Pediatric NMOSD | Part II

Treatment & Symptom Management

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[00:00:00] **Intro:** 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 and Guthy-Jackson Charitable Foundation. This education series is made possible through a patient education grant from Horizon Therapeutics.

[00:00:49] **Rebecca Whitney:** 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.

[00:01:33] My name is Rebecca Whitney, Associate Director of Pediatric Programs with the Siegel Rare Neuroimmune Association. Today, I had a conversation with Drs. Jayne Ness and Silvia Tenembaum, a second part on "Pediatric NMOSD," focusing on symptoms and treatments.

[00:01:49] Dr. Jayne Ness is professor of pediatric neurology at the University of Alabama at Birmingham or 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.

[00:02:21] 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.

[00:02:46] 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. 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.

[00:03:38] Dr. Tenembaum and Dr. Ness, thank you for joining me once again to discuss pediatric NMOSD. We had some excellent questions and answers the last podcast. And this time we'd like to focus on some of the treatment and symptom management in pediatric NMOSD. If I could start off with what are the most common symptoms a child may present with, if they have an NMOSD diagnosis? Are they different than what we would see in adults? Does it differ by the age of the child? Dr. Ness, do you want to start?

[00:04:20] **Dr. Jayne Ness:** Sure. Happy to. I think that, NMOSD, so the classic of course is optic neuritis, especially with the rather fixed visual loss and transverse myelitis. But over a third of our kids have also brainstem syndrome. And so again, one of the core features can be the area of postrema syndrome where there's, intractable, vomiting, and hiccups, but also with a number of brainstem symptoms, and there can also be excessive tiredness. What I've noticed is that these children are often really tired, very sleepy, but they're not really encephalopathic, you know, so they wake up and they can answer a question appropriately and then they fall right back to sleep. I'm almost thinking about them as we go through MRI, it's sometimes, they'll have these really large, often there's headache, there'll be these large lesions that are almost tumefactive.

[00:05:24] And so they're often, they'll be more, you know, I think more, more headache. And again, there'll be sleepy but appropriate when you wake them and then trying to figure out, is this really encephalopathy? I think that's probably the biggest thing. And some kids are truly encephalopathic, but it's a, it's a different flavor than what I see with the ADEM kids. Silvia, do you, have you seen similar as you nodding your head?

[00:05:49] **Dr. Silvia Tenembaum:** I agree with you with exactly your explanation.

[00:05:53] **Rebecca Whitney:** Okay. And by encephalopathic just for those who may not fully understand what that means, is that more of like the, the lethargy, the confusion, what else?

[00:06:03] **Dr. Jayne Ness:** Thank you for, yeah. Thank you for asking for that clarification because often the kid, yeah, but I've seen the doc, is that the kids with truly acute disseminated encephalomyelitis or ADEM, those kids are sleepy, but then they're cranky. They don't know their, you know, almost don't know their parents. Sometimes, which is, I mean, that's, that's pretty severe. And so, you know, are very, you know, our little older, one's confused about what, you know, what day it is or where they are. An NMO kid will be able to answer appropriately but fall right back asleep.

[00:06:42] **Rebecca Whitney:** Okay. Interesting. Thank you. And is that what you see in adults as well, who may be, or that probably is not the most appropriate question for two pediatric practitioners?

[00:06:58] **Dr. Silvia Tenembaum:** But actually, encephalopathic features are more frequent in the pediatric age group. So we are, we are most accustomed to see the dark skies or a way of starting the, or presenting the disease. But in other patients is more than both with the visual acuity or the dysfunction of the spinal cord mainly.

[00:07:19] **Rebecca Whitney:** Okay. And do you see a difference if a child because we know that a diagnosis of NMOSD does not require an AQP4 positive test. Is there any difference in symptoms between those kids who will test positive for AQP4 and those that do not?

[00:07:40] **Dr. Silvia Tenembaum:** In my experience, there is not much difference. Maybe there is a difference among those sero negative for AQP4 which later are positive for MOG antibodies or myelin oligodendrocyte glycoprotein, because indeed they have a particularly way of suffering the disease and the MRI looks different.

[00:08:02] **Rebecca Whitney:** Okay. And how, how does it look different between them?

[00:08:07] **Dr. Silvia Tenembaum:** The inflammation of the optic nerves are quite more severe in the MOG, in the MOGAD group with papillitis the fundoscopy is abnormal. So you have a very inflammation of the optic nerve. So, the child may become blind, absolutely blind, the start of the optic nerve involvement. It's more usually in AQP4 positive children to involve the chiasma, is more posterior the involvement of the optic nerve. And the spinal cord is more usual in the MOGAD group of patients, involvement of the conus and very conus inflammation.

[00:08:50] So the bladder dysfunction is more frequent in MOGAD, in the MOGAD group than in the AQP4 IgG positive group. When the spinal cord is more frequently involved in the upper section of the spine. So, it's more upper, limbs involvement of the medullaris. So, the area postrema syndrome, the vomiting and the hiccups, recurrent vomiting that Jayne have described very well are more frequently the AQP4 IgG group.

[00:09:24] **Rebecca Whitney:** Okay.

[00:09:25] **Dr. Silvia Tenembaum:** And not so frequently the MOGAD. So, the clinical picture is different.

