Pediatric and Adolescent ADEM

You can watch the video of this podcast at: youtu.be/wl8i03gAOw0

[00:00:04] **Dr. GG deFiebre:** Hello everyone and welcome to the “ADEM Academy” podcast series. This is the first podcast in an ongoing series about ADEM or acute disseminated encephalomyelitis. This podcast is titled “Pediatric and Adolescent ADEM.” My name is GG deFiebre from the Siegel Rare Neuroimmune Association and I will be co-moderating this podcast along with Peter Fontanez from The MOG Project. Peter, do you want to introduce yourself?

[00:00:30] **Peter Fontanez:** Hi, yes. My name is Peter Fontanez. I'm with The MOG Project and my daughter, Isabelle Fontanez is an ADEM and MOGAD patient as well.

[00:00:40] **Dr. GG deFiebre:** So, SRNA and The MOG Project are collaborating on this podcast series. We're both nonprofits that are focused on support, education, and research of rare neuroimmune disorders including ADEM and MOG antibody disease. You can learn more about us on our websites, which we are wearesrna.org and mogproject.org.

[00:01:02] **Peter Fontanez:** For today's podcast, we are pleased to be joined by Dr. Jonathan Santoro. Dr. Santoro serves as the Director of Neuroimmunology and Demyelinating Disorders Programs at Children’s Hospital Los Angeles. He is also an Assistant Professor of Neurology and Pediatrics at the Keck School of Medicine at the University of Southern California. Dr. Santoro completed his undergraduate, masters, and medical degrees at Tulane University. He subsequently completed residencies in pediatrics and child neurology at the Stanford University School of Medicine and subsequently had sub-specialty training in neuroimmunology and pediatric multiple sclerosis at Harvard Medical School.

[00:01:42] Dr. Santoro is a passionate NIH-funded physician-scientist who has published over 70 peer-reviewed manuscripts. His clinical and research focus is endocrine dysregulation in pediatric onset multiple sclerosis and the neuroimmunology of Down syndrome. He currently serves on the American Academy of Neurology’s Health Policy Sub-committee and chairs the Advanced Drug Monitoring Task Force. Dr. Santoro is a long-standing advocate for persons with disabilities and has lobbied locally in California and on Capitol Hill. Welcome, and thank you for joining us today.

[00:02:17] **Dr. Jonathan Santoro:** Thank you guys for having me. This is such an exciting topic and such an exciting opportunity to work with both organizations on putting the word out about ADEM to families that need this information. So, very excited to be here.

[00:02:33] **Peter Fontanez:** Well, let's start off with our first question, the first topic we're going to be discussing is diagnosis. With the discovery of the MOG antibody, aquaporin-4 antibody, NMDA antibody,

and other antibodies, walk us through the diagnosis process for ADEM considering other potential causes and differential diagnosis?

[00:02:51] **Dr. Jonathan Santoro:** This is a really important question. I think that ADEM can look different in every patient. And I think that if you talk to enough people in these advocacy groups and rare disease societies, you realize that nobody shows up with the same symptoms and I think that historically ADEM was all encompassing diagnosis. The radiographic or the MRI features were more broad.

[00:03:13] The clinical features could include anything including encephalopathy for the main symptom but in the age of antibodies where we've discovered all of these different causes for these symptoms, it's actually allowed us to be a little bit more specific. But ultimately the diagnosis is still one that is clinical and then paired up with the radiographic or MRI features in many cases. So, although we have more information, we have more tests to do that help us differentiate potential causes and ultimately prognosis and need for monitoring the diagnosis is still what it was many years ago.

[00:03:49] **Dr. GG deFiebre:** And are there any special considerations when diagnosing ADEM in children and pediatrics rather than in adults or is that diagnostic process similar?

[00:04:00] **Dr. Jonathan Santoro:** So, I think this is a really interesting question that we know ADEM is diagnosed more in children but it's not entirely rare entity in adults either. I think that when we look at children and of course I'm a pediatric neurologist by training, we think of it more as this Harold event which was really thought to be monophasic for many, many years. And now we've discovered that with MOG antibodies there is a percentage of patients that go on to have relapsing or multiple episodes of either ADEM or other demyelinating disease.

[00:04:30] And in addition, we found that children who have these initial attacks of ADEM sometimes actually go on to develop other demyelinating diseases like multiple sclerosis that we didn't think were necessarily related to one another. In adults, the secondary causes of ADEM seemed to be a little bit more common. Obviously, you still see some MOG antibody disease in that population as well. But toxic, metabolic, chemotherapeutic causes and infectious causes are a little bit more prevalent in that population and probably are more of a diagnosis of exclusion in adults whereas it's a little bit more inclusive and important to monitor over time in younger patients.

[00:05:10] **Peter Fontanez:** When diagnosing ADEM, is a lumbar puncture necessary, if not when is this used?

[00:05:16] **Dr. Jonathan Santoro:** This is one that comes up all the time. So, really if we just go by the criteria, no it is not necessary. So, the clinical features and then the MRI features are really what help us make the diagnosis of ADEM. I think that in the days now where we can actually test for many of these antibodies in both the blood and the cerebrospinal fluid. And given the importance of ruling out mimics of ADEM, we normally recommend that all patients will go on to get a lumbar puncture, but it is not critically necessary for the diagnosis of the condition. I think that when you have infection of the central nervous system or the brain on the differential diagnosis and a lot of other rare and unusual metabolic or genetic mimics of the conditions, especially in children, it's really important to have that data to support the diagnosis as well. So, while we have these diagnostic criteria, we want as much information as possible to feel really comfortable and confident in making the diagnosis as well.

