Understanding diagnosis of rare diseases

ADEM, AFM, MOGAD, NMOSD, ON, and TM

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[00:00:00] **Dr. Grace Gombolay:** This panel is just going to be an introduction. A lot of you are familiar with these diseases, but I thought just to get started just to understand the diagnosis of rare disease. And that includes the diseases that the SRNA does involve in including ADEM or A-D-E-M, Acute Flaccid Myelitis, MOG Antibody Associated Disorder or MOGAD, NMOSD or Neuromyelitis Optica Spectrum Disorders, Optic Neuritis, and Transverse Myelitis. So first of all, I would like the panelists to get started by introducing yourselves.

[00:00:32] **Dr. Jacqueline Rosenthal:** Thank you. I'm Jackie Rosenthal. I'm a neurologist at the Shepherd Center. Where at the MS clinic there we see MS patients, NMOSD, and MOGAD patients primarily. Happy to be here. Thanks.

[00:00:46] **Dr. Varun Kannan:** Hi, I'm Varun Kanan. I'm a pediatric neurologist with neuroimmunology training. I work with Grace at Children's Healthcare of Atlanta.

[00:00:53] **Dr. Spencer Hutto:** Hey everyone, I'm Spencer Hutto. I'm an autoimmune neurologist at Emory. I work primarily in the hospital, actually next door, and do some work over at the Brain Health Center.

[00:01:01] **Dr. Grace Gombolay:** Great. So, I think first of all these diseases we're going to go in alphabetical order. It's not like we favor one disease over the other but first let's start with ADEM or A-D-E-M as some people call it. And actually Dr. Kannan, I'm going to ask you to talk about this. Can you discuss what is ADEM and what is the difference between ADEM and MOGAD?

[00:01:19] **Dr. Varun Kannan:** I think the biggest confusion we have upfront is we have this alphabet soup of acronyms which is challenging. It's helpful for us as clinicians to put categories to these conditions. But the names are confusing. So Acute Disseminated Encephalomyelitis is basically a syndrome where a child or an adult, almost always following some sort of infection, has an overactive immune response where there is an attack against typically the white matter of the brain, but it can also affect the spinal cord.

[00:01:52] A couple of hallmarks is by definition all patients with this condition have what we call encephalopathy. What basically means they have altered consciousness. And again, all of this is from an overactive immune

response where the immune system was correctly fighting off an infection, but then it doesn't shut itself down after the infection is cleared.

[00:02:13] So it's a clinical diagnosis that we correlate with MRI findings. So, you got to have these clinical features and the symptoms, but then also very characteristic MRI features. There is not a specific test that confirms a diagnosis of ADEM. It's really a judgment call between us and the radiologist to agree that the symptoms fit and the MRI fits.

[00:02:33] Within that, there's a lot of different causes of ADEM. So ADEM is itself not like a specific diagnosis, necessarily. A cause of ADEM that we now understand is a different disease called MOG Antibody Disease. MOG Antibody Disease is an autoimmune disease where the immune system makes an antibody in cells against a specific piece of white matter, which we call MOG, Myelin Oligodendrocyte Glycoprotein.

[00:02:57] This is a different disorder than MS. It's a different disorder than Neuromyelitis Optica. Some cases of ADEM can be from MOG Antibody Disease. The reason we distinguish the two and the reason the testing is important is because having ADEM from MOG versus ADEM from not MOG can actually change the treatment plan and the long-term outlook.

[00:03:21] **Dr. Grace Gombolay:** Okay, great. And so, this next question is actually for Dr. Huro. How do you diagnose Transverse Myelitis?

[00:03:29] **Dr. Spencer Hutto:** So, Transverse Myelitis is in some ways similar to ADEM in that it's an umbrella term that refers to inflammation of the spinal cord. So, there are many different causes of that. And importantly we have tried to move away from diagnosing people in the end with Transverse Myelitis.

[00:03:45] Oftentimes that is something that's a working diagnosis when they're in the hospital, while investigations are ongoing to figure out the specific cause. But in general, patients will present with problems with strength in their arms and their legs. They may have difficulty with sensation. They may have pain associated with that, particularly along the back.

[00:04:02] They may have troubles with controlling their bowel and bladder function. When they come into the hospital, we will obtain some MRIs to look for inflammation affecting the spinal cord. We'll look for lesions along the spinal cord or the substance itself. We'll do spinal fluid testing to get a sense for what's causing it.

[00:04:20] And the goal is to figure out what is the specific cause. Because the specific cause is the thing that best determines what a patient's most likely to respond to in terms of their treatment. So, some patients may also have MOG that is causing Transverse Myelitis. There's a real dichotomy in terms of how old the person is when they first get MOG in terms of what they may present with.

[00:04:41] So if you're a very young person, you may present with ADEM. If you're an adult, you're more likely to present actually with Optic Neuritis. But there are a decent number of patients with MOG who have Transverse Myelitis. And so, we'll send testing for MOG. Neuromyelitis Optica is of course, a very common reason why somebody might have Transverse Myelitis, but a number of other things can do that.

[00:04:59] Multiple Sclerosis can do that. Sarcoidosis can do that. People can have inflammatory disorders that are occurring after they've experienced an infection or maybe a vaccination. And so, there are many reasons somebody might have Transverse Myelitis. And so, we work very hard to send a number.
[00:05:15] So, if you have experienced that, you probably also recall that when you came into the hospital, we drained your blood and we send off 10 different vials of testing for this thing and that thing that could

help define exactly what the cause is. We do the spinal fluid testing for similar reasons to try to identify the cause and also rule out other things that may be similar and that may be adversely impacted by suppressing your immune system.

