the three. In addition, too, may be able to differentiate from sarcoidosis, lupus with spinal cord involvement, infectious conditions involving optic nerve or spinal cord.

[00:30:17] In children, we have a wide range of differential diagnosis, and we are forced to, going across all that list of differential diagnosis to get the final diagnosis of an autoimmune disorder or immune-mediated disorder, allowing us to start an immunotherapy.

Dr. Jayne Ness: [00:30:36] And I would, I agree with you completely, Silvia. That's a very similar, you know, you get this feeling for them. Although, I think the other thing I would like to add is that seeing that clinical outcome over time, I mean, just even after the first attack is, you know, so a child who has a pretty fixed visual loss is often going to be an aquaporin-4 positive. And so that will often be an important clue to, you know, just how, it's the optic neuritis is much more severe.

[00:31:09] And then, you know, follow-up of the lesions, both the aquaporin-4 and the MOG positive, you know, MRI lesions will, you know, be big and fluffy and look horrible and then will often resolve. You know, whereas the MS lesions, you're not going to, you know, you're going to have something, you're not going to lose all your spots.

Rebecca Whitney: [00:31:25] Thank you so much. And with the AQP4, and we touched on this a little bit earlier, but, if they are negative, you're typically not retesting for that later, especially if they are on immunosuppressant therapy, or are you testing for that? And if so, at what time would you test again? And if they are positive, do you continue to do follow-up tests for that? And are there the possibilities that a child can test positive for both the AQP4 antibody as well as the MOG antibody?

Dr. Jayne Ness: [00:32:01] So, I think first, you know, now we test for both after it both MOG and aquaporin-4, after the first attack. And I will, you know, repeat a year later for both, if they're negative, and then I'd like to try and repeat after puberty. And then, of course, you know, if it's a child who's put on rituximab, my hopes, you know, are low, but I try to get at least get, you know, if it's a pre-pubertal child, I'd fine check later.

[00:32:32] Once they're positive for aquaporin-4, I have not been repeating the titers. I don't find them helpful. And I'd also like to mention we're only looking in serum, not in CSF. I think, you know, our residency in trying to be really complete, we'll try and get from everything. So, I'll only get it from serum. And if they're positive for NMOSD, I stop checking.

[00:32:55] With MOG I'm still a little bit on the fence about how to manage this. There are people who are checking every six months. I'll try and check every year or so, just to see where they're going. There's some people who say, you know, it's helpful following them over time and I am waiting for more data. I'm on the fence about that. Silvia, how do you manage these positive or negative antibodies?

Dr. Silvia Tenembaum: [00:33:18] Okay. Unfortunately, when we receive a patient with the acute event, we have not the results very quickly. So, we have to manage the patient unknowing

Dr. Jayne Ness: [00:33:31] Right.

Dr. Silvia Tenembaum: [00:33:32] the real serious status of the patient. So, we focus on the acute therapy, trying to recover the patient as much as possible. We use a lot of plasma exchange, but people believe this was a severe spinal cord or optic nerve involvement, first to steroids and, after that, plasma change directly.

Dr. Jayne Ness: [00:33:54] Yes.

Dr. Silvia Tenembaum: [00:33:56] If I have the more or less quick result with an AQP4-IgG positivity, the child, after the plasma has changed, it's going to start directly with immunosuppression because AQP4-IgG positivity is indication of relapsing disorder, a severe relapsing disorder. So, if I have that result and I could recover the neurological deficit after plasma exchange, I am forced to start immunosuppression right away. So, I started with rituximab soon after the first clinical event. As Jayne mentioned, it's not the same for MOG antibodies because most children started to decrease the titer in zero.

[00:34:41] After the first event, if they are seropositive, they may show the decrease of those antibodies between 12, 18, or 24 months. So, many children may stay or remain as monophasic disorder or disease and there is no need to start immunosuppression. And very frequently, if they are going to have a relapsing disease, they may show an increase again of the antibodies many years after the first event.

