

The Transverse Myelitis Association 'Ask the Expert' Podcast Series

Pediatric-MOG Associated Disease and ADEM Podcast

The audio of this podcast is available at <https://myelitis.org/resources/pediatric-mog-antibody-associated-disease-and-adem/>

- GG DeFiebre: 00:06 Hello everyone and welcome to the TMA ask the expert podcast series. Today's podcast is titled Pediatric MOG Antibody Associated Disease and ADEM. My name is Gigi deFiebre and I will be moderating this podcast along with Peter Fontanez whose daughter Isabel was diagnosed with ADEM and MOG Ab disease.
- Peter Fontanez: 00:27 Hello, my name is Peter Fontanez and I am a member of the TMA and MOG project which is a group of MOG patients and parents of patients who have been working to help with getting information out there regarding MOG. My daughter Isabel was diagnosed with ADEM in 2014, she relapsed in 2016 and was diagnosed with possible multi-phasic ADEM with optic neuritis and finally MOG associated antibody disease in May of 2016. She is still MOG positive and continues to receive treatments but has recovered greatly from past attacks and is doing very well currently. I would also like to mention one of our MOG Project members who I worked with together on putting this work together with putting these questions together for the podcast. Jennifer Gould contributed to this podcast. Her daughter Sophia was diagnosed with MOG antibody disease in January 2018 after a bout of autoimmune encephalitis and optic neuritis. She is currently responding well to treatments and has regained the majority of her eyesight and is an active third grader. Jen and I both are both passionate about spreading awareness and sharing our stories about pediatric MOG antibody associated disease and we are so excited to be part of this podcast as well as The MOG Project.
- GG DeFiebre: 01:34 Thank you so much Peter and Jen and the rest of the MOG Project. The TMA is a nonprofit focused on support education and research of rare neuro immune disorders and you can learn more about us on our website at myelitis.org. Just so everyone knows, the podcast is being recorded and will be made available on our website for download as well as via iTunes. During the call if you have any additional questions, you can send a message through the chat option available in Goto Webinar. For today's podcast we are pleased to be joined by Dr. Brenda Banwell and Dr. Leslie Benson. Dr. Banwell graduated with a degree in medicine from the University of Western Ontario in 1991. She completed a Neuromuscular disease fellowship at the Mayo Clinic in Rochester, Minnesota. In 1999 Dr. Banwell was

appointed as an assistant professor of Pediatrics Neurology at the Hospital for Sick Children and University of Toronto and was promoted to full professor in 2012. Dr. Banwell is now chief of Neurology at the Children's Hospital of Philadelphia and Director of the Pediatric Multiple Sclerosis Clinic.

- GG DeFiebre: 02:36 Dr. Banwell's clinical and research interests are in pediatric multiple sclerosis and other inflammatory brain disorders. She remains the lead investigator of the Canadian pediatric Demyelinating Disease Program. Her clinical studies focus on the cognitive and neuroimaging features of pediatric multiple sclerosis, while the basic science work focuses on T and B cell autoimmunity studies, MRI imaging and studies of viral triggers. Dr. Leslie Benson is an attending physician in the Department of Neurology and the Assistant Director of the Pediatric Multiple Sclerosis and Related Disorders Program and Pediatric Neuro Immunology Program at Boston Children's Hospital and an instructor of Neurology at Harvard Medical School. She completed medical school at University of Colorado Health Sciences Center and pediatric training at Massachusetts General Hospital for Children and child neurology at Boston Children's hospital prior to a two year fellowship in neuro inflammatory diseases. Dr. Benson is board certified in child neurology and her clinical work is focused on care of children and young adults affected by neuroinflammatory diseases including MS, transverse myelitis, AFM, optic neuritis, including MOG antibody associated disease and ROHHAD Syndrome among others. She is involved in collaborative clinical research aimed at improving the understanding and treatment of these diseases. Welcome and thank you both so much for joining us today.
- Dr. Banwell: 03:57 Thank you for having us. Happy to help.
- GG DeFiebre: 04:02 Thank you.
- Peter Fontanez: 04:05 Okay, I guess we'll begin with the questions. First question is going to be for Dr. Banwell. How common is MOG antibody disease in children? Is it more prevalent in certain types of populations, such as gender, race? How about in terms of ADEM, NMO, autoimmune encephalitis, optic neuritis, and TM? How, how common is it in, in those types of cases?
- Dr. Banwell: 04:30 Okay. So, I'll start by saying that the ability to make the diagnosis of MOG associated demyelination is a relatively more recent in that the development of the testing, the antibody that we use to confirm the diagnosis has become increasingly available both in United States and worldwide. This is important because the way that we test this disease, matters. The

antibody testing needs to be in a lab that uses the optimal technology without which one can have some results that are either inaccurately negative or inaccurately positive. I mentioned all of that because this recognition of MOG associated demyelination has obviously been increasing as we've become increasingly able to diagnose it. Within the patients who have a first attack of demyelination, where it is attacking the brain, optic nerves or spine, in children, all comes together, almost half actually in recent studies have been shown to have antibodies against MOG at the beginning. And that group of children or if you're under age 11, tend to be children with acute disseminated encephalomyelitis or ADEM. Which is an illness where children present with confusion, drowsiness, sometimes seizures, a weakness often.