[00:05:38] And so it's a very thoughtful and detailed and labored approach to getting to the diagnosis that's almost stepwise and takes some time, which I know is a bit frustrating, but we wanna be very careful in trying to, wither down that to the exact cause as much as possible. And so that's what we're working on.

[00:05:54] **Dr. Grace Gombolay:** Great. Thank you so much. And then, Dr. Rosenthal, can you talk a little bit about Neuromyelitis Optica Spectrum Disorder, how it's diagnosed, and a comparison with MOGAD?

[00:06:05] **Dr. Jacqueline Rosenthal:** So NMOSD Neuromyelitis Optica Spectrum Disorder is diagnosed primarily off of the symptoms when someone first presents it can.

[00:06:18] The symptoms can be very similar to MOGAD in adults in particular and tend to be very severe. Optic Neuritis, inflammation of the spinal of the optic nerves affecting vision, more likely to affect both optic nerves and as opposed to just one. The inflammation of the spinal cord, Transverse Myelitis tends to be very extensive.

[00:06:40] Getting the entire diameter of the spinal cord, meaning that you're having symptoms affecting both sides of the body. When we say longitudinally extensive, we mean it's basically, it's a long segment. With all of these disorders, or a lot of them, I think we compare it a lot to Multiple Sclerosis because MS is more common.

[00:07:00] And so compared to that, for example, MS lesions tend to be very small and kind of located off to the side where with this longitudinally extensive myelitis that you see with NMOSD, it's involving the majority of the spinal cord and creates a lot of damage to the spinal cord, which is why the symptoms are so extensive.

[00:07:19] So that's the other characteristic of NMOSD or that the symptoms are so severe and the recovery tends to be poorer. So compared to MOGAD, for example, or MS, where the recovery tends to be a lot better. And that is why we are so diligent about trying to spread the word about NMOSD to get early diagnosis and early treatment because it is a very attack driven disease.

[00:07:44] And with each of those relapses significant disability and symptoms can occur, which is always our goal for preventing that. Optic Neuritis and the inflammation of the spinal cord are going to be the two main symptoms. And so, when we see someone come in with very pronounced symptoms like that, it is important to look for the antibody that goes along with NMOSD, an aquaporin-4 antibody.

[00:08:12] That's part of what the disease is compared to other things like MS for example. You do have an antibody that can really assist with diagnosis and it's probably one of the most important things that we do with that diagnosis. And so, getting that antibody is important. We look at the symptoms and that's how we lead to that diagnosis.

[00:08:34] **Dr. Grace Gombolay:** Thank you so much. Finally, let's talk about AFM. Dr. Kini talked about AFM.

[00:08:41] **Dr. Varun Kannan:** Yeah. So, AFM stands for Acute Flaccid Myelitis. This condition, I think, is very different from almost all the other ones that we're talking about today. So, these other conditions like ADEM and NMOSD are mostly autoimmune reactions or most of the neurological injuries happening because of an overactive immune system.

[00:08:59] AFM is different because this is what we think we know about this disorder is that it's actually caused by the infection itself. So, it seems to be caused by a specific class of viruses. And it essentially causes a disorder that's very similar to what we used to see decades ago with polio.

[00:09:15] So basically a viral infection of the cells in the spinal cord that control the movement of muscles in the body. And obviously we've seen eradication of polio across the globe with successful vaccination campaigns. Whatever virus seems to cause this new phase of AFM that we're seeing in the last 10 years is not prevented by the polio vaccination, so it's a different class of virus.

[00:09:40] We first saw a pattern of this happening in children in about 2014 and then we saw increased spikes of this every other year, which is very interesting in 2016 and then 2018. Then in 2020, we didn't see it at all. Obviously, pandemic kind of changed the way viruses spread across the globe with the way that we changed interacting with each other socially.

[00:10:02] And since then we've seen sporadic cases of this condition, but we haven't seen those big spikes that we were seeing in the years prior. And we don't understand why we don't know if we're not checking for it in the right way. It's a very difficult thing to diagnose because the only place that does confirmatory testing for it is right next door.

[00:10:19] The CDC and most clinical labs in the country at your typical hospitals don't have a way to confirm these viruses. It's a very severe disease. We still give immune therapies to see if there might be a component that is mediated by the immune system. But again, it behaves very differently than these other conditions and it can be quite severe.

[00:10:40] **Dr. Grace Gombolay:** Great. Thank you. I also want to start opening up to the audience now that we've chatted a little bit about these diagnoses. If you have a question for our panelists, please feel free to raise your hand. And I'm happy to come around with the mic to see to, so you can ask your questions so everyone can hear. Does anyone have any questions about these diagnoses, or anything related to them? Yes.

[00:11:10] **Audience Member:** I got diagnosed with MOGAD on February 5th. Then I had a relapse on July 1st. How do you keep from getting a relapse if you have MOGAD?

[00:11:26] **Dr. Jacqueline Rosenthal:** I'll just back up a little bit when we talk about the relapses, because not everybody with MOGAD has a relapse. I would defer to my colleague here about the pediatric population, but in adults there are some factors that we try to look at in terms of the symptoms to try to make an educated guess in terms of your risk.