[00:09:30] **Dr. Jayne Ness:** What do you think about the timing of the onset? I think of the, the NMO patients as sometimes being a little bit more stuttering. I mean, I'm thinking of, when we talk about the kids with aquaporin-4 IgG positive we'll often have had like trips to the GI doctors, for example, from vomiting and weight loss.

[00:09:52] And even not, not even have much on their MRI initially, except perhaps like the most subtle. At, you know, area postrema, but you didn't, you know, you don't get a sagittal T2 foot, you know to look at the brainstem yet you, you could miss it at where I'm thinking the MOG kids tend to be. As I'm thinking, in retrospect, it seemed to be a more fulminant onset, often more, but, you know, they were fine.

[00:10:21] And then over a couple of days or, you know, week or so, they become really sick, but I'm thinking a lot of these aquaporin-4 positive children will have had something that in retrospect, you know, that was some weeks or even months ago that you think, oh, that must've been the first, you know, oh, it was the flu. They were really sick. They were vomiting, but oh no, there was no fever. No, there was no diarrhea. Do you, have you noticed that?

[00:10:47] **Dr. Silvia Tenembaum:** Yeah. So, they perform a CT scan just to see if there is a tumor, a brain tumor, you are not going to see or detect the area postrema inflammation in the CT scan, you need a brain MRI to identify the inflammation.

[00:11:07] **Dr. Jayne Ness:** Exactly.

[00:11:08] **Rebecca Whitney:** Okay.

[00:11:09] **Dr. Silvia Tenembaum:** You lose time, you lose time.

[00:11:12] **Rebecca Whitney:** Yes. Yes. Unfortunately, that does seem to be the case when we hear of, of individuals being diagnosed that they've, they've lost time in, in between getting that diagnosis and when they were presenting with those symptoms.

[00:11:28] So you talked a little bit about some of those symptoms that a parent or caregiver, might see in a child, you know, with, those hiccups and it's, those hiccups are severe, persistent. They continue for a long time. And those GI symptoms feeling flu-like, having that vomiting; anything else?

[00:11:50] **Dr. Silvia Tenembaum:** They are refractory to symptomatic therapy.

[00:11:53] **Rebecca Whitney:** Okay.

[00:11:54] **Dr. Silvia Tenembaum:** So, if the pediatrician or specialist in gastroenterology, put symptomatic therapy for the vomiting and the child is not responding well, you have to start thinking in another diagnosis. Probably the central nervous system, the one which is involved. Yes. So, it's refractory to the usual therapy that a child receives far from the neurological point of view. So, they are refractory to the symptomatic therapy.

[00:12:29] **Dr. Jayne Ness:** Yes. Yes. I had actually made a list for Guthy Jackson. This was years ago, and I'm actually looking at my list of that. I have as a weird symptom in peds NMO patients. And I would just be curious Silvia, if you agree, I'm just going to run down the list.

[00:12:46] I don't, it was when they were revising their book and I'd go, oh yeah, let me put down all the weird symptoms that I've seen. So, I had, puberty too early or too late. So, a lot of kids with precocious puberty, I had, or that they had normal menses, and then now young women or girls have very irregular periods, or they have, I've seen accelerated puberty or falling below the growth curve.

[00:13:12] So that was one, I don't know if you've noticed any of those symptoms. Okay. And I've seen, as I'm thinking about some of these examples, some of these I've seen with children who ended up being MOGAD, but it meant most of these were true aquaporin-4 positive patients. The other thing is, I guess this is really goes more to the spinal cord, but just many ephaptic symptoms.

[00:13:33] So when I went back and was looking through our list of, you know, kids like there's children who had, mostly spinal cord, but were like sent home with Benadryl because they had kind of, they said it was a rash, but there's no rash to document. They actually had recurrent itching and it was ephaptic.

[00:13:49] I think it was ephaptic itching. And again, when I started looking for it, it was different, you know, or chest tightness that they thought was panic attack or anxiety, from the abdominal tightness or the chest tightness. So, I've had several children with sudden uncontrolled muscle spasms that, again, I realized were ephaptic symptoms or autonomic instability I had, oh yeah.

[00:14:11] Mottled skin. I'm trying to remember, you know, livedo reticularis almost like a, this kind of a Raynaud syndrome, syncope, dizziness, and then the hiccups and belching. Myalgia is, I had difficulty urinating also. You know, when I'm thinking brainstem syndrome, a lot of soft voice, hypophonia. All the Lhermitte's syndrome. I've developed great, great respect for the spinal cord. At all the symptoms you can have.

[00:14:39] **Dr. Silvia Tenembaum:** The localized itching is a very frequent in children and usually pediatricians do not think about a spinal cord inflammation or involvement.

[00:14:51] **Rebecca Whitney:** That's very interesting. And once you're coming to that NMO diagnosis in the acute phase, what are the typical treatments? Is there an order of priority that you, you begin with for those acute treatments for children? And Dr. Tenembaum, do you want to start with that?

[00:15:10] **Dr. Silvia Tenembaum:** Yes. There are recommended first-line therapy for NMOSD, for whatever, AQP4 positive, negative, or MOG positive. It's typically the high dose intravenous corticosteroids. So, this methylprednisolone, high dose for five days at the minimum. And if the, the patient is recovering not so good, we usually go on for 10 days of intravenous, methylprednisolone. Nevertheless, in cases with severe steroid

corticosteroid resistant, acute events maybe a very severe spinal cord inflammation without recovering walking ability or very severe optic nerve inflammation with no improvement in the visual acuity or children in the intensive unit under mechanical ventilation due to refractory brainstem inflammation, you require a more aggressive acute therapy like plasma exchange, which is a very adjunct, very important adjunctive therapy maybe the second line after the corticosteroid treatment, or maybe the first line, if the patient is so severely disabled that you need to, to act very quickly.