[00:35:16] So, there is a tricky, the MOG antibodies. So, after the first event, I never start immunosuppression. Maybe I prolong or give the oral steroids for three or four months and, after that, to take them away and wait and see what happened. If they relapse, even not knowing if they have again seropositive MOG antibodies or seronegative, I should start immunosuppression, with exception of the relapsing forms of ADEM because ADEM is frequently the first event in the young children with MOGAD.

[00:35:58] The more frequent relapsed phenotype is optic neuritis after the first ADEM. That is named ADEM ON or multiphasic ADEM. Most of the multiphasic ADEM are MOG positive. And probably there is no going on a third clinical event or fourth. No, children have the second clinical, the first relapse, and nothing else.

[00:36:26] So, I would be careful with that relapsing subtypes. But the rest, relapsing optic neuritis, relapsing spinal cord involvement, fulfilling NMOSD criteria, looking at the clinical and MRI phenotypes of relapses, all those MOGAD patients should start immunosuppression.

[00:36:48] After you start immunosuppression, there is no way to test for the antibody serum because you have a great chance of have a negative result. So, I don't request that test after studying immunosuppression because is that were a decided treatment, if I had decided to start rituximab, no way. Okay.

Dr. Jayne Ness: [00:37:12] So, Silvia, how often are you checking MOG antibodies?

Dr. Silvia Tenembaum: [00:37:15] In every kid with an optic neuritis, with a spinal cord involvement, with a brainstem syndrome, with ADEM.

Dr. Jayne Ness: [00:37:24] But at the beginning, absolutely, everybody's getting MOG because that's the most common positive antibody that we get back in our population.

Dr. Silvia Tenembaum: [00:37:32] Yeah.

Dr. Jayne Ness: [00:37:32] But, once it's positive, how often are you following MOG antibody titers?

Dr. Silvia Tenembaum: [00:37:39] If it is a positive, I follow by clinical and MRI. If there is no relapse, one, two three years after the first event, I don't check again, the MOG.

Dr. Jayne Ness: [00:37:50] Okay.

Dr. Silvia Tenembaum: [00:37:50] I'm more confident of the clinical and the MRI evolution than the test. In addition, in my hospital, they are not free. They shouldn't have to pay for the MOG because it's

Dr. Jayne Ness: [00:38:02] Right.

Dr. Silvia Tenembaum: [00:38:03] laboratory results inside my hospital and it's a very expensive study. Here, in Latin America, it's different. We are happy that we have one private institution that performs the test. Many countries in Latin America are not available to these kind of laboratory studies. That is a difficult that we have in Latin America, and I think that many other countries in the world.

[00:38:27] So, there is not so frequent that you have access to, in particular with MOG, the best assay, which is the cell-based assay, that is exceptional because many countries have the commercial kit for MOG and you don't have titers in that way and you may have done some wrong or false positive, and that's another problem.

Dr. Jayne Ness: [00:38:54] Well, I appreciate that. So, there's kids who have access to it, you know, we have access to insurance or, in Alabama, they're pretty well-insured, but even then it's thinking about, you know, how often, you know, do we need to get these mock titers?

[00:39:06] And I, actually, my practice is very similar to yours is I don't chase it. And, you know, I follow the clinical course in MRI. And then I am also a little a little skeptical about, you know, the titers being able to predict the future because certainly I've had patients whose titers have gone down and then we've, they've still come around and had a relapse and their titer may go up You know, one to 40 to one to a hundred, but it isn't like there's major, you know, there's a big change in their titers once they're positive. So I think that's, I think that's something we're still figuring out, but yeah, I'm with you that, you know, I don't think we need to be driving ourselves nuts chasing them.

Dr. Silvia Tenembaum: [00:39:46] Exactly. Yeah, absolutely. I agree. There is no way to continue testing. There are two or three very good papers showing the behavior of those titles on time, because they were funding, funding status. But I don't think they are very useful in the clinical practice, in the real work.

[00:40:10] So, I think it's more useful to carefully follow your children, your patients, from the clinical point of view, examining what is new with the clinical combination. I, I follow them every three months. And requesting a new MRI every six months to see if there is any kind of inflammation that they couldn't check index in the physical examination. And check in the laboratory every six months looking for some index of inflammation in the blood.