[00:11:45] But generally speaking, it's a coin flip whether or not that first attack was a one-time thing or will there be another one. And it's a difficult thing. I tend to talk with my patients about it and explain and say, hey, we can go ahead and put you on something in the long term to prevent another attack, but there's a chance in maybe on a really long-term immune therapy and probably maybe never needed it. We're not sure. I also…

[00:12:08] **Audience Member:** I had Rituxan on June 1st. I guess it did nothing.

[00:12:15] **Dr. Jacqueline Rosenthal:** So, when we do see that it is the relapsing form of MOGAD, so not just a one-time event, we absolutely want to put someone on immune therapy. And this isn't just for MOGAD I'll say for any immune mediated central nervous system disease.

[00:12:32] And this is important just generally speaking too, because sometimes we don't know exactly what we're treating and at the end of the day, we just need to prevent another attack from occurring. And that is ultimately the goal, right? And so, if one immune therapy doesn't work, then we have to try a very low threshold and we go to something else. MOGAD is particularly difficult because there are currently no FDA-approved treatments. So, we are using our, treatment IVIG guidelines off of… Yes?

[00:12:59] **Audience Member:** I'm getting that next week with those…

[00:13:00] **Dr. Jacqueline Rosenthal:** Before you, that we have been able to learn what works and what doesn't work and that's how we move. So you try one thing you said Rituxan for example, if that's not cutting it, guess what? We've got to go to something else, and you keep changing or escalating treatment until we stop having attacks because that's ultimately the goal. And so just staying, and I would encourage that for everybody dealing with something like that. You stay proactive and you try to prevent those attacks.

[00:13:28] **Dr. Varun Kannan:** Thank you. A couple of insights from the pediatric side. It seems like the rates of relapse with this disorder are different depending on your age. A lot of our young children have mostly brain inflammation, like ADEM with this disease, and most of them do not relapse.

[00:13:46] So we treat them acutely with steroids. We taper the steroids off and we counsel the families and say, in all likelihood, this will never happen again. So, we don't want to commit your child to a year or even a lifetime of immune therapy that we don't know that they need because they may have side effects and those can be serious.

[00:14:02] As you get into the teenage years and closer to adulthood, the relapse rates seem to be higher. We don't understand why. So still, it's a case-by-case judgment call where we decide. Do we come off of steroids and put you on something temporarily or do we give you a chance of trying to not need this kind of therapy?

[00:14:20] If you stay on steroids, you'll not have relapses, but as most of us in this room know, you cannot be on steroids at a high dose forever. There's a lot of really bad side effects especially for young kids going through puberty. So, we're trying to figure out if there are drugs out there that give you the same benefit of steroids and control the disease without the side effects of steroids. In kids it seems like IVIG is a treatment that has been effective and safe.

[00:14:47] So that's usually our go-to in the pediatric population when we've confirmed relapsing disease. So, I think that is a good option.

[00:14:57] **Dr. Spencer Hutto:** I'll just throw on here at the end that Dr. Gombolay is actually going to talk about some investigations that are ongoing in MOGAD in just the next half hour or something like that.

[00:15:05] So it'd be really interesting to hear because MOGAD is only recently described in the last five, six years or at least the antibodies being commercially available. And so, there's a lot of science to be done. So hopefully there are going to be some new drugs with some interesting results coming in the near future.

[00:15:23] **Dr. Grace Gombolay:** So, I hand over here next.

[00:15:24] **Audience Member:** Good afternoon. My grandson, he's 13 now. He was 12 when he was diagnosed with MOGAD and started with a simple headache. And the question that all of my family and everybody ask

is, what happened? What, how did he get it? I'm sure we don't know, but what's an answer? What's a good answer I can give them when they ask that we get that question because he was healthy, athletic, good grades, everything was really going well. And just out of nowhere, this just happened. I think we've talked about this

[00:16:04] **Dr. Varun Kannan:** before, face-to-face as well, but there's no clear answer in some cases, but our best guess is still, at least in kids, that it seems like there's a viral trigger for this.

[00:16:17] So again, MOG, this protein is one of the surface proteins of the insulation of the nerves in your brain, eyes and spinal cord called myelin. Weirdly this protein and the surface of myelin look very similar to the surfaces of a lot of viruses. So, we haven't proven this connection, but that's our best guess is that at some point your immune system is fighting off a virus and then instead of identifying the virus is gone.

[00:16:44] It keeps looking for it in places. And it seems like when it finds a similar looking protein in your brain or optic nerve or spinal cord, it thinks it's the virus and it keeps attacking it. And again, sometimes kids have an obvious illness that may have preceded the onset of the neurological symptoms by a couple of weeks, but a lot of times they don't have a clear illness.

[00:17:05] Still, we do know in pediatrics that the average child gets eight or nine viruses a year just by being in school. You may not have clear symptoms of having a virus because the immune system actually does a good job once in a while of fighting off a virus before you even get sick from it. So, there's a lot of mysteries there. I wish we had more clear answers as to why this happened acutely, but I think as a field, our consensus best guess is still an infection.

[00:17:32] **Dr. Jacqueline Rosenthal:** I'll add that MOGAD. We're still, there's still so much we don't know. And compared to NMOSD, for example, where if we find that antibody, you have NMOSD, you have that disease, the same is not true with MOGAD.