[00:16:35] **Dr. Jayne Ness:** Yeah. What I tell our residents is if you can't walk, can't talk, can't think can't breathe. Can't see. That's an indication for plasma exchange.

[00:16:45] **Dr. Silvia Tenembaum:** And it's an extraordinary treatment too, for the acute treatment of this kind of inflammation. We have a great experience. Almost 90% of the patients demonstrate marked improvement after one month after finishing the procedures and almost 98% at six months. So, the treatment continues being with positive impact after you finished the intravenous procedures of plasma exchange, so it's extremely useful. And if we are thinking about starting plasma exchange, we are not going to give the patients IVIG because we are going to wash the treatment.

[00:17:32] **Dr. Jayne Ness:** Exactly. I'll do what I call an IVIG chaser at the end.

[00:17:38] **Dr. Silvia Tenembaum:** Exactly. Plasma exchange protocol, we perform every other day, the procedures, and every day until the end of the treatment, we add cyclophosphamide, oral cyclophosphamide to the patient in order to avoid the increase of the IgG because of the procedures every other day. So, you may have an increasing the IgG activation in the middle, so, cyclophosphamide is absolutely useful. And I think that's the reason we are so, is so well the results that we have with plasma exchange in children.

[00:18:18] **Dr. Jayne Ness:** What dose?

[00:18:20] **Dr. Silvia Tenembaum:** Two milligrams per kilogram, per day.

[00:18:22] **Dr. Jayne Ness:** What day do you start it?

[00:18:24] **Dr. Silvia Tenembaum:** Sorry?

[00:18:25] **Dr. Jayne Ness:** What day do you start the oral cyclophosphamide?

[00:18:27] **Dr. Silvia Tenembaum:** The first day of plasma exchange. And you give it to the patient every day, the day they receive exchange and the day they are not going to be washed.

[00:18:38] **Dr. Jayne Ness:** So, by 10 days?

[00:18:41] **Dr. Silvia Tenembaum:** Yes. Do them the 10 days depending on the number of procedures you need or the number of the procedures the patient need.

[00:18:48] **Dr. Jayne Ness:** And do you continue, do you stop at the last day of plasma exchange?

[00:18:52] **Dr. Silvia Tenembaum:** Yeah.

[00:18:52] **Dr. Jayne Ness:** I've never used that before.

[00:18:54] **Dr. Silvia Tenembaum:** It's a rheumatology protocol, they are very aggressive when they decided to use plasma exchange in the lupus, in the severe events. They are very severe events. So particularly MOGAD patients you need this. Because the chance of having very good evolution of this young patients is to be aggressive in the acute stage. You can manage the sequela, you can manage the residual symptoms, but that's a problem. That's a very severe problem. It's better to avoid the sequela treating aggressively in the acute stage.

[00:19:28] **Dr. Jayne Ness:** Can I ask, do you taper or not taper prednisone?

[00:19:32] **Dr. Silvia Tenembaum:** We usually taper corticosteroids. After finishing the pulse therapy intravenously, we'll start with oral prednisone, one milligram per kilogram per day, 10, 12 days. And after that, we started to go in down with the dose, usually in four or six weeks with cortisol the evaluation in the sediment, sample serum sample in order to see if we can stop the oral prednisone after the six weeks.

[00:20:04] Okay. So, we, we perform tapering, tapering of corticosteroids. Yes. In order to avoid new symptoms of inflammation, particularly MOGAD patients with MOGAD.

[00:20:15] **Dr. Jayne Ness:** So, this is interesting because just to give you an idea, you know, that there's different regional differences in how people do it. And I think it's a lot of it's very institution specific and there's places that always taper?

[00:20:31] But then with the MOG patients, it would seem like you would taper them. And then a week later they would bounce back. I've stopped tapering using a taper the past couple of years, and again, I'm not sure if it's the right or wrong way, but do you have any difficulty with having patients have either aquaporin-4 or MOG positive, that will have recurrent symptoms once they come off the taper?

[00:20:58] **Dr. Silvia Tenembaum:** More frequently, we receive a second opinion children's that looks like a relapse and really, they have not received tapering of corticosteroids that does a stop intravenously. And after one week they started with new symptoms more frequently that relapses or reaggravation of the same first event after stopping intravenous corticosteroids without tapering.

[00:21:27] **Rebecca Whitney:** So, you kind of answered one of my, my next questions in a bit of that conversation there, but the aquaporin-4 antibody levels can be altered with the acute treatments. Is that correct? Am I understanding that correctly? So, if you are giving the, the steroids or even the plasma exchange, those it's adjusting the levels of the antibody that's causing the issues, is that a fair statement? Or...

[00:21:55] **Dr. Jayne Ness:** I'm going to jump in and say theoretically, because once I have a positive NMO or positive, aquaporin-4, I never check again. Unless there's like a reason for a trial or something. And I have seen children on rituximab who then had undetectable aquaporin-4 levels and were able to get into a clinical trial only because thanks be to God, Mayo had kept their positive samples and was able to send them for retesting. To prove that they were positive at one point, to get them into the clinical trial. But that's all I'm going to say about the levels. Cause I don't know.