- Dr. Banwell: 06:02 Sometimes associated with vision loss are the same time. Not infrequently also associated with spinal cord inflammation or myelitis. In children with an ADEM presentation, depending on the study, up to 60 to 70% of those children, particularly those under 11 are indeed positive for MOG from the beginning. In teenagers, it is more common for MOG to be associated with patients presenting with optic neuritis or with transverse myelitis, but particularly optic neuritis. And then we look at what happens next, which is the chronic nature of the presentation. Patients with an ADEM presentation and MOG antibodies, many of those children will not have relapses and if you test them over time, their MOG antibodies go away. Some children with ADEM will then experience relapses, particularly of optic neuritis. And generally those children tend to have antibodies that persist. And finally, and I don't want to talk too long here, but in teenagers if you have MOG antibodies, they are a little bit more likely to persist. Those children who have ongoing MOG-related disease can have more of a neuromyelitis optica picture which is attacks of optic neuritis and transverse myelitis, particularly myelitis that involves a long portion of the spinal cord. Is that what you were looking for me to answer?
- Peter Fontanez: 07:34 I know that the information is still new, so that covers a lot of the bases. Thank you.
- GG DeFiebre: 07:39 Yes, thank you. Thank you Dr. Banwell. What types of physicians treat MOG antibody associated disease and ADEM and how can parents find a physician who specializes in these conditions? Dr. Benson?
- Dr. Benson: 07:57 Hi. Yeah. So I think as Dr. Banwell said we're still figuring that out. But in general, the, the biggest category of physicians who are treating MOG antibody associated disease, are neurologists

in general and certainly adult neurologist may see this, I think pediatric neurologist are seeing it, but even with there are pediatric neurologist and adult neurologist who sub specialize in disorders of the immune system that affect the nervous system. And so like Dr. Banwell and I, we're probably seeing the majority of these patients, but certainly there are areas where there isn't someone with that sub specialization. And I know many pediatric neurologists are increasingly aware of this disorder and the ability to test for it. In terms of finding an expert, I think there's lots of ways to access an expert. There's some different resources online such as the TMA website, the National MS Society. There's also probably with the IPMSSG and also with our national networks that we, we have a website at usnpsc.org. Think those are all resources that show some of the centers with particular experience and research interests into this condition. Especially if patients who are looking to travel for an in person visit, I think increasingly medicine is also moving towards remote consultations and other ways for patients who are not near a center that has particular expertise in this to access care and information.

- | | | |
|--------------|-------|---|
| Dr. Banwell: | 09:41 | I agree. Yep. |
| GG DeFiebre: | 09:43 | Great. Thank you. Yeah, and as you said, Dr. Benson on, on the TMA website, we have a medical professional. I know both those, Dr. Banwell, Dr. Benson are listed there as well as other medical professionals around the country and world. So that's one way to look as well. |
| Dr. Banwell: | 10:00 | Absolutely. I think I would add to the comment just that diagnosis is a critical component obviously but when it comes to decisions, around the treatment of patients with MOG related inflammation and demyelination that really should be a discussion with people who treat children regularly. I am concerned that there may be healthcare providers in the community that gets the test back and immediately react to it by prescribing some kind of immune related therapy, but perhaps not under the guidance of people that have been seeing more and more of these children, and it's extremely important, that we have a conversation and talk through options. Because as I mentioned, particularly in the younger children somewhere between 60 and 70% of those children can have a single event and once they're treated for their initial illness, they don't need to be on chronic medication. That's very, very important that people understand that. |
| Dr. Benson: | 11:07 | I would completely agree. Particularly in the patients who are having relapses, it's important that they see someone who has |

expertise with these medications and it is important to not over treat.

Dr. Banwell: 11:22

Exactly.

Peter Fontanez: 11:25

Okay. The next question is for Dr. Banwell. What is the cause of MOG antibody diseases? Is it genetic and should parents be concerned about siblings or other family members potentially developing MOG antibody disease?

Dr. Banwell: 11:39

So at this point there are several studies that have looked at the genetics in, in children with inflammatory demyelination, particularly in more commonly in children with multiple sclerosis, which we now believe as a separate condition. The genetic studies that have been done to date in children with ADEM, now keeping in mind at the time the genetic studies were done that the investigators may not have known, including my own study, whether the children had, MOG or not, however, we did not find any genetic risk factor specifically for ADEM. So even though we may not have known within that study who had MOG antibodies and who didn't, we couldn't detect any particular higher rate of any of the, what we call risk alleles or genetics signatures implicated, at least in multiple sclerosis, we did not see them being overrepresented in children with ADEM broadly.