[00:06:14] **Dr. GG deFiebre:** And so, you talked about clinical presentation and MRI, going back I guess a little bit, what is the clinical presentation of ADEM, and then also what do you look for on MRI that's characteristic of ADEM.

[00:06:28] **Dr. Jonathan Santoro:** So, the Number 1 thing that you need is encephalopathy or a change in mental status, people not thinking or being able to cognitively be the same. I think that's core feature of ADEM. After that, it's just like in real estate. It's location, location, location. So, where your inflammation is in the brain actually determines what symptoms, you are likely to have.

[00:06:49] So, for instance, if you have involvement of the optic nerve, vision may be the issue. If you have inflammation in the spinal cord, gait or walking may be impaired. If you have inflammation in the cerebellum, the back part of the brain, it may be coordination, but really it is highly variable. All things can be present or only a few things can be present. And I think that this just goes to what we were saying earlier is that every presentation of ADEM looks a little bit different but, really the encephalopathy is the key piece and then everything else is very dependent on the location of the inflammation.

[00:07:23] **Dr. GG deFiebre:** And then in terms of the MRI, are there other particular patterns you are looking for or you're just looking for inflammation in these areas?

[00:07:30] **Dr. Jonathan Santoro:** Yeah. So, the radiographic features are that you have involvement on both sides of the brain. And again, we think of inflammation is not really restricted to one side or the other. The lesions tend to be very broad, confluent, larger than some of the other lesions that we would see in things like multiple sclerosis, neuromyelitis optica, things of that nature. And then we pair those up with the clinical features. So, if you're - if the clinical features seem to match and the radiographic features seem to match, that's where we're feeling the most confident about arriving at the diagnosis of ADEM.

[00:08:02] **Peter Fontanez:** On that note, you're speaking about clinical features matching up with MRI features and things like that. Can a patient present with symptoms consistent with ADEM yet not initially show on the MRI? If so, what actions should healthcare professionals take in this case, including patient's follow-up or additional MRI?

[00:08:20] **Dr. Jonathan Santoro:** This is a great question peter. So, yes and no. So, the criteria really require that MRI feature. But what we know is that no test is 100% sensitive. And so, in these situations where the imaging comes back negative but some of the features or many of the clinical features match, it's really important to just repeat an MRI. I think that we've been surprised when we have patients that have all of these symptoms but then we get the MRI and there's nothing there.

[00:08:49] Sometimes it just takes a little bit of time to actually develop those features on the neuroimaging. So, there have been many cases and in many cases that we've seen over the last few years where we get the MRI early and now, we can get MRI's almost instantly when patients come into the hospital and the imaging features may not be as striking right out front. But a few days later then they actually start to emerge and evolve into what we would normally expect.

[00:09:04] **Dr. GG deFiebre:** And then speaking about MRI, so for adults you can tell adults to get in the machine and stay still. Are there particular recommendations for sedation or really what are those recommendations for small children who need to get imaging?

[00:09:29] **Dr. Jonathan Santoro:** Yeah. And I think this is a complicated issue because we're talking about what's the risk, what's the benefit. The risk of being sedated is there and something to always talk about with the anesthesiologist. There's no sedation that is risk free, but we have to weigh that against having a confirmatory diagnosis and making sure that we're not missing another mimic that could look like ADEM clinically but maybe doesn't have those neuroimaging features. So, I still think it's generally suggested that we go through with the sedation.

[00:09:59] And thankfully at many pediatric hospitals, we have people who are not just trained in pediatrics and anesthesiology, but specifically pediatric anesthesiology. So, well there's no certainty that there is no risk. It's generally very important to have that piece of data to make the diagnosis. Although I will say the youngest patient, we have ever been able to get in the scanner without sedation is about five. So, it can be done. It's certainly the outlier in the situation, but we always want to weigh risk and benefits with any intervention that we do.

[00:10:32] **Peter Fontanez:** On that note, I know this one affects everybody personally because we've all gone through this with this diagnosis. What are some of the diagnostic challenges that some parents and health care providers face and what are some of the ways that they can overcome these challenges?

[10:0:48] **Dr. Jonathan Santoro:** I think Number 1 is being a well-informed parent. I think that ADEM is a surprise diagnosis for many people. I don't think that anyone goes into the hospital thinking that this is what is going on with my child. So, becoming rapidly informed is always the best way to get up to speed and be able to communicate with your physician's your care team, everybody. I think that because ADEM and many demyelinating disorders can look so different in each person, it's a challenge because there's not one feature that I would say oh yeah you definitely need to be evaluated for a demyelinating disease. These conditions are extraordinarily rare.

[00:11:26] As many people listening to this podcast have probably figured out and so really what I look at as a physician is how confident am I in this decision? Conversely how confident am I that this is something else? And this is where all of these diagnostic tests can be really linked in together to help fit that puzzle piece. So, if the clinical features don't fit, the MRI doesn't fit, can I use something like a lumbar puncture spinal tap? Can I use an EEG? Can I use blood testing genetic testing to make sure that we're arriving at the right test so that I can start the right treatments?