[00:17:48] If you were to test everybody in the world for that antibody, you're going to have people that test positive that don't actually have the disease. In fact, I have several patients I treat for MS that happen to have antibodies to, mog, and it's MS. It's not MOG. And so, what makes that antibody presence pathologic or cause problems versus not? There's still a lot that needs to be discovered about it.

[00:18:14] **Dr. Varun Kannan:** The last thing I'll say in that point is most of us send our MOG blood test to Mayo Clinic. That test was clinically available for the first time in 2017, so we're not even 10 years into getting really good data on this condition. 2017 was my first year of residency, so I feel like every year of my training we've learned significantly more about this condition. And every year our knowledge evolves even further. There's a lot left to learn.

[00:18:44] **Audience Member:** I had a question about AFM know when there was a, the last series, it was a, there was a lot of press about it. They were warning that there was going to be another episode probably in October, and I guess that's the year it never even happened. What is the biggest risk, if there is another occurrence because it seemed like it was clustered in certain parts of the country. Is this something that could become like an epidemic or is it just something that's going to show up once in a while?

[00:19:17] **Dr. Varun Kannan:** That is an excellent question. To be honest, I don't think I have an intelligent answer to it. We had basically three years of good data studying it and since then it's not happened as much thankfully. So it's been harder to study beyond that. Again, it seems like there's a specific virus, a specific kind of enterovirus that was associated with this. Why did this enterovirus spike every other year? I have no idea. But yeah, I think without further knowledge, we can't really say is this going to spike again?

[00:19:49] Especially since, I think still since 2020 pediatric virus epidemics have not looked the same. Like we used to see spikes have RSV exclusively in the wintertime, and then we started seeing RSV spikes in the summertime. So, I think as a species, as a population, globally, viruses look different post pandemic, and I think we're still trying to catch up and understand why that is.

[00:20:11] **Dr. Grace Gombolay:** So just to add onto that, so my other hat, I do review AFM cases for the CDC. And so, we've been waiting for this increased outbreak in all of that. Every year we do get a few cases here and there. So, there's this low level somewhere around 20 to 40 ish, not a ton that we still see.

[00:20:29] But yeah, the thought is that the pandemic and with social distancing and masking that changed it. But we have seen pockets of the enterovirus actually cropping up here and there both here and, in the US, and in Europe. And so, every time that happens, we're like, oh, we're going to be on alert. But still it hasn't happened. And why that is, I don't think anybody really knows. Okay. Other questions? Oh, I'll get to you next. Yeah.

[00:20:57] **Audience Member:** Hi, my name is Angela Jackson, and I was diagnosed with Transverse Myelitis, but it was idiopathic. They couldn't tell me what caused it or and I was told that after 18 months, if it hadn't healed, then I'd be living with it forever. So, what's being done about Transverse Myelitis? What's out there?

[00:21:26] I talked to one doctor, and he said it might be hereditary and for me to check my ancestry to see if I had a Native American in my family. So that's where I am with Transverse Myelitis. I am walking and using stuff for my legs to help with keeping them strengthened and save my knees. So that's my question. What's going on with TM?

[00:21:58] **Dr. Spencer Hutto:** That's a very good question. And at the heart of, I think a lot of what we're discussing today. And so, I think over the last decade or so, and especially what we're hearing in national conferences from leaders in Transverse Myelitis is, the growing impetus to try to define precisely, the cause.

[00:22:16] And there's been a lot of excellent research that I think has happened over the course of the last couple of decades to make that a little bit clearer. We have discovered a lot of the causes of Transverse Myelitis, but there still are, I think, a heavy proportion of patients who are not able to figure out the exact...

[00:22:31] Underlying cause. But importantly, NMO was discovered in 2004, MOG was discovered in kind of the mid 2010's. We've been able to attribute patients' myelitis to sarcoidosis at a higher level of confidence than we ever did in the last decade or so. And so, I think as far as I know, most of the research has been centered on trying to figure out what are the causes of Transverse Myelitis in patients who don't have one of these antibodies or one of the known entities that we're presently aware of.

[00:23:02] But there's also a, an awareness campaign, I think, to make sure that especially medical centers that are outside of the academic realm understand that there needs to be a very thorough push for identifying the cause and doing more than thinking about the possibility that this could be MS or NMO or MOG.

[00:23:23] And to make sure that patients are tested very thoroughly for a wide variety of things. And to also consider the chance that sometimes Transverse Myelitis when patients present, they will present with symptoms and signs and even findings on their MRI and findings in their spinal fluid that, sort of seem like it's an inflammatory disorder when it may actually be something else.

[00:23:46] And so one of the things that we see at Emory University Hospital is sometimes patients will be transferred to us for specialized treatment, for Transverse Myelitis and, maybe it's more likely that they've

actually had essentially a stroke of the spinal cord. So, we see that sometimes, and oftentimes those patients are actually treated very similarly in the beginning until we get more time, and we get more data back to determine the cause.

[00:24:06] And so there's a growing impetus to really diving deep and trying to figure out the exact underlying cause and to define it as best we can. But unfortunately, there is a certain proportion of patients who, despite our very best efforts and putting the full weight of current medical science behind the full diagnostic workup, we can't figure out the underlying cause.

[00:24:27] And so in those situations, I think we follow them closely in clinic and we want to make sure that this is not a relapsing disorder. And you may have experienced that in the forms of continued evaluations over time, because sometimes when they test you may be negative, and maybe that's not, maybe it wasn't the very best or optimal time for testing.