Dr. Banwell: 12:38

Definitely we need to do proper research to see if we can find any genetic signature. Now, specifically in children with MOG, there isn't outside of these big studies, there really hasn't been, first of all, there hasn't been any suggestion that this is running in families. We do not tend to see more than one patient, in the family with MOG. In fact, I'm not aware of that happening at all. So to your question of brothers and sisters with MOG related disease at this point, I cannot suggest that we should be screening there, brothers and sisters for antibodies at all. I would definitely not do that. In terms of just more generally conditions like MOG related demyelination, which we think is an abnormal and perhaps poorly regulated immune response. Diseases similar to that, such as multiple sclerosis, neuromyelitis optica with Aquaporin 4 antibodies for example.

Dr. Banwell: 13:36

We really have not found compelling evidence of a specific gene or genetic spelling error that's causing those conditions. So in multiple sclerosis, we know that there's a tendency for multiple sclerosis to happen more in individuals of northern European heritage typically, but not in any way exclusively. In individuals that are white and northern European that relationship may have a higher likelihood of having something called HLA

DRB1*1501, which in English means a specific part of our genetic signature that helps dictate how immune cells behave. But even that only conveys a small increased risk, of multiple sclerosis and many, many, many people have HLA DRB1*1501 and will never have MS. With MOG we haven't even found that kind of signature. So to sum up, I would say that we have no evidence that MOG related demyelination is genetic. We have no evidence that there's rationale for testing brothers and sisters. And at this point we believe that MOG related demyelination is similar to other autoimmune conditions, wherein there's some interaction between the individual, their environment and their immune system that starts this abnormal response.

- GG DeFiebre: 14:59 That's great. Thank you. What are some of the common symptoms of MOG antibody associated disease and ADEM related to MOG? Is it different than an adult and do symptoms vary by person?
- Dr. Benson: 15:17 Yes.
- Dr. Banwell: 15:19 Is that to me or Dr. Benson?
- GG DeFiebre: 15:21 Sorry, to Dr. Benson and then Dr. Banwell if you have anything to add that would be great.
- Dr. Benson: 15:26 I think there's a very long potential answer to this. But if we focus in on the most common presentations, especially since we're trying to talk about ADEM, a fair amount today, ADEM is more common in children but can happen in adults. And it really means that there's multiple neurologic symptoms plus an encephalopathy, which is a big word for confused or sleepier than they should be. And in those neurologic symptoms can be anything from a weakness, changes in their ability to walk, changes in sensations such as numbness and tingling, can be changes in their bladder and bowel function. And then specifically with MOG, we see a lot of optic neuritis and that optic neuritis can be in the setting of an ADEM kind of presentation or it can be separate from without ADEM. The classic symptoms associated with optic neuritis, are pain with eye movements specifically along with blurriness of the vision, which is often in the central vision and can kind of increase outwards, and a loss of color.
- Dr. Benson: 16:35 So things when patients that have one optic neuritis on one side and not on the other, sometimes they'll look at a red object and they'll notice that the red looks more dull in the eye with the optic neuritis. The other frequent manifestation or way to

present with MOG antibody diseases is myelitis, which means involvement, inflammation of the spinal cord. And so the spinal cord sends a lot of messages, particularly for movement or strength and sensation and the bladder and bowel function. And so those symptoms can come from a myelitis in the setting of an attack. And then one thing that we've seen that's interesting with MOG as it can also present like a meningitis, meaning an inflammation of the coverings of the brain where patients can have fever, they can have, a stiff neck, stiff back, and not a lot of other focal symptoms as an initial presentation of MOG antibody disease with or without some of the other symptoms.

- Dr. Benson: 17:43 There's certainly a broad range, those are the most common that we see the symptoms present.
- GG DeFiebre: 17:51 Okay. We got a question. A live question from the Webinar. Someone was asking if the presence of high anti-MOG levels is a byproduct of an infection or is from an infection itself, Dr. Banwell?
- Dr. Banwell: 18:14 We have not found that MOG antibodies are produced directly by any infectious organism or with the result of an infection with any specific infection. We've certainly looked, looking for common viruses that we know of. Testing for viruses that are in the community at the time people present with ADEM or optic neuritis to see if we can find a specific infectious trigger. So to date we have not. Now, in multiple sclerosis we know there's a relationship, although it may or may not be cause and effect. With Epstein Barr virus, children and adults are more likely to have previously been infected with Epstein Barr virus than people who don't have MS. Even though we don't know if the EBV is directly involved in MS by itself, we have not found that, or any specific virus yet for patients with MOG even as a prior exposure situation.
- Dr. Banwell: 19:13 This is work ongoing of course as we now know and learn more and more about MOG related demyelination, and will continue to look, but at the moment, no evidence that there's a specific virus. The only thing I would add to that statement is that what we have seen in a small number of children worldwide is that there are children who develop herpes simplex virus infection or actual herpes simplex encephalitis, which is a very severe illness. Upon treatment and recovery from the herpes brain infection there are some children who develop either MOG related demyelination, so not at the same time. And in fact, people have gone back and found that they did not have the MOG antibodies at the time that they had the brain infection.