[00:12:02] **Dr. GG deFiebre:** And then who typically does this diagnostic process, is it in the emergency room is it neurologists? Do you mind just talking a little bit about, who on the team isn't involved in that?

[00:12:15] **Dr. Jonathan Santoro:** I think that for individuals who are coming in for the first time it's usually through the emergency room. Most of the time, the pediatric neurologists are going to be involved pretty early on in the diagnostic journey. But every hospital system is a little bit different. I mean there are definitely hospitals out in the more rural and suburban areas of the country that don't have a pediatric neurologist available, and you may be worked up by a pediatrician who's trained in hospital medicine. So, it depends on each institution. But what we always recommend is once the diagnosis has been made to reach out to somebody with specialty training in neuroimmunology and specifically pediatric neuroimmunology if that's available as well.

[00:12:57] **Peter Fontanez:** Are there any other diagnostic criteria or testing that a patient can expect when trying to figure out these diagnostics. I know we talked about MRI and antibody testing but is there anything else that a patient can expect to have?

[00:13:10] **Dr. Jonathan Santoro:** Yeah, I think that those are the big too. I think that lumbar puncture the spinal tap is also on there for most patients. ADEM can be associated with seizures. So, often individuals who come in through the hospital will get an EEG as well. And then in addition we've added on additional blood testing over the years and again it's a rule out diagnosis. So, it will depend on what you show up with. But a lot of the time the expectation would be at least an MRI and blood work but very likely lumbar puncture and potentially an EEG. Two of the symptoms fit.

[00:13:44] **Dr. GG deFiebre:** I just have a question. So, we sometimes hear from people that they the inflammation of the spinal cord or an inflammation in the optic nerve and they say I have transverse myelitis, optic neuritis, and acute disseminated encephalomyelitis. Is that how it actually is? Is this a terminology debate? Just curious about your thoughts on that.

[00:14:05] **Dr. Jonathan Santoro:** It's a really good question. Technically that's not incorrect. So, really what we're describing is that there's inflammation in these specific parts of the brain. Optic neuritis just means inflammation of the optic nerve. Transverse myelitis, inflammation of the spinal cord. When we talk about ADEM, I think what we've focused so much on for so long was that the encephalopathy piece and it's very likely we were missing a lot of optic neuritis or transverse myelitis that was happening at the same time.

[00:14:31] So, I think that because we've become better about evaluating it in the hospital and certainly in the outpatient clinics, you can say ADEM and have it be all encompassing. But I think that what is most helpful for me when we evaluate new patients is to know exactly the prior areas that were affected because there is importance for prognostication likelihood of MOG antibodies and then certainly what is the monitoring that is going to be needed for these patients' long term. So, I tend to be on the side of tell me more than tell me less.

[00:15:05] **Peter Fontanez:** We're going to go ahead and move on to our next topic which is treatments. What is the typical treatment for a patient dealing with an active attack?

[00:15:14] **Dr. Jonathan Santoro:** So, when patients come in and the diagnosis is made, most patients are going to receive 3-5 days of IV steroids right off that other therapies that emerge after that or IVIG. And sometimes plasmapheresis and certainly in refractory cases you may be seeing more target biologics or other anti-inflammatory medications. I think a big challenge in ADEMs, there's not ever really been a randomized controlled clinical trial about what the best therapy is. So, while we stick to the dogma of steroids first and IVIG or potentially plasmapheresis afterwards there's a lot of variability hospital to hospital, region to region, and I think that that's certainly an area that hopefully will be addressed by some larger scale studies in the near future. But as we know, in ADEM, MOG antibodies, they're rare and so trying to put together a standardized clinical trial for this stuff is a staggering task in spite of the need for it.

[00:16:11] **Dr. GG deFiebre:** And does the acute treatment differ based on whether someone is MOG positive or not if they aren't? Is that acute treatment still the same?

[00:16:22] **Dr. Jonathan Santoro:** For the acute treatment not too much. What we do know is that individuals with MOG antibodies tend to be more responsive to steroids. So, often what we train our residents and fellows on is to say that, with a MOG associated ADEM the symptoms should melt away, they should be very quick to resolve whereas in non ADEM associated causes it may be a little bit more challenging or require the other therapies.

[00:16:46] But I think many of the neuroimmunologist out there have certainly seen exceptions to that rule where the MOG antibody was found later, and they didn't have that classic melt away response to the steroids. So, it varies. But I think that this is the challenge is we know that the MOG antibody is out there. But are there other blood-based biomarkers that were still missing that could be helpful for determining who's going to respond to what therapy?

[00:17:10] **Dr. GG deFiebre:** And so, moving beyond the acute phase in terms of preventive treatments should a patient be on preventive treatment and if so, what treatments are recommended and does this depend on the cause of the ADEM?

[00:17:25] **Dr. Jonathan Santoro:** So, this is a really important question and I wish I could give you a more specific answer but it's very unclear still. So, I think that again ADEM was thought to be monophasic for many, many patients but now we're finding that there's relapsing associated ADEM. There is ADEM with MOG antibodies that evolves to other conditions like optic neuritis, transverse myelitis, or neuromyelitis optica, and there's other patients who develop ADEM who go on to develop multiple sclerosis. And I think that we've gone back and forth on a community for prevention versus waiting for a second attack before starting patients on it. But I think the jury's still out, and I think that this is another example of there are regional difference, hospital, hospital differences. But we don't have strong data to support preventative therapy at this time.