[00:24:47] And so sometimes you'll have to undergo some repeat evaluations later to see if one of the testings becomes positive subsequently. But that's mainly where I think things are at the moment is that there's still unfortunately so much left to learn. And we're working very hard to sort through that and to also make sure, I think that indeed patients have an inflammatory myelitis and not something that could mimic it.

[00:25:12] **Audience Member:** Thank you. Hi, my name is Layla. We were speaking about like viruses and RSV and things that could trigger disease. I heard in more recent years that there is research that shows that there was like a connection between like EBV or Epstein Bar Virus and MS. And I'm not saying that causes MS, but I don't have MS, I have NMOSD, but my doctor also recently found that I do also have EBV.

[00:25:51] So I was just wondering about, and there might not be a clear answer on this, but what are your impressions on the relationship between diseases like this, which is very common. I heard EBV is very common and that basically just general impressions about like those types of connections since they recently found it more in MS and I think other autoimmune diseases. But just curious about your thoughts on that.

[00:26:16] **Dr. Jacqueline Rosenthal:** EBV is the, virus that episodically just over time gets a lot of attention as it relates to MS, like you mentioned most people are going to have antibodies to that virus, even if you never had the Epstein-Barr virus is the virus that causes mononucleosis or mono that a lot of people have growing up.

[00:26:34] But even if you never actually had that infection, you were probably exposed at some point in your life. And you do have antibodies for 95% of people will have those antibodies. But when they looked at MS patients, a hundred percent of those patients have antibodies to EBV. And so, within the MS population, they're really looking at how that contributes to the onset of MS.

[00:26:56] And then also is it playing a part in chronic inflammation in MS. How that relates to NMOSD is very difficult because it's a rare disease. I would not be surprised if, just like in the general population, lots of NMO and any patient has antibodies to that. But when we think about NMOSD, we know that antibody is one the main thing that leads to the disease process.

[00:27:23] And so compared to something like MS where there is not like one test that we can identify and we look at what causes MS gosh, we're all over the place, right? It's a lot harder to characterize these little things. Going back now just to viral triggers at NMOSD, I'm not sure that we quite know if that is something that can play a part, I would not be surprised if it is in terms of you have its still autoimmune component and could that trigger something?

[00:27:51] Certainly. But I don't know that I would tie it in directly to EBV. There are so many viruses that have been associated with autoimmune disease in general, but in terms of being causative, that's where we're not able to make that link just yet.

[00:28:06] **Dr. Spencer Hutto:** While Dr. Gombolay is moving, I just wanted to mention that. Yeah, so there's this sort of strong relationship between viral triggers and I think MOG antibody disease. But one of the things that we see in NMO is that a lot of patients have other autoimmune disorders actually is very common in NMO.

[00:28:23] And the presence of other autoimmune sort of antibodies, perhaps without an actual autoimmune disease attached to it or something that we very commonly see. So there seems to be really like a predisposition towards autoimmunity in those patients. I don't think we exactly understand the relationship, but we see that quite frequently and actually are now realizing just in terms of yeah, the evolution of how things have gone recently, I'm very interested in rheumatologic disorders.

[00:28:47] And so a lot of patients for instance who were diagnosed with having Lupus Myelitis, so there's another systemic autoimmune disorder called Systemic Lupus Erythematosus (SLE), and one of the neurological complications of that is myelitis. And for the longest time they were diagnosed as having Lupus Myelitis.

[00:29:03] But what we have actually realized is a lot of those patients have NMO and they have actually two autoimmune disorders. They have two so that's very common. And just in terms of something else that we see, that is actually a really strong association in patients who have NMO.

[00:29:18] **Dr. Varun Kannan:** And one last quick point. It does seem like EBV is a strong association with MS, but EBV infection alone is not enough to cause MS because billions of people get EBV infection and almost none of them get MS. So, it's something else plus EBV, like a genetic risk factor for autoimmunity, low vitamin D levels, and maybe even environmental toxins and exposures that we don't understand. So it's a combination of a lot of things that leads to a really complicated disease situation.

[00:29:47] **Audience Member:** Me okay. My name is Patrick Gutierrez. My question is with Transverse Myelitis, we know that it causes a lot of gastrointestinal issues or, but have you heard about myelitis, affecting the esophagus? Affecting the…

[00:30:12] **Dr. Spencer Hutto:** Esophagus?

[00:30:13] I don't think I have personally yeah, I think sometimes Transverse Myelitis, it depends on, I think what part of the spinal cord is affected. Sometimes it can extend so far cranially that sometimes it can affect cranial nerves and some brain stem nuclei and sometimes that can affect a person's ability to swallow and then the ability to essentially get the food down the mouth and through the esophagus into the stomach.

[00:30:44] And so, sometimes yeah, it's very patient dependent. I think another just important point to make about today is that even though people may have the same exact diagnosis it may actually look a lot different in everybody. And so, I tell all my neurosarcoidosis patients that it's very difficult to go online and read about your disorder and on Google and or even in patient forums because everybody's disease actually can look very, pretty much different.

[00:31:07] And so if you have Transverse Myelitis, it also probably looks very different if, depending on who you talk to. And so, if yours perhaps extended further up especially into the brainstem, then you know, that could cause prominent issues with, swallowing and maybe the function of the esophagus in that sense. But I'm not aware of otherwise unless you…

[00:31:29] **Dr. Jacqueline Rosenthal:** I agree. I think when you have symptoms, you carry a diagnosis of Transverse Myelitis as well, and you have symptoms that don't necessarily like to say that word localized. If you can't make it come from the spinal cord, then you have to start thinking of Transverse Myelitis plus something else. Or is there, is it a syndrome of some sort? So, I would encourage anyone that's dealing with symptoms that may, that we may consider atypical, to just discuss it with their neurologist.