So they can experience the second illness, which is a MOG related demyelination or they can develop antibodies that are called NMD receptor antibodies and have a different antibody related illness. Both of those two situations have been reported following but not at the same time as herpes simplex virus infection in a very rare number of children.

- Peter Fontanez: 20:27 Thank you. Question number five, This question is for Dr. Banwell. I know we kind of touched on it during the first question, this is actually a several part question. What are the common pediatric diagnosis is related to MOG antibody disease such as autoimmune encephalitis, optic neuritis, ADEM, and neuromyelitis optica and transverse myelitis. I know there's a lot of illnesses that are connected to MOG. Is there any connection? Um, let's start with that as the first question. We'll break down the other three together.
- Dr. Banwell: 20:48 Okay. Well you listed them all very accurately. MOG related, demyelination can present as we've discussed with ADEM, so encephalopathy and multiple neurological deficits at the beginning, or with inflammation of one or both eyes, optic neuritis, or with myelitis typically involving a longer area of the spinal cord or even the bottom of the cord, or combinations thereof. There are also patients as Dr. Benson was mentioning that has more of an almost meningitis picture with a stiff neck and an inflammation that looks a bit more infectious.
- Dr. Banwell: 21:43 And of course in all patients we rule infection out by appropriate testing. Then there are even a very small number of patients who appear to have a MOG related disease with inflammation around or involved in blood vessels. So a vasculitis kind of picture. Which can manifest with more headaches, arguably maybe a little bit more likely to manifest with seizures, although not all children with seizures have inflammation of the blood vessels. And then, inflammation in the brain. If it hits areas, that are conveying important messages, then those messages don't get through and people have symptoms. So if you have inflammation in the brain stem, which is a pretty important relay station and also the sort of central part of the brain that controls a lot of different functions. You could have double vision, you could have a difficulty with eye movement. You could have, if it goes into the balance center, which is called the Cerebellum, then you can have difficulty with standing still and holding your balance or walking normally. And there are many others because it depends on what part of the brain has been affected or spine or optic nerve.

Peter Fontanez: 22:58 With that being said are, so there is a connection with MOG antibody disease and encephalitis, is retesting for instance, encephalitis patients from MOG. So there is, there is that connection there? Correct?

Dr. Banwell: 23:13 Well, the word encephalitis with, I think we just want to use the right terminology. So, encephalopathy or confusion, altered mental status, not being as aware, is the hallmark clinical feature of ADEM. And as we've said, over half of those children have MOG. Encephalitis, where you, you believe that it's actually an inflammation in the brain, in the cortex or the part of the brain that our brain cells live that are called neurons. If you have an -itis, and by that I mean, a stiff neck, evidence that the covering of the brain looks inflamed, the first thing to do is rule out infection. That needs to be the first imperative. If there is no infection and the person has MOG antibodies, then we would say that they have MOG encephalopathy and we might use the word MOG encephalitis. But I, I just want to be careful because encephalitis, most of the time, is a term that people are referring to an actual infection and MOG is not an infection.

GG DeFiebre: 24:24 And we've talked a little bit about this, but just to be as clear as possible, Dr. Benson, how often is MOG antibody associated disease monophasic in children? Is it similar to the number of monophasic ADEM cases? How do you know something is going to be monophasic rather than relapsing in both MOG and ADEM?

Dr. Benson: 24:52 Yeah, that's a great question and one we are all trying to figure out. The big question. So we, we don't always know if it's going to be monophasic phasic at the start. One of the clear predictors that have come out from studies in terms of determining if it's likely to be monophasic is to follow the MOG antibody titers over time. There is data to suggest that if those antibody titers become negative and are no longer detectable or if they're intermittently lowly detectable but not a lot there or intermittently negative, then the relapse rate or the relapses didn't happen in that cohort within one study. Whereas if the antibody titers remain clearly detectable and positive, then a portion of those children do relapse. Exactly what portion is hard, I think varies a little bit by study. Let me pull up a number here for a second cause there's some beautiful, but complicated charts looking at this in some of the recent literature.

Dr. Benson: 25:56 Some of it depends on what your initial presentation looks like, but it really, I think overall about 50% are probably within this study were remaining monophasic, one time attack, and then about 50%, were going on to have relapses. And that's looking

at all of the types of MOG associated disease including ADEM, NMO and it's just a onetime attack, clinically isolated syndrome and an MS population. I think within ADEM itself, it's a tough thing to compare because ADEM has changed in terms of its diagnostic over time and it's even with as good a criteria as we have now is probably representative of multiple diseases, both MOG antibody associated and other. It also gets used somewhat broadly among physicians at times. So it's a little hard to say for sure, but I think that if you have, ADEM without MOG antibodies I feel pretty confident you're unlikely to have a relapse. Whereas if you have antibodies and those antibodies stick around, then I become more concerned that the patient is at risk for subsequent relapses at some point over time.