[00:18:11] **Peter Fontanez:** I know that certain conditions like MS, NMO, aquaporin-4, and MOG antibody disease, you can have issues with specific treatments that they may not be as reactive to when - so we talk about ones that are reactive. But now for those that aren't reactive, are there any treatments that should be avoided depending on the cause of ADEM example like MOG antibody, aquaporin-4, or, like you were saying, MS? Is there any treatment that should be avoided?

[00:18:36] **Dr. Jonathan Santoro:** Yeah. So, I think that this is really hard in the acute period where you're not necessarily sure which direction to go. For ADEM and MOG antibody syndromes we use a very broad immunotherapy. So, it's rare that we're using something so targeted that we're going to cause additional problems. But I think as we've seen in individuals with neuromyelitis optica when we've treated them, these patients who have aquaporin-4 mediated disease. They go much worse when we gave them MS therapies in spite of the fact that they were very broad MS therapeutic. So, I think it's something that we need to explore a little bit more to see what works and what doesn't. But in the same breath, we haven't really had a lot of experience using targeted biologics or even MS medications in individuals with ADEM or MOG antibody symptoms. But it's certainly on the horizon in an area where we need to pivot and investigate a little bit.

[00:19:26] **Peter Fontanez:** For treatment. So, we talked about acute like patients that are going through acute attacks and treatments for that. But for long-term preventative, what are some options that a patient may be able to be on for preventative treatments long term?

[00:19:42] **Dr. Jonathan Santoro:** So, in individuals who have had more than one relapse and are associated let's say with MOG antibodies, I think an important - the best data thus far has been IVIG or intravenous immunoglobulin, mycophenolate mofetil and then rituximab have been the big three that have been used the most in the literature. For individuals that go on to develop subsets that aren't associated with MOG antibodies, I think that that is a little bit less clear. And individuals certainly go on from ADEM to develop multiple sclerosis, it's a whole different therapeutic class.

[00:20:17] But I think that for at least from MOG antibody-associated disease prevention those have been the big three that we've had the most success with. And I think it depends on the patient who gets what. So, IV therapies are a bear and especially if you're a younger patient going and getting pricked once a month can be a lot. So, we've had success with using high dose mycophenolate. We've had success with using rituximab, but we've certainly had success with administering IVIG. But nothing to say one is superior to the other. So, there again a lot of regional differences with this one.

[00:20:50] **Dr. GG deFiebre:** Related too, so you mentioned how getting IVs for small children can be difficult. Do you find that treatments change over time as children get older or typically stay the same?

[00:21:02] **Dr. Jonathan Santoro:** Yeah. I mean we keep that open dialogue with patients, and I think that certainly for some of our older pre-teens or teenagers they have opinions and that's it would be silly for us as physicians and immunologists to ignore those. So, if a patient comes in and says I don't want to do IV

therapy anymore, that's fine. We're going to have to find something else though. Or similar if they say I can't tolerate this mycophenolate because it's making my stomach upset and I have all these other side effects. Then we have to consider using something else too. I think that during the pandemic there was a lot of concern about infection as well. And so many patients were preferring to be on IVIG knowing that that is an immune boosting medicine in most circumstances as opposed to immune suppressing like the other two.

[00:21:49] **Peter Fontanez:** You were talking about IV access, and I know being a caretaker of a child who had to have IV access monthly. I know it could be very burdensome now with that, very difficult. What are your options between or what are your thoughts regarding IV access on a child versus a port because I know a lot of patients have gone through that in the community and when do you feel the need to switch over from IV access to a port like how long that time frame when you think okay that would be too long let's switch it over?

[00:22:23] **Dr. Jonathan Santoro:** And I think this is a tough and very personal decision for family. So, a port is a central access point that is right under the skin. That basically you don't have to prick an IV anymore. You just going to stick the needle right into this plastic piece that's under the skin over the chest to access. So, it's a lot easier especially for young patients, certainly less traumatic than going through and trying to find a vein. Ultimately there's not a magic number though. So, for us at least at Children's Hospital, Los Angeles, we say if we're going to continue therapy on over a year then it certainly should be discussed and at least be evaluated.

[00:23:02] But there are some families we've spoken to this, there's under no circumstances would we go through with this. And then other families are asking me at the very first visit because they have a traumatic IV placement. So, I think it's something to definitely bring up with your doctor, especially if it's looking like it's going to be more than a few infusions moving forward. I think that many of us as physicians, we don't want to do something that we can't easily track out of. So, if we're going to change the therapy and IVIG is now off the table then having a port in as physicians are like we should have never put that in. So, I think it's something to bring up early and certainly, it's going to be a case-by-case discussion with your doctor.

[00:23:43] **Dr. GG deFiebre:** And then we did get a question from someone listening about the difference between a neurologist and a neuroimmunologist. Are these the same or different?