[00:31:56] **Dr. Varun Kannan:** I think gut health in general is something a lot of us take for granted. And there's a really complex interplay between the brain, neurological disease and gut, and also things like immunity.

[00:32:07] And people ask all the time what is their research going on in that space? And, there is because we don't understand it, so we don't really know how to translate knowing that there's a connection between these three things to like, how does diet change how you feel neurologically. But there are important questions.

[00:32:24] **Audience Member:** Thank you. This actually goes back two questions ago when you were talking about whether it could be a stroke in the spine versus Transverse Myelitis. I was diagnosed with CMV Transverse Myelitis, but I was a medical mystery for the first three and a half years. My neurologist has, when she was explaining it, when she diagnosed me with this CMV Transverse Myelitis, she said essentially the CMV virus, it attacked your spine.

[00:33:06] It essentially caused a stroke in the spine, and now you have incomplete paralysis. So, my question is, how do you tell the difference between Transverse Myelitis and if it was, say, a virus causing a stroke in the spine?

[00:33:23] **Dr. Spencer Hutto:** So, you're just hitting this perfectly in the head of how challenging sometimes these cases are. I think in the hospital and yeah, that, that really speaks to, I think the difficulty there. I think the big push to make sure that patients are tested very thoroughly in the beginning has been an awesome change in how we approach this. Yeah.

[00:33:47] Because for the longest time patients could very simply receive a diagnosis of Transverse Myelitis, get a label, maybe not have very extensive testing from the get-go. When you come into the hospital, that's like your opportune time to get as much testing as you can to really sort things out.

[00:34:08] And once you administer various forms of treatment that may suppress your ability to find the things that you need to do to help define the diagnosis further. So, if somebody were to come in, say, to Emory University Hospital we would do all of those things immediately.

[00:34:27] So we do a full battery of serum tests in the spinal fluid. We oftentimes do actually include pretty extensive testing for viruses because one of the things that you should know I guess about viral infections especially of the spinal cord, is that they look very similar actually in terms of the CSF profile that they generate to autoimmune disorders.

[00:34:46] And so oftentimes patients will have a little bit of inflammation in the spinal fluid in a way that looks just like viruses. And so, without doing some additional testing to sort that out and sending for specific tests that look for a specific virus, you may not ever know it actually. Fortunately, now there is actually a panel that looks for some of the most common infections of the nervous system.

[00:35:12] It's called a meningo encephalitis pathogen panel. And it tests for something like I think the top 13 infections of the central nervous system. And so, usually what we do actually is we send that with our initial round of spinal fluid testing because one of the things that we also want to know and be clear on is there

is a possibility that if a person is infected, perhaps giving them steroids that suppress the immune system that is trying to fight the infection may not be in their best interest.

[00:35:39] And so we will send that and that has been something that's very helpful. But CMV is actually one of the things on that pathogen panel amongst other things we've talked about EBV today that's also on that panel. But there are a number of other things. And so that would be very helpful.

[00:35:55] Certainly infections up the nervous system can contribute to strokes. Strokes of the spinal cord, also strokes of the brain. The MRI oftentimes will be helpful in getting a more clear sense of if a person has had a stroke of the spinal cord, there's a certain sequence on the imaging that can give you a better sense of if it's a stroke or not.

[00:36:18] The problem with that is it's not actually a part of the standard MRI sequences that we gather for the spinal cord, because strokes of the spinal cord are, everything that we're talking about today is actually very rare. So are strokes. Strokes, so the spinal cord are very rare. Strokes of the brain are very common.

[00:36:34] But that sequence is not routinely incorporated into just the standard picture order that we obtain on MRIs of the spinal cord. So, the person you know, who's taking care of the patient has to have that in the forefront of their mind as soon as they see the person and request that on their MRI specifically, and encourage the neuroradiologist together that sequence.

[00:36:57] And so through the combination of spinal fluid testing and the MRI results, we may get a better sense if a person has had a stroke that is potentially superimposed on top of, whatever the primary insult is, if that's an infection or, otherwise.

[00:37:14] **Audience Member:** So mostly I'm thinking I should have gotten sick close to Emory University's hospital. Alas, I did not. I went into the ER with 104 fever and was just sent home saying that it was just a fever of unknown origin. And so, nothing was done at the time. So, everything for me was after the fact when my legs weren't working. And so, everything I had done was some months after the active virus. See, so anyway, but thank you. I was very curious how you tell the difference, but mostly it would need to be done right when the virus is happening, isn't it?

[00:38:01] **Dr. Spencer Hutto:** That's the most opportune time. The MRI is also most sensitive in that period as well, especially as it pertains to stroke. I think a lot of people in this room can attest to the fact that once you've had some inflammation of the spinal cord from X, Y, Z reason, you will find that there's going to be some residual findings on there.

[00:38:19] Once the active inflammation kind of dies down and goes away, you'll have some sort of evidence that you've had a prior attack subsequently and, perhaps even into perpetuity. That's very, especially true for NMO, maybe less true for MOG, but when it comes to strokes of the spinal cord, that sequence is called Diffusion Weighted Imaging, DWI is most sensitive during the time that a person's actually having the stroke and the ability to detect that signal change really dies off particularly after a couple of weeks, I would say.