Dr. Banwell: 27:29

I think that the published literature absolutely supports everything Dr. Benson just said. The challenge with some of what's been published is, it relates to who was studied. So when MOG antibodies were initially being recognized as contributing to relapsing optic neuritis or to children with ADEM who had optic neuritis, then the proportion of patients that were positive and persistently positive from MOG was much higher because of course they'd been preselected by the fact that they are already demonstrating a chronic, ongoing relapsing illness. As we've moved to testing more uniformly, those numbers of course are now diluting down. So in a study that we've recently completed where we sampled, we ran about 1400 samples, where we didn't pick patients who relapsed because these were all children who presented for the first time and we had stored their blood for future analysis.

Dr. Banwell: 28:24

We found slightly different results, which was that much higher percentage of children with ADEM remained single attack, more like 70 to 80% did not relapse in this particular population. Antibodies to MOG tended to disappear over the first year. But we had a group of patients who had persistent MOG antibodies, both with ADEM and with optic neuritis so far, at five to 15 years, still have not had a relapse. And we found that some children whose antibodies disappeared, relapsed a year or two later. So the main message is overall, if your antibodies are present and they continue to be present over time, you probably are at a higher risk of relapse in someone who doesn't. But until you've relapsed, we really don't have a good way of knowing whether you're going to, and I realized that's not the most satisfactory answer, but it is, it is actually what most of the studies are now starting to show. So I think it's different. If you are relapsing and you have MOG antibodies, we would manage you appropriately as someone with relapsing MOG disease. But before that point, it is very difficult to be accurate in predicting

and antibodies that persist do not guarantee that you're going to relapse.

- GG DeFiebre: 29:50 So just moving on to medications. So you know, acute treatments as well as long term management strategies with medication. What are the typical acute treatments that are used to treat an episode or attack of, for example, optic neuritis or ADEM encephalitis, transverse myelitis in the context of MOG? Dr. Benson?
- Dr. Benson: 30:12 So fortunately in the context of MOG or even before we get the MOG antibody back in the setting of optic neuritis or ADEM or myelitis, our acute treatments are generally the same. They're pretty standard to use IV steroids as an initial treatment. And then depending on response, consider treatment with IVIG and or plasmapheresis. And that's fortunately fairly commonly used across the demyelinating diseases that we see. And so the fact that we have to offer treatment before we have these antibody test results back allows us to proceed with treatment. It's really the longer term treatments that are influenced by the overarching diagnosis.
- Peter Fontanez: 31:01 Okay. With that, this is again, this question is going to be for Dr. Banwell. Well, this is going to be a multipart question. I'm going to try to knock it all out all in one, one part. What are the most common medications prescribed to children as preventative? I know you touched on that earlier. When should a patient begin preventative treatments? What happens with the treatment if the child eventually test negative for MOG antibody? And I know in some studies, some kids tested positive but did not have a relapse. Should they still be also be put on preventatives and are the treatments different than adults?
- Dr. Banwell: 31:40 Okay. Okay. I'm going to say that first of all, an important very honest statement is that we are learning real time as a community on management strategies for children and adults that have MOG antibodies. That we as an international community, so wearing my chair of the International Pediatric MS Study Hat, as well as, both Leslie and I and the various pediatric networks that were also part of within the United States, North America, etc. We are all communicating with each other and trying to develop best practice and ultimately I hope get to a point where we actually formally create a treatment; a shared treatment strategy and follow patients in the same way so that we can look to see which treatments are good, optimal, and that may be in a clinical trial or in some kind of version of a clinical trial.

- Dr. Banwell: 32:36 In the absence of that, we are all using our best judgment, and expert opinion, but we need to be humble and recognize that's what it is and that we don't yet have rigorously done clinical trials to really do this to the optimal degree yet. So with that being said, I will share my view and I'm keen to have Leslie, Dr. Benson, add hers. And in no way would I suggest that my view is the gold standard. I think everybody is trying very hard to be rational, effective and safe. So personally, in terms of preventative therapies in general, I would not start them unless a person has had a second event. Every child that I see is of course an individual person. I look at them, their family, the circumstance, and weigh all of that in making a decision.
- Dr. Banwell: 33:28 So there are, you know, for example, a few teenagers whom I've met with MOG related very severe optic neuritis and who have had spinal cord lesions at the same time. Given how severe their presentation is there I have started some of those children right away on preventative because of the severity of their initial event and the clear desire to prevent a second one that might rob them of their vision or their ability to, to walk normally if they have severe disease. Other than that though, and then, and in the majority of children I've seen that are MOG positive who recover quickly from their first event, I follow them closely. I obviously see them very, very quickly if they have symptoms of a second event and treat the second event itself quickly. And then that would be my time point where I would say we need to put you on something to prevent further events.
- Dr. Banwell: 34:20 The current options that people are using include, and this is very individual. There's no script that says one of these is better than the other or that each are equally appropriate for any one child. This definitely requires an expert and it requires a very careful look at the child's general immune system, their vaccination history. There are some medicines that really ought not to be given if you're not fully vaccinated against infections in the community. And there are rules about what vaccines for example you can give while you're on some of these therapies in terms of making sure the vaccine works. So there's a lot that goes into making this decision but the treatments that are appropriate in the right person include a medication called Rituximab, which is a target of one arm of the immune system called the B cells that contribute to making antibodies.
- Dr. Banwell: 35:10 We could go into that for a long time but I think that's a straight forward answer to using a drug like rituximab. Immune Globulin, which is a monthly IVIG people call it, has worked very well for some children and is often quite well tolerated. In Europe, there is a tendency to use oral prednisone for quite a