[00:22:32] **Rebecca Whitney:** Okay.

[00:22:33] **Dr. Jayne Ness:** Silvia, I, you don't know if you do differently if you follow the levels.

[00:22:36] **Dr. Silvia Tenembaum:** Oh, I agree with you. I agree with you. So that's the reason it's so important

to take samples, CSF, and serum samples before starting any acute therapy, because you need to check the antibodies before starting treatment and after being positive for MOG or for AQP4 I do not check those titers anymore, because if a patient is acute before they need a chronic therapy after the acute management forever. And do you believe that with MOGAD, too?

[00:23:10] No, no, no. MOGAD is different. You need the first evaluation before starting therapy because after treatment or without acute treatment, its titers go down within six, 12 or 18 months.

[00:23:27] So you lose the chance to detect the positivity to name the disorder, MOGAD. If you don't perform the titers very early. And if I have to start this very earlier, they were positive. I'll start acute treatment. But with no chronic therapy is different from AQP4. In MOGAD, I will wait until the second event.

[00:23:53] **Dr. Jayne Ness:** Correct, so do I.

[00:23:55] **Dr. Silvia Tenembaum:** MRI with a huge inflammatory sign within the spinal cord, the optic nerve of the brain. And only when those circumstances occur, I start immunosuppression is different in that way from AQP4. AQP4 forces you to start immunosuppressive treatment. And it's not the case with MOGAD.

[00:24:17] **Dr. Jayne Ness:** I agree. And again, similar, you know, I don't, you know, as I said before, I don't follow the aquaporin-4 levels once you're positive, you're positive and call it a day.

[00:24:27] But, and I had been following the MOGAD levels and I'm not sure that it means anything. I know there's people say you should check every six months. And I, I'm thinking about MOG antibody titers almost along the line of the aquaporin-4 titers, except for, you know, the treatment decisions.

[00:24:49] Again, similar to Silvia is I wait for a second attack before I drop, because there's kids that, you know, not once the MOG antibody became commercially available from Mayo, you know, late 2017. And I started, you know, going through and checking out the, you know, there were kids who had had only one attack and were MOG positive. And some of them had higher titers and the kids would have recurrent, you know, a couple of attacks, so...

[00:25:16] **Dr. Silvia Tenembaum:** MOG antibodies are tricky because we, you may have a patient that converted to sero negative after being positive. And after one, five, or 10 years they have relapsed.

[00:25:28] **Dr. Jayne Ness:** Yes. Yes, they can. They can go years.

[00:25:31] **Dr. Silvia Tenembaum:** And other patients that remain low positive, low positive, low positive, and never have a clinical relapse and the MRI stayed silent. So, you are not going to give immunosuppression according to the serostatus. I don't think it's useful at least today. I think there is not useful to continue checking the serum levels of MOG antibodies in pediatric patients, at least. I don't have experience with others, but I think it's the same story.

[00:26:03] **Dr. Jayne Ness:** Thank you. But yes. Yeah, very good. These MOGADs, we're still getting it.

[00:26:11] **Rebecca Whitney:** It's so interesting and interesting to hear how the MOG differs from the AQP4. And obviously with the AQP4, like you said, you, if you have it, you have it, immunosuppressant therapy is necessary. And so that's something that we know they'll have a recurrence if they are not treated on those immunosuppressants.

[00:26:34] So does the level of the antibody that may be present at the initial attack in AQP4. does it determine the risk of relapse? Does it determine if it's going to be more severe? That the, the symptoms are worse or the, the disability becomes worse?

[00:26:53] **Dr. Silvia Tenembaum:** If I understand well, we're trying to express if the very high titers of AQP4 antibodies have a prognostic value for very severe ongoing disease. And I don't think that is real.

[00:27:11] **Rebecca Whitney:** Okay.

[00:27:11] **Dr. Silvia Tenembaum:** You're positive. You might be low positive or very high positive. It's just NMOSD AQP4 IgG positive disease and you need to start immunosuppression. Okay. Every well, all the relapses, you may observe in a patient after the first event in AQP4 or in MOG patients in MOG positive patients, maybe the risk is to have more residual deficits after the following relapses, because you are having inflammation after an optic nerve, for example, that have already been severely attacked or inflamed with the initial event.

[00:27:53] So that's the reason you are aggressive with immunosuppression and try to follow the cycles of the treatment in order to avoid or suppress the following relapses because the children are going to finally be blind. Right? Very severe sequela from NMOSD and from MOGAD for MOG positive children, so the, the trick here is to sustain the immunosuppression in a way that you avoid the relapses independently of the level of the antibodies.

[00:28:31] So that's a problem of rituximab, for example, that you may consider giving an additional dose every six months, but children's particularly younger children, may have an increase of the antibodies in serum before the CD19 baby may become positive above the value of 1% before the six months. And there you have a relapse, a severe relapse.

[00:28:59] So you have to decide the best way of following those kids under immunosuppression particularly with rituximab. Mycophenolate, you have, it's an oral immunosuppressive drug. You have to adjust the dose to the body weight. So, every immunosuppressive treatment requires a very close follow up in order monitoring the very close monitoring in order to avoid relapses because that's the objective of a starting immunosuppression.