[00:38:50] And so once you're beyond that timeframe, it is a little bit less useful. And so, then you have to back up and put on your Sherlock Holmes hat and think about here's the information that we had and what makes the most sense? And so, one of the things that Johns Hopkins has a Transverse Myelitis center.

[00:39:09] They see a lot of patients who have at least carry a diagnosis of Transverse Myelitis. And so, they're seeing a lot of referrals for patients who do have Transverse Myelitis. They're also seeing a lot of

patients who were initially diagnosed with that. And in subsequent review of sort of their workup in terms of their MRIs, their blood testing, their spinal fluid testing, it becomes a little bit clearer, at least with time that maybe actually they have something else.

[00:39:33] And that was true for I would say a relatively sizable number of patients in their cohort, in the adult population. And so, they've done a very good study, just looking back on the experience of the patients that were referred into this clinic, highly specialized for that. I should also just acknowledge that a lot of times at Emory, we have the benefit of some time because not everybody comes to our hospital first and patients will be transferred in.

[00:39:58] And, so we have what I would describe it as a luxury of having the time of other things having happened before they get to us, which often provides a lot of clarity in terms of what's going on with the patient. And so, we have that benefit, whereas it can be very challenging if you're the first person to see somebody and so I recognize that, we have that added advantage.

[00:40:22] **Audience Member:** My, my grandma used to say that they call it practicing medicine for a reason. Sometimes that is very true. I think that's true. But anyway, thank you. So, thank you so much.

[00:40:31] **Dr. Spencer Hutto:** You're welcome.

[00:40:33] **Audience Member:** Thank you. Good morning. Based on your last answer and your response to her question, it brought up a question in my mind around the amount, the frequency of having, of getting, of having a lumbar puncture, which is where you get the spinal fluid and determining how much gets taken to run all those tests versus regular MRIs. I was diagnosed 13 years ago with Transverse Myelitis and my lumbar puncture, which at the time I could feel my back, so I don't know how much fluid they took out, but recently working with a different neurologist in a different state we went through, but she had a lot of spinal fluid pulled out to do a lot of battery of tests because I just had another occurrence of it.

[00:41:30] But so who makes that determination? How do you determine, particularly going into the emergency room, which I think is how much spinal fluid to take out, because the protocol I went on was to get MRIs with and without contrast every three months, then every six, then a year as they tried to determine if I was going to have MS.

[00:41:55] **Dr. Spencer Hutto:** This is a very good question, and I'd be curious how the other panelists, what they think about this as well. But I think certainly when a person presents in the active phase, when they're acutely inflamed, that's an opportune time to gather additional information. And especially if you suffered a relapse after really such a rather prolonged period of time, then it was important I think to revisit can we define this further and, more clearly.

[00:42:21] So whenever a person comes with an event concerning for dysfunction of the spinal cord, especially if it's something that's relatively acute we, we want together spinal fluid because yeah, that's the time that, that things are awry and off and probably going to be the most sensitive in terms of our testing.

[00:42:39] And we are so just we drain people's blood for testing for antibodies and this thing and that thing and it's, really a lot and I try to prepare patients for that. And similarly obtaining spinal fluid is obviously more challenging than obtaining a blood draw.

[00:42:57] And so our general approach in the hospital next door has been to try to gather everything that we need with the first round. And that may not always be the case. Sometimes patients will need a second

lumbar puncture. Sometimes patients may even need a third lumbar puncture. It just depends, especially if the concern is, chiefly, cancer.

[00:43:17] A lot of times having multiple samples would be more helpful than a single sample. But in general, with the first spinal tap, if we are able, we try to take a reasonable volume to ensure that we have enough to test for the myriad of things that we do. And if you were originally diagnosed 13 years ago, things have, fortunately things have changed a lot in the last 13 years.

[00:43:41] And so there is actually a lot more that we can send specific tests for. And so how much fluid you had gathered 13 years ago may have been just the right amount for what was available at the time. But now the number of tests available have significantly increased. And so, yeah, so in general if, a person as long as a person's there's something called an intracranial pressure.

[00:44:06] When fluid is in your spinal column, there's a pressure and there's a normal range and people feel comfortable when they're in that normal range. As you drain the fluid, the pressure goes down and that can create some issues with at least headache once the pressure starts to go down. And so, you may have some limitations in terms of how much you can take at one time based on that number potentially.

[00:44:25] But as long as the number kind of stays within the normal range, we gather as much as we can in light of the extensive testing we intend to pursue. If you're not able to quite get as much as you ideally had hoped for, then maybe that does necessitate a sort of an early second lumbar puncture.

[00:44:40] But I think in terms of constantly thinking about what could be going on with somebody if it wasn't figured out during the initial hospital stay, certainly if a relapse occurs, that's a clear indication, at least in my mind, if we don't have a firm diagnosis to obtain repeat spinal fluid testing if you had a diagnosis of NMO and you had a relapse and everything makes perfect sense for NMO, then a repeat lumbar puncture may not actually be necessary.

[00:45:06] But if it's an undefined problem, then a repeat lumbar puncture makes kind of sense in my mind. But I don't know if you have that.