long period of time whereas in North America we try probably to avoid prolonged exposure to corticosteroids because of their effect on growth and blood sugar and weight. We tend to use them less in a more restricted way only at the time of an acute attack. And then people have used medications like, like Cellcept or Mycophenolate Mofetil which is an oral tablet that also has an effect on controlling abnormal immune responses. And there are others, but those would be the more commonly used treatments at this point.

- Peter Fontanez: 36:08 What happens if the patient tests negative for MOG during preventative treatments?
- Dr. Banwell: 36:15 This a great question, that we all would love to know what to do with exactly. So again and again, I'm happy to have Dr. Benson, weigh in on her strategy in this situation. So for me, if I have a patient who has been doing extremely well clinically, and by that I mean no brain lesions, spinal lesions or optic nerve lesions while on treatment. So the disease is well controlled, no clinical relapses, using truly the type of protocol we used to use for patients with vasculitis. I have gone sort of a two year window and if the patient is completely under control for two full years and their antibodies are now negative on more than one time point, at least a month or two apart. I discussed with the family the option of trying to stop therapy and watching the child closely.
- Dr. Banwell: 37:08 This decision and is influenced just like the treatment decision on how the patient has been doing and what their history was before. So there's no script for this because some patients, were very difficult to get under control, took a while to find a medicine that got their disease to settle down. And those families tend to rightly as do their doctors want to be treated and safe on therapy for quite a long time. Other patients may have only had one or two early relapses. Have come under control very quickly, have been completely stable for a long window of that two years without any activity of disease and might want to come off therapy more quickly and, and we may all feel that that's appropriate as a clinician. So it really isn't possible to be accurate and say this applies to everyone, but that's my general guideline. And Dr. Benson, do you have anything to add?
- Dr. Benson: 37:59 No, I would agree with that. I don't have any specific time point where I would take patients off, I would be influenced by how well they're tolerating their treatment in addition to the features that Dr. Banwell mentioned. In terms of going back to like who starts on a treatment, it really does depend on the

severity. I've seen patients who go seven years between attacks respond nicely to steroids. I don't put necessarily put everybody on a preventative, even if they've had a relapse. On the other hand, if I have a patient who I can't get off steroids because they keep having symptoms where every time we try to taper, those are the ones I'm going to go more quickly to a long-term treatment for in addition to looking at severity and frequency and the things that Dr. Banwell mentioned.

- GG DeFiebre: 38:47 Okay. Thank you.
- GG DeFiebre: 38:52 So, and then I know you, Dr. Banwell and Dr. Benson, you both talked about these preventative medications. Are there any long-term effects of these medications like Rituximab, Cellcept, steroids, IVIG? Can they, you know, impact the reproductive system or can puberty have an effect on these treatments and conditions? Dr. Banwell?
- Dr. Banwell: 39:13 All right, so all therapies have side effects, risks and benefits. So there isn't any treatment that I'm aware of that is completely without some risk. And that risk varies by person obviously by many other factors. But broadly put, if we're talking about immunoglobulin, the general risks of immunoglobulin are some, some are related to the infusion itself so people can have a headache, can have some nausea with it, some people could be allergic to it, react against it, which is why when we give the infusion, we have pre-medicated our patients with a strict protocol and we always have on hand all of the treatments one would need if someone did indeed have an allergic reaction. IVIG is a human product. It doesn't contain blood cells, but it is a donor derived product and even though it is carefully screened and heat treated, there's always a theoretical risk of infection being passed through IVIG.
- Dr. Banwell: 40:17 Although that risk in the North American IVIG pool is extremely low. So, you know, I think that that's in general, there's no reproductive effective IVIG that anyone has ever documented and it certainly doesn't have a different risk for men or women that I can, that I can think of. Rituxan is obviously designed to specifically drop down one part of the immune cell population, the CD 20 B cells. So in doing that it alters your immune dynamic. There is a small but not enormous risk of certain infections. Importantly, as I mentioned before, it is very essential that certain vaccines be given ahead of time. So I would not give Rituxan to somebody who was, who was not vaccinated or not immune to chickenpox. We require that we screen for their Hepatitis vaccination and show that they don't

have active Hepatitis and that they are immune because serious infections on a medication are always important.