[00:29:33] **Dr. Jayne Ness:** I agree with you Silvia. I find that the I think, you know, when we kind of getting at the original start of the question does a higher titer predict worse disease? I've seen terrible disease with someone who had rather low titers. And of course, in the beginning we just got, you know, the results I got was positive or negative.

[00:29:52] I never got a titer back. And so, I, I agree that I'm not sure that the titers are very predictive because I've seen people, you know, kids with high disease, especially now more recent with MOGAD that have super high disease that have not had, have done have been pretty uneventful courses in children with low titers, I'd have done it have been a struggle for me.

[00:30:15] And then how with the kids on rituximab, which is all the NMO kids. Once they become, you know, I put them on rituximab. You know, I treat their stairs, you know, we have three things for acute relapses. Maybe now it's three plus, you know, steroids, steroids immune globulin, which I think is a little bit more helpful maybe in the MOGADS, you know, and again, I use it after the plasmapheresis as does Silvia.

[00:30:44] And then and then plasmapheresis that now I'm going to add a little a dusting of a cyclophosphamide, but you know, that really hasn't changed. But then for long-term I immediately put the kids that, you know,

regardless of, you know, the NMO, the aquaporin-4 positive on rituximab. And I can tell you a story of one child who had a non-focal exam except for nausea and vomiting and just barely, barely anything in that area poststrema on, we argued about what was, if there was something the spinal cord or not, and I didn't treat her, you know, it was kind of a, you know, discuss it with the family.

[00:31:23] And a year later she had a horrible relapse. I mean, she recovered, but it took a really long time. I learned my lesson. I mean, I knew the numbers in the literature about 70% chance of relapse with a positive aquaporin-4 titer. And aquaporins, you know, I think of the aquaporin-4 positive patients don't take a cognitive hit in the same way that I feel like the MS patients do. I'm still undecided about the MOGAD patients. I've certainly seen it happen, although I think for sure in the aquaporin-4 patients there it's, the cognitive issues are driven, or just neurologically poor outcomes are driven by the relapses. And if you can prevent the relapses, I think we can prevent a lot of other problems cognitively and physically.

[00:32:20] And then, so I follow B cells and, and I certainly have seen patients who have repopulated their B cells and I try and keep their B cells below an absolute number below five or less than one. We'll just use five as a cut off and redose some. And there it usually, but usually just automatically we dose every six months, but if they repopulate earlier and then some kids, I have to squeeze together every three to four months, rituximab, and then after, follow them. And if they're zero for, zero B cells for a while, then I'll stretch them back out to six months again.

[00:32:50] **Rebecca Whitney:** Okay. Alright. So, you talked a little bit about some of those ongoing treatments with the rituximab, the mycophenolate, any other treatment options for the ongoing immunosuppression that you use in children. And you touched on this just a little bit as far as can they outgrow that treatment?

[00:33:11] Does it need to be adjusted or changed and is it possible for a child to, and I believe we've already answered this, but I just want to ask it one more time, for a child to outgrow the diagnosis? Can they go years on an immunosuppressant therapy with absolutely no recurring attacks to then be able to come off of those therapies?

[00:33:36] **Dr. Jayne Ness:** So, this is what I tell my patients, is that if they're aquaporin-4 positive, this is a lifelong disease. And in the current year I've been saying this, since we found the antibody that this is considered, you know, for the time being that they should be planning to be on therapy lifelong.

[00:33:59] **Rebecca Whitney:** Okay. And have you had to adjust medications, whatever those immunosuppressants might be, because the one may no longer work, and they have a recurrence? Is that something that's monitored? You know, you mentioned, you know, checking B-cell levels and doing that. How, how are those patients monitored?

[00:34:20] So just thinking, you know, if a child is diagnosed when they're, when they're five and then they're 15 you know, monitoring for the changes that happen just during the stage of growing, does that impact those therapies that they may be on?

[00:34:37] **Dr. Jayne Ness:** So, puberty of course, is a big issue. Do they get normal or not? But I think that the puberty is more disrupted by the aquaporin-4, you know, being present. My experience has been that actually our aquaporin-4 patients do really well on rituximab. The biggest side effect I've seen has been that some of them will develop recurrent upper respiratory infections.

[00:35:02] And I've had a few kids too with pneumonias that one child ended up switching to satralizumab. The IL-6 interleukin, six receptor inhibitor that was known as Tocilizumab used intravenously. But then now

that it's a subcutaneous injection once a month. and so, I've had two patients, you know, switched to that for those reasons.

[00:35:26] And I haven't used any of the, the newer, the other, I haven't used as a compliment inhibitor yet. It's the MOGAD positive, the MOG positive patients who have failed rituximab. In my experience. I mean, the ones that didn't do well, they were the aquaporin-4 negative. And then in retrospect, they ended up being MOG positive and those, those kids seem to not do as well on rituximab. I don't know Silvia, what's your experience? I'm eager to see what you think.

[00:35:54] **Dr. Silvia Tenembaum:** Yes. There are clinical responses to rituximab, not as good in children with MOGAD. That's real. So, we start anyway, we start with rituximab because we still think that is a very good immunosuppressive therapy for particularly pediatric patients.

[00:36:12] But after we realized that we are failing because you have an additional relapse, even having CD 19 in zero, children with MOGAD may relapse. So probably is different. pathophysiology that we still do not understand quite well. So, after having that, we may add oral mycophenolate mofetil attentive to the rituximab.