[00:23:53] **Dr. Jonathan Santoro:** Great questions. So, all neurobiologists are also neurologists, but not all neurologists are neuroimmunologist. So, the way to think about it is it's the specialty that really only is dealing with ADEM, MOG, autoimmune encephalitis, optic neuritis, transverse myelitis, that's what we do day in and day out. So, we have ability to remain up to date on the literature. We're participating in the clinical trials, the natural history studies but a neurologist in many situations is going to be up to speed on MOG is going to know the basics of the treatment and can certainly reach out for assistance. Not every center has a pediatric-trained neuroimmunologist and I think that that's something whereas a community we try to be as collaborative as possible. We're always answering emails getting on the phone with people, but it just may not be possible in some circumstances and that's totally okay.

[00:24:46] **Dr. GG deFiebre:** So, do you mind we're going to move on past that the treatment phase, acute phase and talk a little bit about outcomes and the long-term care. So, do you mind just talking - you talked about monophasic ADEM, and how that was what we thought ADEM was for a long time. Can you talk a little bit about monophasic ADEM versus multiphasic ADEM and what that means?

[00:25:07] **Dr. Jonathan Santoro:** Yeah. So, I think that the name tells you right off the bat. So, monophasic meaning it happens once and you're done relapsing while multiphasic ADEM meaning it's happening more than once. It's interesting because for many years with monophasic ADEM we labeled somebody as a patient

is having ADEM and then we said, okay, call us if you need us. And so, we didn't know if those patients were actually relapsing for the longest time, or they would have another attack. But now it was optic neuritis, and we weren't really drawing that connection between the ADEM, optic neuritis, transverse myelitis whatever the next attack would be. I think now because we're following patients in neuroimmunology clinics, we have this natural history that's become very robust and we know that certain antibodies for instance MOG are more likely to be associated with those relapsing courses. I think that we're monitoring and actually identifying that relapse whether they're multiphasic ADEM meaning ADEM that happens more than one time, or ADEM that transforms into optic neuritis, transverse myelitis, or neuromyelitis optica is much more common than we originally thought.

[00:26:12] **Peter Fontanez:** As you were talking about how it transitions to with optic neuritis - so I know that there was also - I don't know if this is still considered a diagnosis, but it used to be one of the other ones. There was monophasic ADEM, recurrent ADEM, and multiphasic ADEM. Is recurrent ADEM still a thing or is that something that has been phased out since?

[00:26:35] **Dr. Jonathan Santoro:** Yeah. You can never really phase out the terminology. I think it's certainly probably come more under the umbrella of the multiphasic ADEM. So, we use the terms interchangeably when there is a second attack. But I think that many of these terms are arbitrary as well. Like even for ADEM when you have an attack that is very closely associated with the original attack, we didn't know for the longest time whether to say that all of this is part of the original attack or actually these are two discrete events. So, if you put 10 neurologists in a room, you're going to get 10 different answers on how it should be named and what it should constituted. But I think for all intents and purposes we're putting them under the same umbrella right now.

[00:27:20] **Peter Fontanez:** With that, is there a difference between multiphasic and recurrent ADEM or - because you're talking about using them interchangeably. But is there a difference between the two?

[00:27:29] **Dr. Jonathan Santoro:** Yeah. For historically we thought is the recurrent form is like the exact same process happening again like the same symptoms were coming back. Whereas multiphasic I think help identify that there is not just a different point in time that this is occurring, but the symptoms may be different even though they're meeting criteria for ADEM at that time. So, again it's a little bit of more argon than anything. I think that any neurologist and any parent who is looking at the patient is going to go okay well this is recurring or multiphasic ADEM whereas the exact terminology doesn't impart as much understanding about what the disease process is.

[00:28:09] **Dr. GG deFiebre:** And so, you talked about an onset if someone has for example inflammation of the spinal cord, they might have issues with gate visual issues for optic nerve inflammation. So, what might be the outcomes or long-term impacts of an ADEM attack?

[00:28:25] **Dr. Jonathan Santoro:** So, for most patients who develop ADEM the outcomes are generally excellent. Now that depends on antibodies. It depends on response to treatment, and it depends on the location of the inflammation as well. So, what we know for instance is that if you have optic neuritis as part of your ADEM and its MOG antibody responses, generally the visual outcomes are quite good. Whereas if you have optic neuritis without the MOG antibodies you can expect to have some impact on it. But again, there's always exceptions to the rule what we found most is whether it's monophasic or relapsing, there have been long-term neurocognitive outcomes associated with ADEM.

[00:29:04] And that includes things like ADHD impulse control, behavioral disturbances that many of us have observed very subtly but maybe don't actually carry that diagnosis. It's another important thing to bring up.

But then again like other things are much more obvious. So, recovering from transverse myelitis you may be left with permanent gate issues or walking issues or have a long-protracted rehabilitation course. So, it really just depends on where those insults are, which is why it's so important to be able to recognize it quickly and treat it quickly as well.

[00:29:40] **Dr. GG deFiebre:** And so, you mentioned these long-term symptoms. Is it also possible to have seizures or additional behavioral or cognitive issues too?

[00:29:51] **Dr. Jonathan Santoro:** So, neurocognitive issues are really interesting because we've phenotyped them very poorly. Most neurologists especially neuroimmunologists are so focused on ADEM, so focused on MOG antibodies that were glazing over some of the behavioral issues that emerge in school. So, again ADHD, impulse control sensory processing issues come up quite a bit. We've had a few patients who have had ADEM very early who have high functioning autism later on. And again, it's not that they are developing autism because of the ADEM, but there is something about this process that's affecting brain development that may be associated with this.