Dr. Banwell: 41:20 I am not aware of Rituxan having any long-term effects on a subsequent fertility. And we probably would know that because Rituxan has been around in the oncology world as a treatment for B-cell related cancers for a very long time. So in isolation used as that therapy, I'm not aware of there being any concern about reproductive health with Rituxan. Although like almost every medicine that we have, we would not want to be giving these medications necessarily during a pregnancy. Obviously that's not, hopefully a major issue for most of our MOG-positive children. But it is a very important issue in our young adult population. There are, and I don't want to get into all of that, there are entire teams looking at what treatments are safe for individuals who wish to have families.

Dr. Banwell: 42:12 There are strategies to make medications, even medicines like Rituxan actually, as an option for, for women. But that's beyond this, this call and relates to a lot of things we don't have time to talk about in terms of timing and dosing. Steroids, so in the short term, for like for three to five days at the time of a relapse, as every parent who's ever had their child treated, knows, it can make a child somewhat irritable when the infusions are happening, poor sleep, they have effect on blood sugar and your blood sugar can go up. They can bring up your blood pressure sometimes to a level that we have to treat although not too usually. They can predispose to thinning of the bone even though that doesn't tend to happen in the short term infusion. If you were to take oral prednisone for a long period of time all of the things I just mentioned become chronic risks. And in particular also chronic prednisone can suppress growth. Like anything, there's always a way to manage side effects and to work hard to pick the right medicine for the right child. And there are people that cannot tolerate one medicine but can tolerate another. That's again, back to the art of all of this, which is to be very sure that we use the right treatment for the right person.

GG DeFiebre: 43:39 And then relatedly, in terms of kind of long term concerns, are there any long term issues potentially with MRIs or CT scans that parents should be aware of? Dr. Benson?

Dr. Benson: 43:50 Yeah, certainly. So I think the most well-known risks are the risks of radiation with CT or Cat scans. And we generally avoid CT scans in our practice here. I know in some parts of the world there may not be availability of MRI, but where there is availability of MRI, most of the time it's the more useful study to

give us the information we need when we're thinking about things like ADEM or MOG-antibody associated disease. There are occasional situations where there's a reason the child can't have an MRI. And then in that situation, certainly a CT may make sense. With MRIs we don't really know of any long-term risks with the MRIs themselves. There has been increased attention to the MRI contrast dye and whether there may be any long-term risks associated with that. And so there's one of the older generations of dyes that were used in MRI scans was demonstrated to build up over time in the brain.

- Dr. Benson: 44:54 I'm not aware of any known symptoms or actual impact on those patient's health, but because we know that we do think about whether patients definitely need contrast in order to make treatment decisions at the time of the scan. And so whenever the answer to that question is no, we can, all we need to know is are there new lesions or where are the new lesions? Then sometimes we avoid the contrast dye but it's still relatively safe and I use it when I feel like it will be helpful to decision-making around the patient's management.
- Peter Fontanez: 45:37 Thank you Dr. Benson. Another question for you. Dr. Benson is should children with MOG-antibody disease and/or ADEM receive vaccinations and should there be a difference between live and dead cell vaccinations and also can treatments such as IVIG or Rituximab have an impact on vaccinations? Because with IVIG, you already have the antibodies from the donors, so could they have an effect on the vaccinations as well?
- Dr. Benson: 46:04 Yeah, there's lots of considerations around vaccinations. I think the overall message I want to give is that yes, patients should be vaccinated but we have to pay attention to do that safely. There is some concern that following ADEM or other demyelinating attacks that there's a risk of activating the immune system and exacerbating an attack or bringing on another attack if given shortly after the attack. So usually in the acute setting within a month or three months of an attack, I ask that families hold off on vaccinations, but once things are settled down and the patient is stable again, then oftentimes they can go ahead and receive most of their vaccinations. The other questions really depend on what treatment they're on. So if the patient is off treatment, then there's no restrictions on live vaccinations versus other vaccinations in our practice here is my opinion.
- Dr. Benson: 47:05 The medications make a difference though so things like steroids and Rituximab do lower your ability to mount a response to the vaccine, right? So you give them vaccine, the immune system needs to become activated and respond to that

in order to protect the body after the vaccination. And the immune system will not necessarily respond the same in the setting of an immunosuppressant medication like steroids or rituximab, or mycophenolate. There are some other specifics. You don't want to give a live vaccination if the patient is immunosuppressed on one of these medications either. And then lastly, IVIG has its own separate set of considerations. Yes, it is giving you other people's antibodies which may help protect from infections and there are specific restrictions on which vaccination should be given within what time frame of having received IVIG because it also may alter the response to a vaccination.