[00:36:41] That's one way to try to control the disease. And if you additional have another relapse, you may stop one of those particular rituximab, for example, and continue with maintenance IVIG. So, every month receiving one dose of intravenous IVG for chronic therapy, not for the acute attacks, you know, for chronic therapy, not exclusively would IVIG, but was an add-on therapy with mycophenolate, for example, we still do not have approval the three new molecules eculizumab or inebilizumab or satrilizumab for its use in pediatric patients. We do not have those new treatments approved, so we cannot use it nowadays. And if finally, you fail again with the addition of IVIG, we have to sustain oral steroids because MOG antibodies positive patients are still responding to corticosteroids.

[00:37:45] So probably they only need chronic therapy with the corticosteroids, with all the secondary effects cataracts, osteopenia, that's a very bad with the chronic therapy with corticosteroids, but many kids that have no other option. So, it's very hard, the chronic treatment of the patient with MOGAD with a relapsing form of MOGAD is very severe.

[00:38:09] But okay. Probably in my experience is just the three, 4% of all the MOGAD pediatric population that have so refractory behavior of the disease. Because MOGAD patients with positive antibodies that require immunosuppression, they maybe need to sustain the treatment for just two years. And after two years of being the disease stable from the clinical and in their imaging point of view, you may try to start separating the immunosuppression and many patients tolerate quite well that management, you cannot do that in AQP4 IgG positive patients. So that's another difference. Very important difference between the two diseases.

[00:39:01] **Rebecca Whitney:** Okay.

[00:39:01] **Dr. Jayne Ness:** Could you repeat that again? The last sentence? About MOGAD, something about their antibody as you taper, right before you taper, what do you do? Or wait before any therapy? Trying to come off therapy at two years?

[00:39:15] **Dr. Silvia Tenembaum:** After two years. Yeah. In very severe when you can do it after four years of immunosuppression. So, between two and four, if the patient's absolutely stable. I repeat MRIs every six months. So, if I have new signs of inflammation, particularly in the spinal cord and the optic nerve, a single isolated issue in the white matter doesn't mean nothing for me, but inflammation in the spinal cord or the optic nerve means different impact in the functional neurological sequela, potential sequela. So absolutely

stable from the new imaging point of view and absolutely clean from the clinical examination, and with no relapses, you can start to take out the immunosuppression.

[00:40:04] **Rebecca Whitney:** And that's specific to MOG?

[00:40:08] **Dr. Silvia Tenembaum:** MOG. Only for MOG. AQP4, absolutely not.

[00:40:14] **Dr. Jayne Ness:** NMO, they're on forever, And I keep on hoping, you know, that we get some adult data, but I, I, you know, so I think, you know, thinking about planning for, you know, you cause many of our, majority of our aquaporin-4 patients are female is thinking about family planning and yes, you can have babies, but you know, these have to be planned babies.

[00:40:36] And you know, that, that's what, we send them off to the adult neurologist. But, but, you know, again, in many ways that they you know, cognitively actually do very well. But preventing the relapses is really essential.

[00:40:52] **Rebecca Whitney:** That's the critical piece.

[00:40:54] **Dr. Jayne Ness:** Yup. Yes.

[00:40:55] **Rebecca Whitney:** So, and thinking about these, ongoing, lifelong immunosuppressants for these kids. Are there additional tests, precautions that need to be considered? You mentioned earlier, some who may struggle with having upper respiratory infections. Are there things that that should be checked that need to be thought of when they're starting on that immunosuppressant therapy?

[00:41:21] **Dr. Silvia Tenembaum:** Before starting immunosuppression, you need to check for antibodies to varicella because it's a live vaccine, a live virus vaccine, and for hepatitis B, because if the patient is seronegative for those viruses, you have to vaccinate the patient before starting immunosuppression. If you have time. If you have to wait until you seroconvert to IgG positive for varicella and hepatitis. And after that you can start immunosuppression and checking for IgG because hypogammaglobulinemia is a complication of the chronic therapy with rituximab. So, in those cases, if the hypogammaglobulinemia is symptomatic, the patients have upper respiratory, recurrent, upper respiratory infections.

[00:42:13] You need to give IVIG to increase the level of IgG, continue sustaining the immunosuppression because the patients need that. In the middle of the pandemic, it was another problem. We have the vaccines for SARS-CoV-2. And we avoid that in order to wait until their CD 19 was positive above the level of two, 3%.

[00:42:46] And that's what a window of opportunity to vaccinate the patient for COVID. Okay. And after completing the two doses, three weeks after the second dose, we give the additional intravenous dose of rituximab. So, we do not have, usually during these two years, we didn't have difficulties with that. So, it's possible.

[00:43:11] **Rebecca Whitney:** Okay.

[00:43:12] **Dr. Jayne Ness:** And now the, the American, Centers for Disease Control actually recommended that patients who are immune suppressed should actually have three doses of the mRNA vaccine to be considered even minimally vaccinated. You know, as a baseline for vaccination. So, you know, dose one, this is really referring to the mRNA vaccines, then three or four weeks later, dose two, and then four weeks later, and dose three to really be considered to be, you know, to be fully vaccinated.

[00:43:47] And I think the probably repeat, you know, a dose four, you know, five or six months later, and who knows about, another subsequent follow-up dose. So, I, you know, we're learning, as we go along.

[00:43:59] **Rebecca Whitney:** And is there a need for annual MRIs? Do you do MRIs if there is not any, clinical symptoms or do you do them in case there are any silent lesions that may be present?