[00:30:30] Seizures are very interesting. If you have seizures up front, you are likely, or at an increased risk of having epilepsy in the long term. What we've observed so far - and our group is looking to actually publish some of this data is that with MOG antibodies, if you have seizures up front, you go through this quiescent period for usually a year or two and then are developing epilepsy on the back end of it and it's often not associated with the MOG antibodies, meaning that there's been some injury to different parts of the brain that are creating epileptic foci or areas where seizures come from just from the nature of having an attack of ADEM and specifically in this situation with MOG antibodies.

[00:31:13] **Dr. GG deFiebre:** And then if a child is experiencing some of these behavioral or cognitive issues, do you typically refer them to see a neuropsychologist or who manages those cognitive issues?

[00:31:24] **Dr. Jonathan Santoro:** It depends on the symptoms. So, I think that in general, we're always referring to neuropsychology because it allows us to get a baseline. So, few patients are going to have some type of assessment before their symptoms develop that getting that immediate baseline and being able to track that longitudinally over time, is super helpful and can identify strengths and weaknesses of the individuals so that way they can be receiving extra help in the school system if they need it. Some patients need a psychologist, that type of therapy, behavioral modification, some patients need actual pharma co-therapy.

[00:31:56] So, therapies for their ADHD or impulse control which are often administered by a psychiatrist. But it's a multidisciplinary effort. So, everybody is involved with the care of the same exact patient. But having that open discussion with your neuroimmunologist or your neurologist who's usually the quarterback for the team to help point in which direction your child needs those resources can be very helpful. I think one of the hidden secrets is having an education specialist that you work with. Sometimes they're social workers, sometimes they're former teachers or have a background in educational advocacy. Those are all really important things to optimize educational outcomes in individuals who have this.

[00:33:29] **Peter Fontanez:** What are some of the signs and symptoms that a parent should look for during a possible ADEM relapse, like example, what are some of the signs and symptoms for ADEM, optic neuritis, or what are some of the signs and symptoms for multiphasic?

[00:32:51] **Dr. Jonathan Santoro:** Yeah, it's a great question and again, it can look like anything which makes it extra complicated for families and caregivers. So, Number 1, if it's ADEM there's going to be encephalopathy or that change in mental status. Again, if there's optic neuritis, visual complaints, double vision can be a

problem, eye pain with movements can be a problem. Again, if it's more - in the brain, it can be a weakness, it can be sensory changes. If it's in the cerebellum, it can be gait abnormalities, ataxia, and meaning it's difficult to point to objects and certainly for the spinal cord, what we worry about is weakness, difficulty walking, and potentially even bowel or bladder syndrome.

[00:33:27] So, I think that that's one of the underscored things that we've found about MOG antibodies is it tends to hang out at the bottom of the spinal cord, which can cause something called the neurogenic bladder, meaning you can get all the urine out so it can look like many different things which makes it challenging. But I think that what we always tell families is if the mom, dad, aunt, grandma, grandpa radar is going off, that's enough for you to be contacting your neurologists and reaching out.

[00:33:54] **Peter Fontanez:** With that, we're going to take a question from the community. Are you seeing any patterns regarding which MOG positive ADEM patients relapse versus which ones don't?

[00:34:05] **Dr. Jonathan Santoro:** In the single digit age group, not necessarily. I think we've been basing it much more the continued presence of the MOG antibodies more than anything. In the post puberty crowd, we found that optic neuritis has a much higher rate of relapse, transverse myelitis has a higher rate of relapse. So, we stratify it more by age and on the initial onset less so than some of the core clinical features. But in the same breath ADEM is much more common in the single digit age group then optic neuritis and transverse myelitis is in the older age group. So, hard to make heads or tales of that.

[00:34:40] **Dr. GG deFiebre:** And then is rehabilitation useful after an ADEM diagnosis? And if so, what types of rehabilitation should patients consider for the best outcome? So, the occupational therapy, physical therapy, speech therapy, when does this vary on the potential lingering symptoms that someone might have?

[00:34:58] **Dr. Jonathan Santoro:** So, early evaluation for therapy services is great if you're in the hospital setting. So, some centers have inpatient rehabilitation which is fantastic if you can access it but it's going to depend on what the leftover symptoms are. So, certainly if there's weakness or if there's coordination problems, physical therapy, occupational therapy can be fantastic and very helpful. For people who have had dysphagia, difficulty swallowing, difficulty with language, or some of those cognitive complaints, speech therapy can be very helpful. And then we've had a number of patients that have gone on to inpatient rehabilitation for a week or two on the back end and really benefited from that. So, in general, we always recommend it where it's available and it's one of those two things as a doctor, I can prescribe therapy and it's not going to harm the patient. There's no side effect of getting those extra therapies, extra support whether it's on the impatient side or the outpatient side.