[00:45:13] **Dr. Jacqueline Rosenthal:** I'll just add that. When you go to an ER and what the ER physician is looking at and what we would be interested in very significantly. And that's fair to an extent, when you go to the ER, they're thinking immediately life-threatening, so you know, meningitis and things like that.

[00:45:29] And so they're ruling out certain infections and they're not thinking of these rarer neuroinflammatory disorders that we may want to look for. And so, people do get second lumbar punctures for that reason, even within the same hospitalization sometimes because different goals in terms of what we're looking for.

[00:45:48] **Dr. Varun Kannan:** And some unique challenges in the pediatric population are even things like MRIs and six, seven-year-olds, they're not going to be able to sit still, so they're going to get anesthesia for it.

[00:45:57] We try to be as little invasive as possible when we're doing diagnostic workups. So, we usually are sedating the kids through the lumbar punctures too because it's hard for them to understand what that discomfort looks like. So ideally we'd like to go stepwise and do just blood tests first or just an MRI first, but because we're thinking about anesthesia and the kids are trying to basically cluster everything together, so we'll say since we're given the child anesthesia, we'll scan the brain and this whole spine and we'll do the lumbar puncture and we'll get as much fluid as we can so that we can freeze it and run more tests if we need to later rather than putting the kid through anesthesia again unnecessarily.

[00:46:40] **Audience Member:** Hey, good morning. So, relating to MOGAD is there studies or upcoming studies for it being hereditary? because we have children, we know the signs and symptoms, the way they are displayed and represented for him, but could that be different for our children and should we be proactive in testing for those antibodies and being prepared if something was to happen from a hereditary point of view? Yeah. And she's seven right now.

[00:47:07] **Dr. Varun Kannan:** That's a really good question and an important concern. I think the short answer is probably not, it's probably not hereditary. Like we talked about, unlike NMOSD and some other autoimmune diseases, it seems like MOGAD is less associated with having systemic autoimmune issues in general.

[00:47:24] So it seems like it's more likely to be a viral response. So, we don't really see high rates of people with MOGAD having family members with MOGAD, which is different than MS and NMOSD and my adult colleagues can correct me on that if I'm off. That being said, we don't know if there's subtle genetic risk factors that still make you more prone to having reactions to viruses like this, but I think for the purposes of your question, I don't think she's at risk of MOGAD and unless she develops neurological symptoms, I don't think there's a reason to test her for it.

[00:47:58] **Dr. Jacqueline Rosenthal:** And, they are mod they are we're learning more and more. There's lots of registries, patients are being followed for this, so they're looking for those patterns. But I will say, just generally speaking, like when we talk about, like you said with Multiple Sclerosis, we do know that children have a higher risk, but it's still far more likely than not that for most they will not develop MS 2 to 4% versus less, far less than 1% in the general population.

[00:48:25] So it's not it's something that I would, if you were my patient, I would say let's not put that on our worry list. And the other thing I just, I recommend just generally to all of my patients who ask about their children. because there's so much, we don't know. I recommend just have your kids take vitamin D. It's something that's easy. We don't know for sure that it'll help. It certainly won't hurt and there's some evidence just to suggest that it may be beneficial.

[00:48:47] **Audience Member:** Okay. I'm sorry, I have a two-part question. So, the second part of that being an autoimmune response and things. Siblings, he has four siblings, he has three other siblings, he's the fourth.

[00:49:00] They all have different autoimmune level diseases. So could that play a part in how his body responded to MOGAD relating to how they respond to their different things and none of them were vaccinated as children. Yeah.

[00:49:17] **Dr. Varun Kannan:** Yeah. I think the short answer there is, yeah, there must be something there.

[00:49:21] **Audience Member:** Yeah.

[00:49:21] **Dr. Varun Kannan:** I think there's some sort of subtle genetic risk factor at play. Now could the vaccination and exposure to viruses early on in life also play a role? Maybe. I think it's really hard to prove these things. There are genetic tests you can consider that look at genes related to immunity. They're interesting results but they don't always help you. But so, it's something you can talk about with your doctor team.

[00:49:48] But again, having an answer for the genetics there may not directly impact how your treatment goes. Does that make sense?

[00:49:55] **Dr. Grace Gombolay:** Yeah. Thank you. Great. I think this is going to be our last question for this session, but I just wanted to tell everyone, we have lots of panels throughout the day. There'll be time to ask questions, even if it's not particularly to that particular panel topic. We're happy to answer questions because these are really important questions.

[00:50:13] **Audience Member:** Hello, my name is Cheryl Bean. I have NMOSD that was diagnosed about nine years ago. I have a twin sister that has Optic Neuritis, but no MS, no NMOSD. She does have Sjogren syndrome and I was just wondering, responding to her too, that we were worried about the genetic component to it and could we pass it down to generations of our family.

[00:50:55] **Dr. Jacqueline Rosenthal:** I think the only thing you could really take away from this, as mentioned earlier, we do see autoimmune disease and clusters, right? Even with NMOSD. So, what I think you could take away is that there's autoimmune disease in your family and that for that reason, your family just generally speaking, is going to be at higher risk for autoimmune disease compared to other families.

[00:51:14] But what exactly is that risk? What will it look like? That's the part we don't know. And we see, I see that frequently. One person has Lupus, one has MS, one has Crohn's disease, and it's like, why is it coming out that way? We're not sure, but there's something going on. Yeah. Thank you.

[00:51:34] **Dr. Grace Gombolay:** Great. Thank you everyone for your questions. Thank you to our panelists.