[00:44:15] **Dr. Silvia Tenembaum:** During the first two years under treatment for AQP4 or for MOG, I perform MRI, complete MRI, dedicated orbital, brain, and spinal. You repeat every six months during the first two years. If the patients are absolutely stable in AQP4, I perform yearly. Every year, I request for an MRI, and it is not so clear if the silent new lesions have some impact announcing that a new relapse is near because it's, as I expressed previously, it's not the same to have a silent lesion in the middle of the brain, white matter, a single small dot that you have a longitudinal new enhancement in one optic nerve. And the patient is still not suffering from any visual is completely different.

[00:45:10] **Rebecca Whitney:** Okay.

[00:45:10] **Dr. Silvia Tenembaum:** One is near to be symptomatic in the near future, the one involving the optic nerve. So, it's not so clear, the prognostic indication, indicator of a silent lesion in the AQP4 and it's not so clear in the MOGAD group. Very recently during ECTRIMS, it's the European Congress of MS, two separate papers were presented both in adult patients and one, including children with MOGAD and for MOGAD patients, adult patients they'll have what's an indicator, a new silent lesion was indicated, indicative of a near close relapse going to, to occur. In the other paper with the pediatric patients, the ones from the Philadelphia group, including Canadian children demonstrated that new silent lesions have not so predictive value of a relapse in the MOGAD group.

[00:46:10] So it looks like it's different experience in adults and in children. I think we need more cohorts being evaluated in order to establish the value of the new silent lesions. In the meanwhile, I perform, I'm wanting an MRI. If the patient is an adolescent and is okay, I don't want a more, he's very stable under immunosuppression during the last seven years, 10 years, probably I will examine every year, the patients from the neurological point of view and request an MRI after three years from the previous one. That's adjusted according to the patient. But during the first two or three years and more closely follow these kids.

[00:47:00] **Dr. Jayne Ness:** And I would agree that I followed similarly, follow them more closely. I will do like every you know, three to six months later, depending on how sick they were, and then, you know, maybe six months later and then a year later. And then if they've looked pretty clean that the end of the aquaporin-4 positive patients, I've tended not to follow with the annual MRIs, but more with exam.

[00:47:26] I used to do annual MRIs and then I sort of fell away from it because they were, you know, it was really driven more by their symptoms then by their MRI. I wasn't seeing really very many silent lesions at all in the MRIs of the aquaporin-4 positive patients.

[00:47:41] The MOGAD patients can have silent. It can definitely have silent lesions that sneak up on you and bite you. But you know, those kids, I'm fine, you know, typically doing every year and again, and the MS patients, which I know this isn't a talk about MS, but, you know, So, you know, I think of that as my framework and then how do I differ depending on their antibody status a little bit. So, I've actually fallen away from chasing the aquaporin-4 patients as frequently with MRI, but maybe I'll go back to what I used to do.

[00:48:15] **Rebecca Whitney:** If a parent or caregiver of a child is on immunosuppressant therapy and they believe that they may be experiencing a relapse, what are some of the indicators that you may give to them

to look for to help determine, is this really a relapse or are they coming down with another illness that may be almost seeming like they're going through this, this relapse again? Do you follow kind of a 24-hour rule? Anything like that that would give families an indicator as to when they need to reach out to say, I think something is happening?

[00:48:51] **Dr. Jayne Ness:** I'm going to start with, so with our MS patients, we say, wait 24 hours before they call us, but we usually hear about it before, but if it's 24 hours, it's going to be something, but we want to know about it. The MOGAD and NMO patients, oh no, I mean, they can go blind overnight. You know, so we're going to, you know, so it becomes a lot harder. It does seem like kids seem to have sort of the same flavor. I mean like a headache, you know, a headache may accompany it, but often kids will be able to tell you there's a difference. I have a low threshold to look sooner and eventually we kind of get the hang of it and I'll rescan. I have a low threshold to rescan quickly. So, I treat that, I jump on that, MOGAD, especially the aquaporin-4 positive patients, a lot faster. But again, the aquaporin-4 patients on rituximab really do nicely.

[00:49:47] **Rebecca Whitney:** Okay. And the same in your experience, Dr. Tenembaum?

[00:49:51] **Dr. Silvia Tenembaum:** Yeah, absolutely. It's a complete, absolutely different from MS. Here you have to pay attention to the patients, and I teach the children not the parents, the children.

[00:50:03] **Rebecca Whitney:** Yeah.

[00:50:03] **Dr. Silvia Tenembaum:** You have to, you have to check your visual acuity while you're seeing television, try with one eye and the other, you know, if example, do that. Okay. When you have time do that and check yourself and tell your mama to bring you to the hospital because if there is some difference you need an MRI. Or you need a fundoscopy because in MOG you have papillitis, immediately, the kid is saying, I see different with this eye.

[00:50:33] And you look at the fundoscopy, and you will see the inflammation of the optic nerve so that is an optic nerve relapse. Or some different syndrome, muscle strength with one leg or the other or bilateral. So those are signs that the kid is going to come and tell you. Okay. I think it's different. I have something even with the headache, they may have headaches in the meanwhile, but this is different.

[00:51:03] They can tell me, this is different, Dr. Silvia, this is behind my left eye. So, this is different. Kids are great. They can describe perfectly well. Yes. I think I have something different.