- GG DeFiebre: 48:08 Thank you. Sorry, is there another,
- Dr. Banwell: 48:16 I was agreeing, I was just going to echo that this again emphasizes
- Dr. Banwell: 48:19 the importance of people that are treating children with these diagnosis, really working with people that have read through all the evidence and have a strategy. These are not trivial things to, to think through and do need to be done with the right supervision.
- GG DeFiebre: 48:36 Very good point. Thank you. Just quickly, very briefly talking about kind of like the emotional and psychological perspective before we move on to, to research and the future. How does MOG impact children and families from an emotional and psychological perspective? For example, some children might have behavioral changes, you know, why does this happen? And, what is the role of something like neuropsychology testing? Dr. Banwell?
- Dr. Banwell: 49:06 Sure. So of course it depends on the context. In patients with ADEM who recover very thoroughly, go back to regular classrooms and seem to be doing incredibly well then, you know, neuro psych testing may not be needed. I always advocate for it if there appear to be any concerns. Children with optic neuritis or transverse myelitis, tend in general if that's their isolated presentation, not to have formal cognitive impairment, but of course, may have school impact if they have any residual visual deficits and may need modifications to gym class or access for other important day to day functions if they haven't yet fully recovered from a spinal cord episode or if they don't have a full recovery. So clearly there, an interaction between the team and the school is always important. Emotionally I think any illness in a child impacts their entire family.

Dr. Banwell: 50:02 And we need to be both aware and supportive of the impact of any child's health, on their siblings, on their parents and extended family. In our clinic we have an absolutely amazing social worker who is available and a resource to provide a supportive counseling. As we go through both acutely, when people are clearly not yet seeing the child recover and we're working through the, the initial few days of treatment and then longer term if patients ongoing health issues and emotional impact of these. So I think that's true across all of pediatric health that it is important to think about the cognitive and emotional needs of the child, the teenager, their parents and their siblings. At least within Pediatric Multiple Sclerosis, which, arguably we know more about because we've been studying it more formally for a longer period of time, there's no question that emotional health is a component of the management of children with MS, and parents of children living with MS, report that they as parents, have emotional consequences of the uncertainty of their child's future.

Peter Fontanez: 51:19 Thank you, Dr. Banwell. To both Dr. Banwell and Dr. Benson this is going to be the last question. I know Dr. Banwell, you're part of the International Pediatric Multiple Sclerosis Study Group so you might have a little bit more input on this, wit it being the chair. When will there be a specific protocol or diagnostics criteria from MOG antibody disease and what does the future hold for our children's long-term prognosis, things of that nature?

Dr. Banwell: 51:46 Okay. So, as you know, I have had the opportunity to talk with people looking after children with both MOG-related disease and other inflammatory diseases, both in the international realm, in North America-wide and in different forums. I just attended an international workshop on MOG that had representatives from over 20 countries and that particular meeting will generate a formal report that synthesizes what as a collective group of experts we feel are the priorities for next steps in research and will lead to a preliminary diagnostics algorithm, which means a sort of a step by step guide to when to consider testing for MOG and what to think of in patients who might be MOG positive, what else to think about. And then a goal identified by the meeting, but there's a lot of work to make this happen still..

Dr. Banwell: 52:38 ...would be to, to have a collective opinion on rational decisions around treatment and follow patients and their family and their outcomes very carefully together. This will be an engaged process with families. The only way we're going to know how patients with MOG-antibody related disorders do, is if we can

have a community effect where people are interested in contributing clearly in an anonymous way, in the sense that we will not put their name on these things, but maybe a code number that can't link to an individual person, but can be reliably used to identify the long-term course, of how a given child is doing so that we can actually answer that question with data. Not just with each person's individual clinical experience, which may have varying influences such as the community you live in, access to health care, differences that different parts of the world will see, differences in different patients. So the, the short answer, which I don't think it's very short here, I apologize, is we are learning the long term outcome as a community because we're living it, we're learning as we get to know these families and children better and see how the kids that we're treating are doing. We need to have a more formal process and a very, very large number of people are keen to have that happen.

- GG DeFiebre: 54:03 We're towards the end of our time. But, first Dr. Benson and then Dr. Banwell, do you have anything else to add? Is there, you know, what does any kind of research that's happening or what does the future look like or anything else you want to add that you feel like we didn't adequately talk about today?
- Dr. Benson: 54:18 So I'll just add that I was excited to hear about all that doctor Banwell just talked about and anything we've learned as we've gone with many of these demyelinating diseases and evolving diagnostic criteria, I'd add that there are some proposed diagnostic criteria that came out in 2018 from the Mayo group. And so as a first step and then this next report will be another step, and I'm sure over time we will learn from our patients and refine them. That is one area of research. There are a lot of groups nationally and internationally who are gathering data on MOG-antibody associated diseases and their patients. And so I'm certain we're going to learn a lot more about this disease in the years to come. And it's, it's a very exciting time for us in that way.
- Dr. Banwell: 55:09 I agree.
- GG DeFiebre: 55:12 Great. Well thank you so much for your time today. We really appreciate it. I know we could do a, you know, 10 more podcasts on all of these, these questions individually. So, you know, we really appreciate your time and effort and hope to continue the conversation in future podcasts. I also want to thank Peter and Jen and the whole MOG crew for helping with this podcast. It's been great. So thank you all so much. Thank you guys.

Dr. Banwell:

55:35

Thank you for setting this up. We really appreciate it. Thank you. Nice talking with all of you. You too. All right. Okay.