[00:35:53] **Peter Fontanez:** Dr. Santoro on a follow up to one of the questions you just answered about what are some of the symptoms that a patient parents should look for. You mentioned all these symptoms like you said ADEM can look like just about anything depending on where the attack is occurring, where I know that there's also pseudo relapses as well as like things like Utah phenomenon which can trigger things that seem like relapses. At what point should a parent or a caretaker time frame wise? Like if a patient has a headache, obviously you don't want to call the doctor for five minutes of a headache, but if they have a headache last or they're having mobility issues for a whole day, like what's the time frame that you're talking about these neurological symptoms? Because obviously with pseudo symptoms, pseudo relapses, and Uhthoff's phenomenon where do we draw the line that, okay, this may be a new neurological attack versus just a small side speed bump?

[00:36:50] **Dr. Jonathan Santoro:** This is a fantastic question. So, three important things. The first thing is if your concern radar is going off, just contact your doctor. If your gut is telling you that something is wrong,

just call, just show up. Nobody's ever going to fault you for being overly concerned. For recrudescence or the Uhthoff's phenomenon or pseudo relapse those symptoms should generally look like exactly what happened before and an important piece of this that you can think about as a caregiver is, is there some stress on the body that could be allowing for this? Is your child sick? Are they sleep-deprived? Are they stressed out? Is there something else going on that could help explain it?

[00:37:34] For instance, Uhthoff's phenomenon is often seen when there's high heat, and then all of a sudden it feels like a relapse is coming back. If you can pair, it up with some type of temporal stressor and then removing that environmental or temporal stressor results in improvement of the symptoms. Generally unlikely or less likely to be a relapse. But that other piece, well, what about the time frame? We all make up numbers and let's be honest as an immunologist, we say 24 hours if it's less than that, it's probably not anything serious. If it's longer than that, we definitely want to get the evaluation. But again, like always follow this in order. So, Rule 1, if your gut is telling you something is wrong, then something is wrong. Number 2, if it looks and you have - looks similar to what you had before and there's another explanation for it wait it out and then the third is that magic 24-hour window. So, if it's lasting too long, just call in and get evaluated.

[00:38:32] **Peter Fontanez:** With that, what are some of the effects that a pediatric ADEM can have on a child's education such as like cognitive or behavioral issues in school and things of that nature?

[00:38:43] **Dr. Jonathan Santoro:** Yeah, this is really important. And something that we're realizing in real time. So, now while the prognosis neurologically is excellent for most patients who develop ADEM, school issues crop up a lot and they can be soft. So, attention problems in school impulse control issues are not something that are usually getting flagged and are getting brought up to a neurologist. So, always talking about it, getting that neuro-psych assessment, and then finding the strengths and weaknesses on those neuro-psych assessment so you can advocate for better resources within the school district tutoring or pharmacotherapy in some situations is really important. So, we know that even a single attack of ADEM can cause these augmented or different outcomes long term. So, I tend to favor the side of let's get the testing and see if we can help out with any needs. But thus far we haven't found something that reverses that effect. But again, I'm hopeful that in the future we're going to find that early identification, early treatment can actually benefit patients in the long term.

[00:39:46] **Peter Fontanez:** On that, how do you distinguish - especially like a tween/teen child, how do you distinguish an ADEM or long-term cognitive behavioral issues versus just puberty that we deal with as parents because I know that's one of the difficulties I have with my child?

[00:40:07] **Dr. Jonathan Santoro:** Yes, and an important one. And this is where I still thank myself that both of my children are under four still and I don't have to deal with. But I think it's a challenge. And I think that that's where having that baseline testing is really important because if you get the baseline neuropsychiatry and it looks the same at 13 as it did at 10 then I think we feel a little bit more reassured, and we can say this is probably more teenage stuff. Obviously, it's a little bit more challenging if the ADEM happens at the time when all of these changes are going on too.

[00:40:36] But I think that erring on the side of do we need to treat this or do we need to intervene or not is always important. But that's where the multidisciplinary care comes. As a neurologist, neuroimmunologist, I can tell you with confidence I am not great at figuring out the nuances of ADHD and educational issues, but I need to ask for help. I need to ask for help from our neuropsychologist from our psychiatrist to make sure that we're doing as much as we can for our individuals. But again, Peter like having those baseline assessments makes it really easy to say like this is something we need to worry about, or this is something that is just hormones and being a team.

[00:41:15] **Dr. GG deFiebre:** We got some questions from some listeners. One said why was ADEM discovered so long before MOG? And how was it discovered?

[00:41:25] **Dr. Jonathan Santoro:** It's a really cool question. So, I mean, the discovery of it just like with anything neurology is the phenotype. So, if you go back, whether it's Parkinson's disease, Alzheimer's disease, multiple sclerosis, we describe as neurologists what we see. And so, these presentations as you all know, are very dramatic in children, the encephalopathy, the other neurologic deficits that show up, the seizures that can be present, it's not a very subtle thing that springs up. So, the initial reports were just descriptions of what was going on. The funny thing is that when MRI came around, it was still very difficult to obtain. So, we didn't have great radiographic description of ADEM until the 80s and 90s. And once we emerged from there, we started pairing up like this is the clinical piece. This is the radiographic piece. This seems to be what ADEM is.

[00:42:20] But I think that, from the get-go ADEM encompassed many, many different things and it was encompassing MOG. It was in encompassing other demyelinating conditions and only now we've been able to differentiate it, the MOG antibody has been known about 40 years. It's just we never put two and two together and understood that this was pathologic because in our basic science experiments it didn't seem to be causative of the type of demyelination that we observe in individuals who have ADEM. And I think that some of this is because the animal model, so the way that protein is expressed from MOG and mouse and rodent or rat models is different and causes different symptoms in different radiographic patterns in humans and that held us up a little bit, but ultimately, it took us a while, but we got there and I think that it's really revolutionized how we look at this condition in children and adults.