[00:40:41] So, this is, I am confident with that follow up. If I have a new relapse and I have the opportunity to check again, the MOG antibodies, I'm going to do it. But anyway, I'm going to start immunosuppression. If they're seronegative or seropositive, they have a relapsing disease, they need treatment, that your chronic immunotherapy.

Dr. Jayne Ness: [00:41:01] How, for the MOG patients, how long will you treat? Maybe we're getting, I might be jumping ahead. I might be jumping ahead. I'm sorry, I didn't mean to be the person who's asking the questions, but this is a fun clinical discussion.

Dr. Silvia Tenembaum: [00:41:15] Absolutely. Absolutely. And that's the way we are all growing in our knowledge, changing. Okay.

Dr. Jayne Ness: [00:41:22] Yes.

Dr. Silvia Tenembaum: [00:41:23] Our experience, I will say in the last five or 10 years, I was very afraid to interrupt the immunosuppression after the patients were quite stable. But after the experience in Europe, the group for Denmark, I think, that they start taking out the immunosuppression after two years of a very stable clinical and MRI disease. And so, I started to do so, and they are doing quite well. If during two years under immunosuppression in MOGAD patients is showing no relapses, stable clinical examination, and in the middle three or four MRIs without any acute inflammatory signs, you may start deescalating the treatment.

[00:42:12] And maybe I will give the infusion longer periods or leaving the patient to increase the CD19 up to three or four, looking for the new MRI. If there is nothing there after two or three years with a stable

disease, I stop the infusions and wait and see. It's not the same for AQP4. In AQP4, I'm not... that experience. Absolutely not.

Dr. Jayne Ness: [00:42:41] Yeah. And I would be sitting on weeds. Yeah, we tell our MOG patients we'll sign you up for two years. And then, you know, and this isn't, and again, in the MOG children who have relapsed, not the, you know, the one time, you know, they're positive. You know, about half of our kids have had a relapse and half of our kids have not had a relapse with MOG. And with the NMOSD, they're all going to relapse eventually.

Dr. Silvia Tenembaum: [00:43:10] Exactly.

Dr. Jayne Ness: [00:43:10] So, excuse me, it was aquaporin-4 NMOSD.

Dr. Silvia Tenembaum: [00:43:14] Yeah. Yeah.

Rebecca Whitney: [00:43:17] That was actually one of my questions that was coming up is, is it something that they could eventually grow out of? But so, a child with the AQP4 with NMOSD, that is a lifelong diagnosis?

Dr. Silvia Tenembaum: [00:43:30] What we know today, it's for life.

Dr. Jayne Ness: [00:43:34] Yes. Yes. That's it. And until a cure comes along, which, you know, with the supportive of, I mean, what, what's happened with Guthy Jackson, you know, three approved drugs. And, I mean, you know, I think the sky's the limit. And, I hope in my patients' lifetime, maybe not in mine, that there will be a cure for aquaporin-4 NMOSD. But, you know, the disability in the aquaporin-4 patients is really driven by relapses.

[00:44:03] And so, the goal is to prevent relapses at all costs because, you know, that's what can be devastating. My sense is that the MOG patients recover better, even with a scary-looking MRI in the beginning. Although, I think, you know, I've certainly seen MOG positive patients with incomplete recoveries.

[00:44:23] I've also seen MOGs also separated out, you know. Some for, have had, you know, an event and then develop events later on. Although these are kids who we don't know what their MOG titer was at the beginning of their disease. So, those are ones who continue to teach me.

Rebecca Whitney: [00:44:38] Yes, absolutely. Well, thank you both so much for joining me today. I sincerely appreciate it.

Dr. Silvia Tenembaum: [00:44:47] Thank you for helping us.

Dr. Jayne Ness: [00:44:49] A pleasure.

Dr. Silvia Tenembaum: [00:44:49] Thank you so much.

Dr. Jayne Ness: [00:44:50] Thanks.