[00:51:16] **Dr. Jayne Ness:** Or the other thing is itching. Sometimes it'll be tingling in the feet. They'll be some little vague sensory symptoms that almost don't make neurologic sense, it'll be a bilateral, you know, tingling in their toes, tingling in their fingers.

[00:51:30] And you know, we want to lay eyes on these kids. And sometimes it might take a couple of visits, you know, before I pull the trigger. Because I met, you know, I tell my patients when I first meet them, it takes me a year to get the hang of you and you a year to get the hang of me, you know, to really sort of, you know, learn how that child's going to respond.

[00:51:48] **Rebecca Whitney:** Okay. Okay. But definitely good to know when they're experiencing those, those symptoms and they're AQP4/MOG positive, it's not a wait and see it's let's get on this now. Yep. Absolutely. Alright

[00:52:08] **Dr. Silvia Tenembaum:** We have the huge number of double seronegative patients.

[00:52:12] **Dr. Jayne Ness:** Yes.

[00:52:13] **Dr. Silvia Tenembaum:** And the care is the same. We will not suppress those children. If they have a relapse, it's a huge number of patients, more than those who are seropositive, for MOG or for AQP4, they do experience NMOSD, a clinical picture. So yes, management is the same.

[00:52:34] **Rebecca Whitney:** Okay.

[00:52:36] **Dr. Jayne Ness:** Yeah. Thank you for pointing that out.

[00:52:37] **Rebecca Whitney:** Yeah, definitely. Thank you. And just one last question. Pain, neuropathic pain.

[00:52:44] Is that an issue for children diagnosed with NMOSD? Is that something that you, see? Very prevalent? And, and how is that managed for children?

[00:52:55] **Dr. Silvia Tenembaum:** I think that it depends on the mean age of your cohort. If you have more adolescence or near to be adult patients, probably pain is an issue. I do not have so many patients.

[00:53:12] We have a younger, very young population. There is, that's not a problem. It's exceptional that I have to use medication for neuropathic pain. For adults is absolutely the first residual symptom or symptom they have to manage with a medication. I don't know if for Jayne it's the same experience.

[00:53:35] **Dr. Jayne Ness:** It's interesting. I mean, there is, I think that the NMO patients can have that pain can be a little bit more problematic, especially if they've got, if they've had a lot of, you know, a bad cord relapse, a little, it seems to get better with time. But sometimes, and again, a lot of times it's wanting to sort of figure out pain.

[00:53:53] It's often the, you know, again, a lot of great respect for the spinal cord. And now I know to ask children when they've had a cord relapse, regardless of what their antibody status is, if it's neuromyelitis optica but to ask about ephaptic symptoms, because they're just weird and, you know, again, the itching, the, the, that the paroxysmal symptoms.

[00:54:18] And so I think about, I, I try and figure out, you know, is it something that comes and goes as five minutes at a time? And then it goes away. There's another three to five minutes at a time, and then it goes away. And if it's that flavor, I typically use seizure medicine that either carbamazepine, Tegretol in the states or oxcarbazepine Trileptal, which is really effective.

[00:54:41] And patients who had both told me that the oxcarbazepine is less sedating. And so that's usually now what I use as a first line for that kind of pain. And then if it's a continuous pain, I usually use Gabapentin and I'm not afraid to push the dose.

[00:54:57] **Dr. Silvia Tenembaum:** It's exceptional for me, really exceptional.

[00:55:00] **Dr. Jayne Ness:** But, but it's more, it's more kind of the, ephaptic or sometimes I get some sustained burning, but I think I have a lot, I have a lot of, I have a lot of adolescents.

[00:55:09] **Dr. Silvia Tenembaum:** Okay. Probably that's the reason.

[00:55:10] **Dr. Jayne Ness:** The most common, you know the age of onset it's typically between, you know, it's right. You know, at the onset of puberty. I mean, again, I have a few younger NMO patients, you know, onset as young as age four, but most of them have been the, you know, early, 10, 11, 12, 13 onset.

[00:55:30] **Rebecca Whitney:** Alright. Well, that is all of the questions that I have for today. So, thank you both very much for your time and sharing your experience and expertise with us. It is truly appreciated.

[00:55:43] **Dr. Silvia Tenembaum:** Thank you for inviting us.

[00:55:45] **Dr. Jayne Ness:** Yes, thanks. Yeah. I mean, I've learned so much. It's been a great experience to, you know, it's a little, it's reassuring if I'm on the same page as Silvia, I always be like, that's a great thing, but learning a little, I'm going to add the cyclophosphamide to the plasmapheresis.

[00:56:00] **Dr. Silvia Tenembaum:** It's great to share the experience of a North American country and from a very South American country like Argentina. So, I think it's very nice to put together the experience of two pediatric neurologists.

[00:56:16] **Rebecca Whitney:** Absolutely.

[00:56:16] **Dr. Jayne Ness:** Absolutely.

[00:56:17] **Rebecca Whitney:** Absolutely.

[00:56:18] **Dr. Silvia Tenembaum:** It was a great idea, thank you, Rebecca.

[00:56:22] **Dr. Jayne Ness:** And, it was great learning for us.

[00:56:24] **Rebecca Whitney:** Yes, well I'm glad I could be of help in that way.

[00:56:30] **Dr. Jayne Ness:** Very fun.

[00:56:31] **Rebecca Whitney:** Yes. Well, thank you both so much. I really do appreciate it.