[00:43:17] **Peter Fontanez:** On that Dr. Santoro, you have answered - these questions have been incredible. Thank you so much for your time. We wanted to ask you some final thoughts on ADEM, the direction of ADEM. I know there's going to be like a long dark question, but your final thoughts on ADEM, the direction you see it going in. Is there any research you currently see that's all - that's coming up or ongoing for pediatrics and just ADEM patients in general and anything in particular that you're working on for neuroimmune diseases because I know you're heading up a lot of incredible things right now. Give us some information on some of the nuances, the things that are coming up around the corner that you are working on and with ADEM in general.

[00:43:59] **Dr. Jonathan Santoro:** Yeah, I think that it's an exciting time to be a neurologist in research here. So, we're learning so much more about what this condition looks like over time. We're learning very quickly who we need to treat and who we don't need to treat. And I think that the finding something that is both specific and effective for the treatment of MOG ADEM, non-MOG ADEM and all of these other different phenotypes that can emerge from there is becoming increasingly important. So, I think as a young neurologist - and you guys can't see my gray hair, but it is starting to crop up on the side of my head it's such a cool time because I'm able to collaborate with people who are very senior and have done this type of research in multiple sclerosis, already, who have done it in neuromyelitis optica and aquaporin-4 disease.

[00:44:52] So, I feel like if anything ADEM and MOG associated demyelinating conditions are probably on the fast track for actually having breakthrough immunological developments because we can apply what we've already learned in other conditions over. For us, what we've pivoted to is looking at the common genetic links for many of these conditions and in a paper, we published with one of our fellows just over the summer, we found that not just in MOG but ADEM and then other desalinated conditions. There seems to be common pathways that are explained from a genetic predisposition standpoint, which could explain how these conditions, not just evolve over time, but mix and match. ADEM becomes MS in some situations, MOG stays as MOG. Relapsing optic neuritis versus transverse myelitis versus going back and forth.

[00:45:44] I think we're finding that there's more similarity than difference at a very basic level, even though the phenotype may look completely different. So, exciting time, but there's going to - we still have work to do. And that's the thing is that while I feel like we've made a lot of progress, we still don't have a randomized clinical trial. We still don't know who to treat with preventative therapies versus waiting for a second attack. We still don't have something that is specific for ADEM. So, we've got a lot of work to do. But it's an exciting time and I'm very much looking forward to what the next decade is going to bring.

[00:46:18] **Dr. GG deFiebre:** So, with the clinical child's form MOG, what do you think it'll take for clinical trials for ADEM to launch and are there different considerations for studies with children versus adults? This is a question we got from an audience.

[00:46:34] **Dr. Jonathan Santoro:** So, I'm really excited about the MOG trials, but ultimately, we can be more all-encompassing and MOG because there's different phenotype that we can pull in. Whereas ADEM is a little bit more narrow. It's a little bit more rare. Now when we think about clinical trial design as we mentioned, ADEM in children seems to be a little bit more homogeneous and more likely to be demyelinating whereas in adults while we still see it and it often is inflammatory, there can be other explanations for the ADEM too. So, if I had to make a guess, I'd say we're probably closer to a pediatric ADEM study as opposed to an adult ADEM study, but both will be tremendously important. I'm hopeful, but it's a little bit harder to recruit these very tiny populations as opposed to with MOG where we can pull in optic neuritis, pull in transverse myelitis, and pull in ADEM patients all in one breath.

[00:47:24] **Peter Fontanez:** We have one question from the Facebook community as this is Facebook live. And their question is - I got to read this because it's within the whole paragraphs. So, I got to find where I'm at. Though she has recently been diagnosed with a syringomyelia, could there be anything to do with her having ADEM? A patient that was I guess recently diagnosed with syringomyelia, is there any relation to that with ADEM?

[00:47:51] **Dr. Jonathan Santoro:** Hard to know. Usually, we won't see something like that in the acute period, but it's certainly possible to find afterwards. There's probably another explanation for it. And again, this is one of those things where when you have a diagnosis of ADEM or MOG, anything after that is the first thought is oh this must be related, but it could be that it's just a variant, it could be caused by something else. So, certainly a discussion to have with your doctor but hard to know without knowing more information.

[00:48:21] **Dr. GG deFiebre:** Thank you. I know we asked final thoughts. I don't know if you have anything else to add, but this is really great. We got through many questions, and we really appreciate your time.

[00:48:30] **Dr. Jonathan Santoro:** Of course, now, very happy to be joining with you guys and like I said, super excited about what's to come. We've got a great community, a lot of neuroimmunologists, neurologists care a lot about advancing this condition, all rare neuroimmunological diseases. So, it's an exciting time to be a physician and certainly we're always out there. We're a phone call, email away if you guys need anything and looking forward to the next couple of years.

[00:48:57] **Peter Fontanez:** Dr. Santoro, thank you.

[00:48:58] **Dr. GG deFiebre:** Thanks so much. Bye everyone.

[00:49:00] **Peter Fontanez:** Thank you guys. Have a good day.